ANGLIA RUSKIN UNIVERSITY

FACULTY OF ARTS, HUMANITIES AND SOCIAL SCIENCES

MUSIC THERAPY PROTOCOL TO SUPPORT BULBAR AND RESPIRATORY FUNCTIONS IN PATIENTS WITH EARLY AND MID-STAGE AMYOTROPHIC LATERAL SCLEROSIS: A FEASIBILITY STUDY

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A thesis in partial fulfillment of the requirements of Anglia Ruskin University
for the degree of Doctor of Philosophy

Submitted: May 2020

ACKNOWLEDGEMENTS

This study would not be possible without the access to clinical and laboratory resources provided by the study host organization, ALS Centre Moscow (Moscow, Russia), and the tireless support from the administration, the volunteers and the medical team of the Centre, including research assistant Dr. Marina Bialik, research assistant, music therapist Maria Pakosh (Ilchenko), research nurses Yana Batmanova, Sergey Korneychuk and Daria Puzanok, administrative director Anna Kasianova, coordinator Andrey Prokofiev, music therapist Ruslan Semenov, volunteer coordinator Ksenia Nazarova, and the medical director of the study Dr. Lev Brylev, who also served as a field supervisor for this study.

The author of this thesis is immensely grateful to all the external expert advisors who have helped to move this research forward: Dr. Richard Sloan at West Dorset MND Association (UK); Natalia Semina at Rehabilitation centre “Aprel” (Moscow, Russia); Dr. Jordan Green, CCC-SLP, at MGH Institute of Health Professions (Boston, USA); Dr. Emily Plowman, CCC-SLP, at the University of Florida (USA); Dr. Yana Yunusova, CCC-SLP, at the University of Toronto; Anastasia Beltukova, music therapist, at “Turmalin” (Moscow, Russia); Tina Georgievskaya, vocal coach (Moscow, Russia); Alex Sherman at the Neurological Clinical Research Institute at Massachusetts General Hospital (Boston, USA); Prof. Alfredo Raglio at University of Pavia (Italy); Victoria Edwards, speech and language therapist (SLT), Siofra Mulkerrin, SLT, and the MND team at Arthur Rank Hospice (Cambridge, UK); Dr. Kirill Gorbachev at Buyanov Moscow City Clinical Hospital (Moscow, Russia) and Dr. Vera Fominykh at Institute of Higher Nervous Activity and Neuropsychology (Moscow, Russia), Terri Handler and Dr. Matvey Lukashev at ALS TDI (Cambridge, MA, USA).

Indispensable for the research process was direct help with the research design and pseudonymized data analysis from Jufen Zhang, statistician from School of Medicine, Anglia Ruskin University (Chelmsford, UK), Zhanna Bottaeva, SLP, at Clinical and Research Institute of Emergency Pediatric Surgery and Trauma (CRIEPST); Dr. Ashley Waito, CCC-SLP, researcher at Bulbar Function Lab, Sunnybrook Research Institute (Toronto, Canada), Dr. Marziye Eshghi, CCC-SLP, researcher at Speech and Feeding Disorders Lab, Massachusetts General Hospital (Boston, MA, USA), Fyodor Soykin, IT specialist at Canopy Education Inc

(Cambridge, MA, USA), Daria Ivanchenko, logopedist (Moscow, Russia), and Ekaterina Bruno, CCC-SLP (Dallas, USA).

A heart felt thank you to Dr. Alexander Street, music therapist and the first academic supervisor for this research project at Anglia Ruskin University, who provided continuous advice and support during all the stages of this research, and to Prof. Jörg Fachner, the second academic supervisor for this project, who helped to define the research subject and to formulate the study aims and design.

Above all, the author is grateful to all the research participants and their caregivers, as well as to Maria Gostintseva, Andrey Demidov, Pavel Andreev, Victoria Petrova, Sergey Borisenko, Anthony Carbajal and many other persons living with ALS, to ALS caregivers, volunteers and care specialists who have inspired this research.

This study was generously sponsored by The Stephen Hawking Foundation (UK), BOSE Corporation (USA), Remedywave (USA) and crowdfunding donations through Palliative Care Initiative (USA). Thank you.

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ABSTRACT

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May 2020

Background and aims. Respiratory failure, malnutrition, aspiration pneumonia and dehydration contribute to mortality in ALS. Loss of natural communication impacts quality of life. Previous studies demonstrate that music therapy exercises are effective for rehabilitation of patients with neurological conditions. The aims of the study were to investigate the feasibility of conducting home-based research, measuring the effects of a new music therapy protocol on bulbar and respiratory function in persons with ALS. It is the first biomedical music therapy research to do this and the first study of any kind to systematically look at supporting bulbar and respiratory functions in ALS.

Methodology. Eight newly diagnosed patients were recruited. The music therapy protocol was delivered to all participants twice weekly for 6 weeks. The study duration was 16 weeks, with run-in, treatment and wash-out phases. Feasibility data (recruitment, retention, adherence, tolerability, self-motivation, personal impressions) were collected. Bulbar and respiratory changes were objectively measured.

Results. High recruitment rate (100%), retention rate (87.5%) and mean adherence to treatment (95.4%) provide evidence for feasibility of the study protocol. The treatment was tolerated well. Mean adherence to the suggested independent exercise routine was 53%. The outcome measurements to evaluate the therapy-induced change in bulbar and respiratory functions were defined. Findings suggest that the protocol is safe to use in early and mid-stage ALS and that music therapy was beneficial for the participants' bulbar and respiratory functions. Mean trends suggesting that these functions were sustained or improved during the treatment period were observed for most outcome parameters: Maximal Inspiratory Pressure, Maximal Expiratory Pressure, Peak Expiratory Flow, Center for Neurologic Study – Bulbar Function Scale speech and swallowing subscales, Maximum Phonation Time, Maximum Repetition Rate – Alternating, Maximum Repetition Rate – Sequential, Jitter, Shimmer, NHR, Speaking rate, Speech-pause ratio, Pause frequency, Hypernasality level, Time-to Laryngeal Vestibule Closure, Maximum Pharyngeal Constriction Area, Peak Position of the Hyoid Bone, Total Pharyngeal Residue C24area.

Conclusion. The suggested design and protocol are feasible for a larger study, with some modifications, including: aerodynamic measure of nasalance, abbreviated voice sampling and psychological screening.

Key words: music therapy, amyotrophic lateral sclerosis (ALS), motor neurone disease (MND), bulbar, respiratory, home-based

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SUPPLEMENTARY MATERIALS

Audio recording of the post-intervention exercises for independent practice for each participant (in Russian), with music accompaniment, are available on a flash drive and as a temporary password-protected internet link (until 01.01.2023).

For online access use the following address:

https://alsmusictherapy.org/about/supplementary/

Password: MusicALS2020

LIST OF APPENDICES

INTRODUCTION

> When we are unable to think or speak or move or be who we once were, we still have this music. It helps us express and communicate. It helps us feel good. It moves us, often deeply, always naturally.
>
> – Billy Joel, 1993

ABOUT THIS THESIS

This doctoral thesis comprises a detailed report on a feasibility study of a music therapy protocol to support respiratory and bulbar functions of persons with early and mid-stage amyotrophic lateral sclerosis (ALS).

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a rare group of neurological diseases that leads to deterioration of nerve cells in the brain and the spinal cord. The current lifetime risk of developing ALS, adjusted for other-cause mortality is 1 in 347 men and 1 in 436 women (Ryan *et al.*, 2019), and prevalence is increasing (Longinetti and Fang, 2019). The majority of ALS cases (90% or more) are considered sporadic: the disease seems to occur at random with no clearly associated risk factors and no family history of the disease (Qureshi, 2006). The median survival time from onset to death is estimated at from 20 to 48 months, but 10–20% of ALS patients survive longer than 10 years (Chiò, 2009). The disease is almost always fatal, and the treatment options are few, limited to prolonging survival moderately at later stages of the disease (Fang *et al.*, 2018; Knibb *et al.*, 2016).

Music therapy (MT) is the professional clinical use of music and its elements to enhance human health and wellbeing. Application of music therapy principles in neurorehabilitation allows treatment of cognitive, sensory, and motor dysfunctions. There is limited evidence that music therapy may be beneficial for persons with ALS and their caregivers.

The thesis provides a rationale for creating a music therapy protocol to support bulbar and respiratory functions of persons with early and mid-stage ALS. It outlines the process of developing such a protocol and defining the measurement tools to assess its effectiveness. A detailed description of the clinical experiment and its results are provided and the theoretical and practical implications of this research are discussed.

Trial registration at ClinicalTrials.Gov (U.S. National Library of Medicine): NCT03604822.

Kindly be advised that the following text contains information that may be emotionally triggering or upsetting, especially if you or your loved ones have been diagnosed with ALS.

IN FIRST PERSON: HOW THIS RESEARCH CAME TO BE

Reading through a large body of previously published work is one of the first steps on the way to scientific discovery. It may be captivating or overwhelming at first, but eventually, through all the hypotheses, numbers and graphs, the reader learns to distinguish the personalities, and the questions start flooding: what drives this researcher? Why has this particular research direction been selected? How has one been affected by one's clinical practice, academic exploration and, maybe most importantly, personal experience? In healthcare studies, these are all the more constitutive, almost moral questions, as the researcher chooses to invest their effort and time into finding an aid for one particular condition at the expense of not engaging into (or limiting) practice and research with other clinical populations. The statement of the aims, thus, becomes a personal statement of sorts – not essential for the purposes of a particular study, but highly relevant for understanding the process of scientific inquiry as a human activity. This is why, before proceeding to define the focus of this thesis in more detail, I would like to inform the reader briefly on the substratum for my idea to explore music therapy as a rehabilitative treatment for ALS. Conveniently, being a music therapy researcher, i.e., an artist to the same degree as a scientist, somewhat entitles me freedom to express my thoughts less formally in the introductory part of this thesis. And I would like to start with a story.

When asked, at the age of 6, what I wanted to be I would say: "I shall be a doctor, and in the evening, I shall perform music in the circus". I grew up in Russia, my childhood and teenage years coinciding with the grandiose collapse of the Soviet Union empire. The ruffled economics of the rising democracy were to blame for my fainting, age 10, on stage during a Mahler performance at the Moscow Conservatory Great Hall, after going without food for three full days. Becoming a professional musician was not an option at the time, my secondary education was not good enough to allow me pass the exams to enter medical school, I had no inclination to become a lawyer as my parents wished, so I went on to study philology, with specialization in linguistics. I enjoyed studying phonetic systems, reading spectrograms and learning about human speech production, but knew that was not what I wanted to do with my life.

At 22, family matters brought me to reside in Seattle, USA. Music and medicine finally came into focus as, after studying film and classical composition, I entered the music therapy degree program at Berklee College of Music in Boston in 2010. I was fascinated by both the interpersonal and neurological dimensions of evidence-based, goal-driven music therapy and the powerful effect it had on the clients I worked with. I wondered why I had never heard about music therapy in Russia, searched the web and discovered almost nothing. The music therapy profession was yet to find its way to my country of origin.

Upon completing my training, I spent several years advocating for music therapy in Russia. One of the organizations that expressed interest in collaboration was ALS Moscow Centre. When a representative of the Centre approached me in 2013 with the question: “What can music therapy do for persons living with ALS?”, I had to go to the library and do some research. This was before the ALS Bucket Challenge of 2014 - the planetary-scale advocacy event to promote global awareness of the disease, and there was not much information and not much hope.

I consulted the medical team and visited patients to learn more. When making music with persons with ALS, I sensed that active music therapy worked surprisingly well, almost magically for persons living with this disease. I recalled the same sensation from past clinical experience working with persons who had frontotemporal dementia. Music immediately "turned on" social interaction and speech, then movement, in those who just seconds ago were silent, motionless, expressionless...

I prepared a protocol with interchangeable blocks of music therapy activities, matching a wide range of needs in ALS, and trained a group of musicians-volunteers to implement it with patients. However, only partial implementation was possible, with goals such as basic psycho-emotional support of the patients and their families, light physical exercise through playing simple musical instruments to preferred music and relaxation to improvisatory live music. Other parts of the protocol, including those addressing respiratory and bulbar function, required more clinical expertise from a provider and could potentially cause harmful fatigue and emotional distress to the patients, if not practiced with proper understanding of neurological and psychological aspects of music therapy interaction.

It was my hope that applied research of the protocol to support respiratory and bulbar functions in early and mid-stage ALS would become the much-needed evidence of music therapy benefits in rehabilitative care of persons with ALS.

PURPOSE OF THE STUDY

The aim of this research was to determine the feasibility of a home-based music therapy protocol as an intervention to support respiratory and bulbar functions in early and mid-stage ALS. Additionally, inquiry was made into the most sensitive and feasible tools to assess the treatment effect on respiratory and bulbar functions in ALS.

The ultimate goal of this work is to eventually produce a safe, standardized music therapy protocol to be used by ALS care teams worldwide and to provide solid scientific evidence for successful integration of music therapy services into a clinic-based multidisciplinary care approach, thus enhancing experience and effectiveness of ALS treatment. This would require a sufficiently powered follow-up pilot study, for which the current feasibility study provides foundation.

SIGNIFICANCE OF THE STUDY

This is the first study to examine possibilities of music therapy in the rehabilitative care of persons with ALS, with the purpose of supporting their bulbar and respiratory functions.

This research serves an immediate purpose of addressing the need for continued scientific inquiry to understand the role of exercise in supporting bulbar and respiratory functions of persons with ALS (Plowman, 2015) and providing a foundation for higher levels of evidence (Hanson, Yorkston and Britton, 2011) – in particular, delivering the necessary feasibility data for a large cohort clinical trial. The importance of rigorous clinical trials to support alternative ALS treatments has been emphasized with the dual impact of ensuring ethical medical care, as well as protecting patients from the onslaught of pseudoscientific, often harmful practices (Anonymous, 2020; Adams, Lee and Peng, 2018; Bedlack and Hardiman, 2009).

One essential feature of this research is that, from the very start, it has been a genuinely multidisciplinary collaborative project, initiated at the request of a social worker, conducted and supervised by music therapists, advised by neurologists, palliative care specialists, physical therapists and speech language specialists internationally, monitored by local visiting nurses and clinical care coordinators.

This is the first study to systematically look at supporting bulbar and respiratory functions in ALS. Swallowing, vocalization and breathing are tightly coordinated, and a close relationship exists between these processes, in terms of location and activation of the neurons (Matsuo, 2008). The overall emotional and physical condition of a person has a great impact on these processes as well. However, support of these functions in persons with ALS has been traditionally disunited and apportioned between various medical and allied professionals, such as speech language therapist, nutritionist, physical therapist, ear, nose and throat specialist, etc. Though specialist expertise is essential for the deep insight into the nature of each function, this disunion may be disadvantageous from the standpoint of integrative patient care. Drawing from the wealth of expert knowledge and supported by multidisciplinary collaboration, a music therapist who, by professional standards, has training in vocal technique as well as basic knowledge of anatomy, physiology, neurology and psychology, may be in the unique position to provide a crosscutting outlook for bulbar and respiratory support in ALS.

Finally, as of 2018, this was the only music therapy clinical research study taking place in Russia that was registered with ClinicalTrials.Gov (Figure 1), among 4915 studies in other disciplines registered in the same region (Figure 2). ClinicalTrials.Gov is a database of privately and publicly funded clinical studies conducted around the world, an open resource by the U.S. National Library of Medicine. At a time when the field of music therapy is still in the early stages of establishing as a health care profession in Russia, this study serves as an advocacy event, exemplifying a globally recognized standard for professional practice.

Figure 1. Map of music therapy clinical trials registered with ClinicalTrials.Gov, found through search using “music therapy” as keywords, retrieved on 08.08.2018

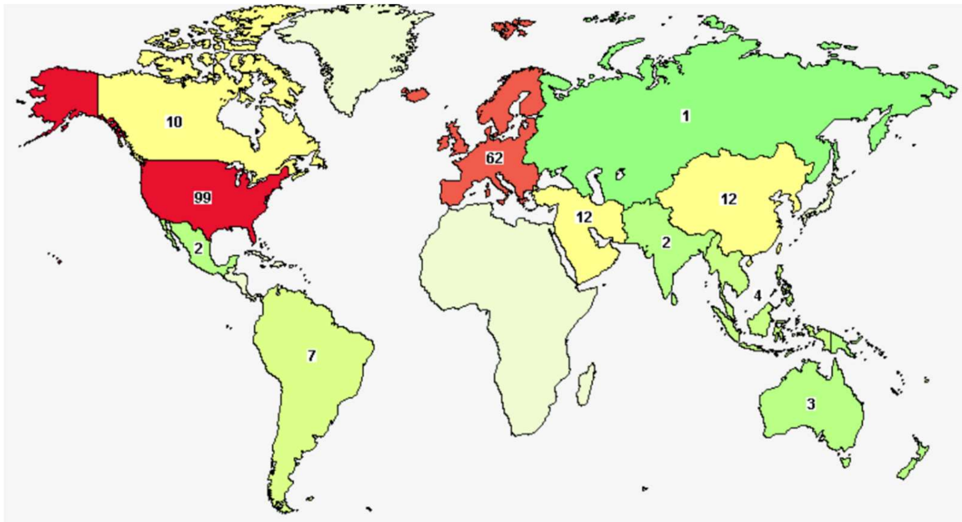
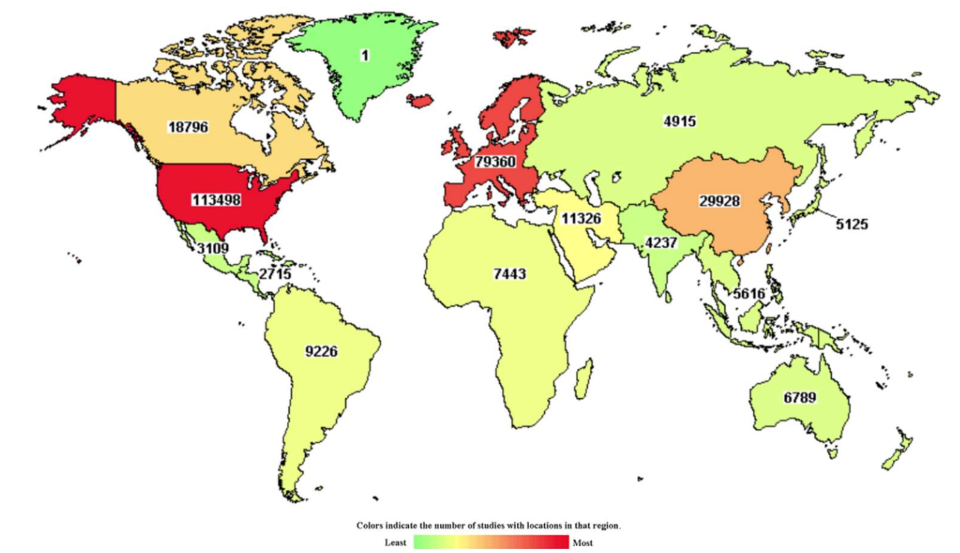


Figure 02. Map of all clinical trials registered with ClinicalTrials.Gov, retrieved on 08.08.2018



LITERATURE SEARCH AND PROFESSIONAL CONSULTATIONS

The main literature search was conducted in the period from August 2017 to December 2018, when the first draft of this thesis was created. Google Scholar, PubMed and Anglia Ruskin University library online databases were searched, using the terms cited below, as well as combinations of these terms: ”ALS”, “MND”, “prevalence”, “decline”, “music therapy”, “exercise”, “caregiver”, “burden”, “speech disorder”, “respiration”, “respiratory”, “bulbar”, “swallowing”, “dysarthria”, “dysphagia”, “measure”, “decline”, “palliative” “rehabilitation”, “community services”, “home-based”, “progression”, “relaxation”, “vocal”, “voice”, “randomized control trial”, “complementary”, “alternative”.

Additionally, the reference lists compiled by The Academy of Neurologic Music Therapy and presented at their official website were studied. A manual book search of relevant literature was conducted, using Anglia Ruskin Library, Berklee College of Music library and the personal library of the researcher. Experts in ALS research and clinical care were consulted through email correspondence, communication during visits to research laboratories and care centres, and at the field-oriented conferences.

Considering that ALS research has been rapidly evolving over recent years, mostly due to growing public awareness of the disease and increased funding available for ALS clinical trials after 2014, a new search, within the same databases and with the same terms, was conducted during the final stages of thesis completion in early 2020, to keep up to date with the latest scientific evidence.

OUTLINE OF THE THESIS

The first chapter, Chapter 1. Amyotrophic lateral sclerosis: clinical presentation and care, offers an overview of the literature on clinical symptoms, epidemiology and multidisciplinary care of ALS and the emerging evidence for the beneficial role of exercise for persons with ALS. Chapter 2. Music therapy potential in multidisciplinary ALS care, defines music therapy as an allied healthcare profession, provides brief analysis of existing literature to support music therapy application with ALS, describes music therapy service as a part of multidisciplinary care at ALS Centre Moscow and gives a rationale for continued research.

Chapters 3 through 5 explain the study methodology, including study aims and design (Chapter 3), choice of outcome measures (Chapter 4) and full description of the music therapy protocol (Chapter 5).

The results presented in chapters 6 through 9 provide detailed analysis of the study results, including recruitment data, feasibility data and biomedical data. Then a summary outline of the results is provided.

Case studies follow in Chapter 10. Case study sketches offer a deeper insight into the process of home-based music therapy protocol implementation with study participants – Moscow residents who have early and mid-stage ALS.

Chapter 11. Discussion, provides interpretation of the study results, limitations to the study, reflection on its process and implications for future research. The Conclusion highlights the main study findings. References and Appendices follow.

CHAPTER 1

AMYOTROPHIC LATERAL SCLEROSIS: CLINICAL PRESENTATION AND CARE

ALS AETIOLOGY, PRESENTATION AND SURVIVAL

Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease (MND) or Lou Gehrig's disease, is a group of rapidly progressive fatal neurological diseases involving the brain and spinal cord. The disease affects over 400,000 of the world’s population and leads to over 100,000 deaths every year. Clinical presentation is phenotypically heterogeneous and depends on the type of onset. Limb onset is the most common, its first symptoms include compromised gait and manual dexterity. Bulbar-onset ALS patients first experience the symptoms in head and neck region, such as slurred speech or difficulty swallowing. There are also rare truncal-abdominal (axial) and respiratory onsets. At least 90% of ALS cases are considered sporadic, which means the disease seems to occur at random with no clearly associated risk factors and no family history of the disease (Qureshi, 2006). The pathophysiology mechanisms behind ALS are not clear and may include oxidative stress, protein misfolding and aggregation, skeletal muscle dysfunction, glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, and apoptosis (Patel and Hamadeh, 2009). The median survival from onset of the disease is estimated to range from 20 to 48 months, however 10–20% of ALS patients survive longer than 10 years (Chiò, 2009).

It is estimated that the number of ALS cases in the world will increase from 222,801 in 2015 to 376,674 in 2040, representing an increase of 69% (Arthur *et al.*, 2016). The demand for supportive treatment and care will increase proportionally. Whilst ALS impacts its sufferers profoundly in many ways, it is essential that novel treatments address the aspects of the disease most crucial for the patients’ quality of life, functional independence and survival. A brief overview of some ALS symptoms and their presentation follows, in order to provide a rationale for the suggested music therapy treatment protocol.

BULBAR AND RESPIRATORY INVOLVEMENT IN ALS

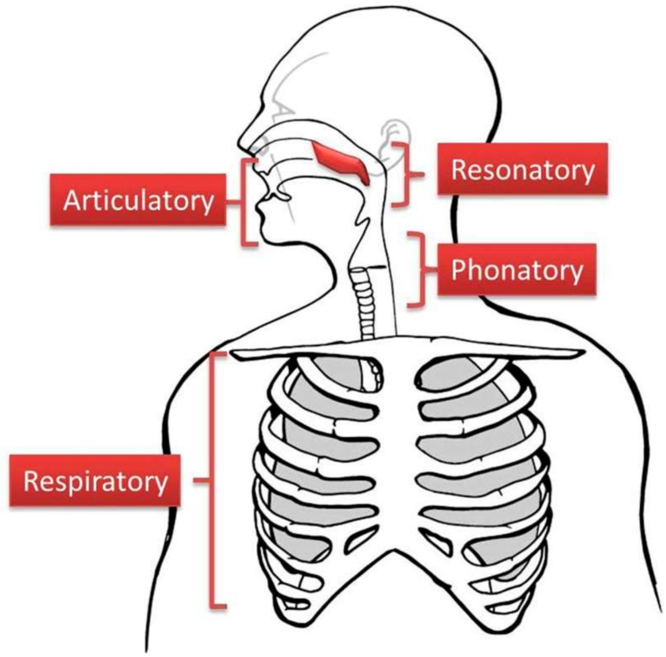
People with ALS have multiple and complex needs. Among physical symptoms of the disease are respiratory dysfunction, dystussia (disordered cough), dysphagia (difficulty swallowing) and dysarthria (motor speech disorder).

Respiratory dysfunction, manifested as dyspnea on exertion and orthopnea (Green *et al.*, 2013) is common in ALS. Nocturnal hypoventilation disrupts normal sleep and leads to excessive daytime fatigue, morning headaches, insomnia and impaired cognition. Expiratory muscle weakness leads to ineffective clearance of airway secretions and, subsequently to higher risk for aspiration, bronchitis, and pneumonia. (Schoser *et al.*, 2017). Weakening of the respiratory function and adherence to noninvasive ventilation (NIV) are the leading causes of anxiety of persons with ALS (Kaub-Wittemer *et al.*, 2003; Miller *et al.*, 2009), and respiratory failure has been cited as the leading cause of death (Corcia *et al.*, 2008; Wolf *et al.*, 2017).

Most persons with ALS, regardless of the onset type, will experience bulbar symptoms (del Aguila *et al.*, 2003). Bulbar dysfunction is recognized to have a major negative impact on quality of life and longevity in ALS (Smith *et al.*, 2017).

93% of persons with ALS experience speech impairments at some point during the disease progression (Plowman, 2015). Loss of natural communication is regarded by the patients as one of the worst aspects of the disease (Hecht, 2002). Human speech requires highly coordinated work of all four speech subsystems: respiratory, phonatory, resonatory and articulatory (Figure 3).

Figure 3. Four speech subsystems



Source: (Green *et al.*, 2013)

Weakening of respiratory musculature results, among other changes, in increased amount and frequency of pauses during speech (Green, Beukelman and Ball, 2004).

Changing pattern of vocal fold vibration and viscoelastic properties of vocal fold tissue lead to disordered phonation: abnormally high or abnormally low vocal pitch, limited pitch range, interrupted or uneven tone production due to instability of vocal fold vibration, and high noise-to-harmonic ratios (Green *et al.*, 2013).

In the resonatory subsystem, velopharyngeal muscle weakness leads to continual opening of the velopharyngeal port during speech, which results in abnormal air emission through the nose and, consequently, increased nasal resonance (hypernasality), which, in severe cases, makes speech unintelligible. Hypernasality affects most persons with ALS (Carrow *et al.*, 1974).

Articulation requires well-coordinated work of tongue, lips and jaw. With ALS progression, articulatory movements become smaller in extent, slower in speed and longer in duration (Mefferd, Green and Pattee, 2012). Speaking rate has been observed to gradually slow at early stages of ALS even as speech intelligibility remains relatively high (Beukelman, Fager and Nordness, 2011; Nishio and Niimi, 2000).

Dysphagia occurs in up to 85% of ALS patients throughout the disease course (Pattee *et al.*, 2019). Patients with dysphagia reported social isolation, fear and decreased mental health (Paris *et al.*, 2013). Dysphagia and malnutrition contribute to 25.9% of ALS mortality and increase the risk of death by 7.7 times (Chiò, 2009; Desport *et al.*, 1999; Yang, 2011). Aspiration pneumonia and dehydration have also been cited among the leading factors contributing to mortality in ALS (Corcia *et al.*, 2008; Czaplinski, Yen and Appel, 2006a).

Emotional lability (pseudobulbar affect, PBA) is frequently correlated with bulbar involvement in ALS. PBA manifests in rapid, often exaggerated changes in mood, such as uncontrollable laughing or crying or heightened irritability. The symptom may be extremely confusing and disruptive, especially when communicating with those who are not aware of the nature of the problem (Hanson, Yorkston, Britton, 2011).

COGNITIVE, BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS IN ALS

Whilst in the past ALS was considered distinctly a disorder of the motor system, current evidence suggests that some cognitive impairment (ALSci) or behavioural impairment (ALSbi) occurs in up to 50% of cases, and co-morbid frontotemporal dementia (ALS-FTD) occurs in approximately 14% of patients with a new diagnosis of ALS (Phukan *et al.*, 2012). There is currently understanding that “pure” ALS and “pure” frontotemporal dementia (FTD) present, as neurodegenerative conditions, along a clinical, pathological and genetic continuum. This idea is supported by identification of similar biomarkers and gene causative in both diseases (Hardiman, 2012; Illán-Gala *et al.*, 2018; Ji *et al.*, 2017; Lillo *et al.*, 2010).

ALS patients with frontotemporal syndrome are more severely impaired in executive function, attention, language and memory than patients with pure form ALS and also have shorter survival times than those without cognitive or behavioural impairment (Oh *et al.*, 2014). Cognitive impairment has potential to influence the treatment and equipment needs of persons with ALS and to impede their safety and medical decision making; emotional perception deficits may lead to impaired relationship with caregivers (Achi and Rudnicki, 2012). Formally assessing cognitive-behavioural status of patients may be necessary when providing medical care recommendations or recruiting for research, which is routinely done using recently developed Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams *et al.*, 2014).

Depression is prevalent in ALS. It is associated with disease severity at initial assessment and has detrimental effects on survival and quality of life (Thakore and Pioro, 2016). It is reported that high levels of anxiety are often present in persons with ALS during the diagnostic phase and the earlier period after the diagnosis (Vignola *et al.*, 2008). Depression and anxiety are undertreated in ALS, and psychological and pharmacological for their prevention and treatment are only minimally addressed in literature (Kurt *et al.*, 2007).

BRIEF SUMMARY OF ALS SYMPTOMS

Though initial symptoms and rate of ALS progression vary greatly from patient to patient, the disease onset is typically gradual. Progressive muscle weakness due to degeneration of motor neurons results in compromised gate and manual dexterity, stiff muscles, cramps, fatigue, and, eventually, immobilization. Bulbar involvement leads to slurred speech, difficulty breathing and eating, and emotional lability. Respiratory and bulbar dysfunction has a major impact on mental health, quality of life and longevity in ALS. ALS-specific speech impairments and the loss of communication are regarded by the patients as one of the worst aspects of the disease. Dysphagia leads to malnutrition and social isolation, whilst aspiration pneumonia and dehydration are considered major factors contributing to mortality in ALS. Pseudobulbar affect causes disruption in everyday life situations. Cognitive or behavioural impairment occurs in up to 50% of ALS cases. The recently developed and now routinely used Edinburgh Cognitive and Behavioural ALS Screen (ECAS) allows to assess cognitive-behavioural status of the patients when providing medical care recommendations or recruiting for research. Depression and anxiety are prevalent in ALS, but these conditions are currently undertreated.

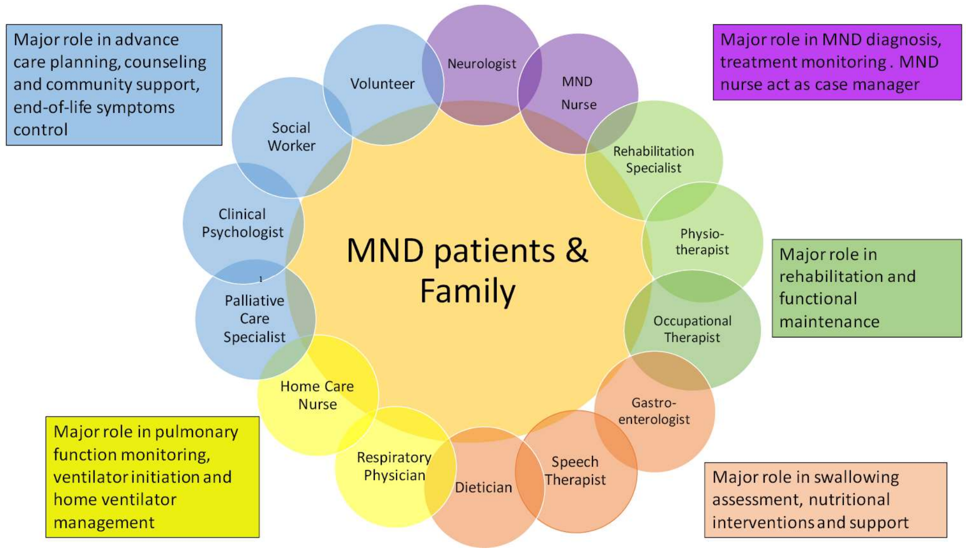
THE ROLE OF CAREGIVERS IN ALS CARE

Caregivers' physical and emotional health and quality of life are significantly impacted when ALS occurs in the family (Qutub *et al.*, 2014; Williams *et al.*, 2008). Family caregivers play a key role in ALS care, providing care for 47 hours per week on average (Galvin *et al.*, 2016) and actively participating in clinical decision making (Aoun *et al.*, 2013). Since nearly any treatment or rehabilitative activity intended for persons with ALS requires the caregivers' participation and directly affects their quality of life, it is important to include the caregiver's perspective when designing and researching ALS supportive care.

MULTIDISCIPLINARY ALS CARE

Considering the complex needs of persons with ALS, coordinated care using a clinic-based, specialist ALS multidisciplinary team approach is suggested by the National Institute for Health and Care Excellence (UK) guideline (NICE, 2016). The Academy of Neurology recommends that patients are seen by a comprehensive team of health care professionals who each focus on specific health domains including walking, breathing, speaking, eating, activities of daily living, and psychosocial needs during one clinical visit (Plowman *et al.*, 2016b). Such a team often includes a physician – neuromuscular specialist, a physical therapist, an occupational therapist, a speech language pathologist, a respiratory therapist, a nurse coordinator, and a social worker. Additional specialists, such as nutritionists, pulmonologists, gastroenterologists, assistive technology experts, psychologists, palliative care providers, chaplain or priests, may also be present (Majmudar, Wu and Paganoni, 2014; Andersen *et al.*, 2012; Rooney *et al.*, 2015). Multidisciplinary ALS care has been shown to increase survival of persons with ALS and to improve their quality of life (Van den Berg, 2005) (Figure 4).

Figure 4. ALS multidisciplinary care model



Source: (Cheng *et al.*, 2018)

TREATMENTS AVAILABLE FOR ALS

Non-invasive ventilation (NIV) for respiratory support, gastrostomy feeding for dysphagia, and riluzole and edaravone medications at the last clinical stage of ALS (Fang *et al.*, 2018; Khairoalsindi and Abuzinadah, 2018) are the only recognized and approved methods known to prolong survival for persons with ALS (Knibb *et al.*, 2016).

The use of complementary and alternative treatments - non-mainstream treatment used in addition to (complementary) or instead of (alternative) standard evidence-based care - is highly prevalent among persons with ALS (Adams, Lee and Peng, 2018; Bedlack *et al.*, 2015). These treatments include diets, nutritional supplements, cannabis, acupuncture, chelation, energy healing, massage and yoga (MacNeill, 2015; MacNeill, 2016). In the recent critical review of complementary and alternative medicine use in ALS (Adams, Lee and Peng, 2018) acupuncture, vitamins, Chinese medicine, massage therapy, and dietary/herbal supplements are listed among the most popular alternative treatments among persons with ALS. Risks and benefits of complementary and alternative treatments for ALS are not well understood. These treatments can be expensive and potentially harmful (Bedlack and Hardiman, 2009). ALSUntangled (http://www.alsuntangled.com) is the authoritative online platform that offers reviews of off-label ALS treatments by researchers and scientists to assist ALS practitioners and persons with ALS in treatment choices. No review of music therapy or of exercises for bulbar and /or respiratory dysfunction in ALS was available among the ALSUntangled reviews, as of May 2020.

THE ROLE OF EXERCISE IN ALS CARE

Until recently, persons with ALS have been discouraged from exercising based on the assumption that exercise can lead to muscle fatigue and increase patients' disability (Sinaki and Mulder, 1986). This assumption however is not supported by scientific evidence (Bello-Haas, 2007; Drory, 2001; Lisle and Tennison, 2015; Pinto, 2012; Pinto *et al.*, 1999). To the contrary, there is evidence that physical inactivity secondary to ALS may lead to cardiovascular deconditioning, disuse weakness and consequential muscle atrophy. Reviews by Chen (Chen, 2008) and Almeida, Silverstre et al. (Almeida *et al.*, 2012) support evidence for moderate physical exercise in ALS, whilst highlighting the importance of supervised, individualized training programs. A Cochrane review (Dal Bello-Haas and Florence, 2013) concluded there was no solid evidence to deem exercise in ALS beneficial or harmful and emphasized the need for further research. Recent data suggests that such exercise may be beneficial for cellular and morphological adaptations in motor neuron function and thus may help to maintain motor function (Plowman *et al.*, 2016b). New studies (Kitano *et al.*, 2018; Lunetta *et al.*, 2016) suggest that strictly monitored exercise programs reduce motor deterioration and improve functional independence of persons with ALS. Most clinical studies to date suggest that exercise training including stretching, resistance, endurance or concurrent training, has beneficial impact on the quality of life of ALS patients, because it increases their functionality and, in some cases, their muscle strength and/or their cardiorespiratory function. However, small sample sizes, non-representative control populations, heterogeneous disease stage of patients, and the presence of confounders are common in such studies (Tsitkanou *et al.*, 2019). Further, rigorous research is necessary to understand the impact of physical exercise on persons with ALS.

EXERCISE TO SUPPORT BULBAR AND RESPIRATORY FUNCTION IN ALS

A literature review entitled "Is There a Role for Exercise in the Management of Bulbar Dysfunction in Amyotrophic Lateral Sclerosis?" examined a total of 18 exercise-based intervention studies published in peer-reviewed journals between 1960 and 2014 (Plowman, 2015). Of these, no experimental studies examined the impact of targeted exercise on speech or swallowing function. Mild to moderate intensity limb or respiratory exercise, applied early in the disease, was noted to have a beneficial impact on motor function and survival. It was concluded that the research to support or refute the role of exercise in the management of bulbar dysfunction in ALS represents a critical area of future investigation.

The evidence has been emerging in recent years which suggests that respiratory training may have a positive effect on respiratory and swallowing functions in ALS and that such exercise may be beneficial for cellular and morphological adaptations in motor neuron function and thus may help to maintain motor function (Pinto, 2012; Plowman *et al.*, 2016b; Tabor *et al.*, 2016). Although there is lack of evidence supporting the use of strengthening exercises for improving speech in persons with ALS, there is no evidence of such exercises being harmful (Hanson, Yorkston and Britton, 2011).

The next chapter of the thesis outlines the unique benefits music therapy may offer to persons with ALS and provides a rationale for developing a music therapy treatment protocol to support bulbar and respiratory functioning in early and mid-stage ALS.

CHAPTER 2

MUSIC THERAPY POTENTIAL IN MULTIDISCIPLINARY ALS CARE

MUSIC THERAPY DEFINITION

Music therapy is the evidence-based professional clinical application of music and its elements to improve psychological, emotional, cognitive, physical and social health and wellbeing of human individuals and communities (Davis *et al.*, 2008; Pedersen and Wigram 2002; Wheeler, 2015; Hanser, 2018). Professionally trained music therapists are well equipped to provide symptomatic care for people with neurodegenerative diseases (Magee, 1998). They can adapt interventions to the increasing and changing disability of each patient as the disease progresses, whilst maintaining a trusting therapeutic relationship. The growth of scientific knowledge about music perception and production and the effects of these on non-musical brain and behavior functions has led to the development of clinical techniques to treat cognitive, sensory, and motor dysfunctions resulting from neurological injury or disease (Thaut and Hoemberg, 2016).

MUSIC THERAPY FOR ALS: EXISTING EVIDENCE

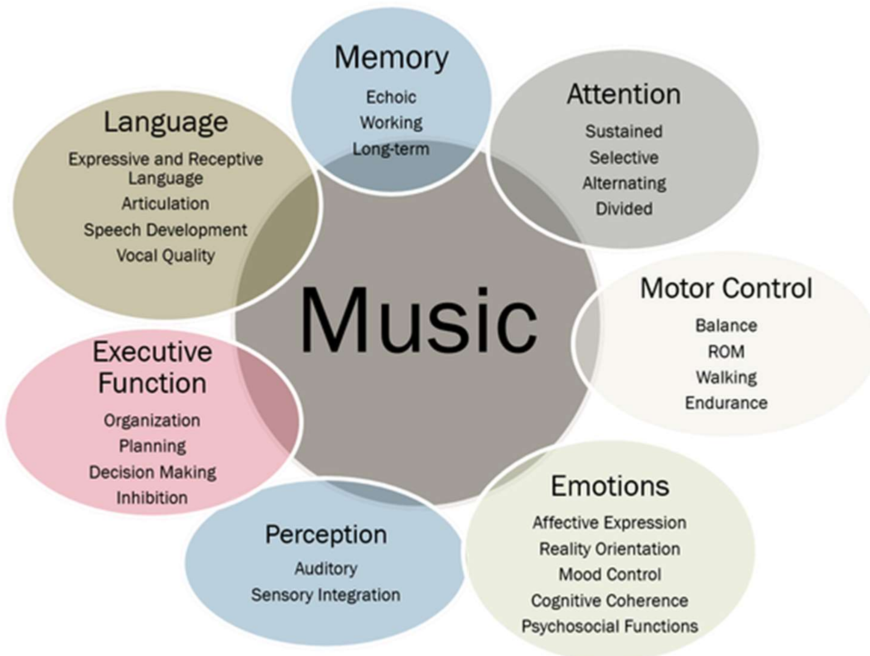
Research in clinical music therapy applications for ALS is limited (Horne-Thompson and Grocke, 2008) and presents significant challenges for a researcher due to the heterogeneity of ALS clinical presentation and progression. There is also a poor scientific understanding of the disease mechanisms (Bonafede and Mariotti, 2017) and the ethical issues of research involving terminally ill people (Byock, 1999). It has been suggested that MT could contribute to interdisciplinary ALS care (Petering and McLean, 2001). There is anecdotal evidence that MT increases mind-body connection (Lings, 2014), reduces distressing physical symptoms such as dyspnoea and pain, and associated feelings of loneliness, anxiety and sadness for patients with advanced ALS (Forrest, 2002). It is further suggested that MT is "pleasant and restorative" for persons with ALS who have a tracheostomy and for their families (Kondo, 2017a). It provides families affected by ALS with opportunities for shared meaningful activities (Schmid, 2016). The first randomized controlled trial of active music therapy with ALS found that active music therapy increased communication, improved quality of life and decreased the physical symptoms of the disease for participants during hospital stay (Raglio *et al.*, 2016). Music-assisted relaxation may be a useful strategy to reduce discomfort of noninvasive ventilation experience for persons with ALS (Davies *et al.*, 2016). This evidence demonstrates that, albeit currently underused, music therapy could be one of the modalities of supportive rehabilitation in ALS, potentially providing multiple benefits for persons with ALS and their families.

TARGETING NEUROPLASTICITY IN ALS

The literature review conducted for this research did not locate any studies addressing the use of music therapy techniques for the neurorehabilitation of persons with ALS (e.g. supporting motor, cognitive, respiratory, swallowing, speech functions). Empirical evidence and research with other clinical populations suggest that such interventions may be beneficial (Gregory, 2002; Särkämö *et al.*, 2008; Tamplin, 2008; Bukowska *et al.*, 2016; Kim, 2010). Patient's motivation to work towards therapeutic goals may increase with the use of music (Thaut and Hoemberg, 2016), and since loss of motivation is a major factor in persons with ALS, music-based interventions may be of help (Lillo, Mioshi and Hodges, 2012).

Music is a form of multisensory stimulation that has a positive influence on neuroplasticity because it requires integration of audiovisual information along with appreciation of abstract rules necessary for development of music production skills (Shaffer, 2016). Advances in neuroimaging and growing scientific evidence have made it possible to use music more effectively to treat cognitive, sensory, and motor dysfunctions that come from human neurologic diseases (Sihvonen *et al.*, 2017). Music engages a vast network of regions located in both hemispheres of the brain, that share processing components with other functions, such as those involved in language, movement, reasoning and experiencing emotions (Thaut, McIntosh and Hoemberg, 2015; Koelsch, 2014; Peretz and Zatorre, 2005; Zatorre, Joyce and Virginia, 2007) (Figure 6).

Figure 6. Schematic representation of shared processing for music and non-musical functions



Source: © The Academy of Neurologic Music Therapy, 2018, https://nmtacademy.co/

Neuroplasticity, the capacity of brain cells to modify, change and adapt its structure and functioning in response to experience, plays an increasingly important role in clinical neuroscience (White, 2011). In the past, it was believed that neuroplasticity only took place at time-limited epochs during early development. Recent findings, however, suggest that plasticity mechanisms can operate throughout lifespan. Moreover, (Voss *et al.*, 2017) argue that degraded sensory inputs can trigger plasticity within primary sensory cortex, possibly as a result of an adaptive mechanism in cases of neurodegenerative and neuropsychiatric conditions where plasticity mechanisms are dysregulated, like, for example, in dementia.

Benefits of music therapy for persons with dementia are currently recognized and are being actively researched (Langhammer *et al.*, 2019; Livingston *et al.*, 2017; Raglio *et al.*, 2008; Raglio *et al.*, 2012; van der Steen *et al.*, 2018; Baird and Samson, 2015). As discussed in Chapter 1, ALS and FTD present a disease spectrum (Ng, Rademakers and Miller, 2015). It is also known that proprioceptive sensory neurons are affected by ALS-causing mutation (Vaughan *et al.*, 2015). We may speculate that plasticity could be triggered in persons with ALS, making music therapy applications beneficial for the ALS population, via similar mechanisms to those in dementia. This is a novel idea, however, and it calls for diligent attention of clinicians and researchers.

MUSIC THERAPY FOR ALS: DEVELOPING CLINICAL APPROACH

Active (participatory) music therapy treatment with therapy goals from the physical domain (respiration, speech, swallowing) is a novel concept in ALS care, as are rehabilitative exercises for ALS, in general. The principal researcher was invited to develop an ALS-specific music therapy program for the patients of ALS Centre Moscow in 2013. ALS Centre Moscow is a collaboration between three Moscow hospitals providing home-based multidisciplinary care for persons with ALS and their families since 2012. No organization specialized in helping persons with ALS existed in Russia before that. An experimental music therapy protocol consisted of interchangeable blocks of exercises and addressed the varying and constantly changing physical, social, communicative, cognitive and spiritual needs of the patients and their families. Parts of this original protocol aimed at bulbar and respiratory function support became the prototype for the music therapy protocol used in this study (see Chapter 5. Music therapy treatment protocol).

Drafting of the innovative music therapy protocol was based on the in-depth study of the existing literature (see previous section “Music Therapy for ALS: Existing evidence”), the consultations with the medical team of the ALS Centre Moscow, the clinical experience of the principal researcher with other adult populations and the informal learning about personal experiences and perceptions of the disease from ALS patients.

Disbelief, grief, anger, confusion, distorted sense of self, and social disconnectedness are common consequences of ALS diagnosis. Evidence from psychosomatic and health psychology research fields demonstrate a close bilateral interrelation between mind and body, with emotions affecting cardiovascular and immune system responses and physiological events impacting an individual’s psychological state (Särkämö *et al.*, 2008). Based on this evidence and previous clinical experience with various adult populations, the principal researcher hypothesized that music therapy, in the form of song singing, song writing, lyrics substitution, listening to and discussing music, meditating and reminiscing to music, and interactive improvisation, may decrease stress, strengthen the mind-body connection and help persons with ALS to regain coherent self-image. Similarly, it was hypothesized that music assisted relaxation could be used to alleviate anxiety, to ease manifestations of pseudobulbar affect and to provide relief from distressing thoughts.

Overwhelming emotions and co-morbid cognitive and behavioural impairments, especially apathy, may prevent persons with ALS from making timely, informed decisions regarding their treatment, such as use of the non-invasive ventilation, gastrostomy or tracheostomy. Whereas patients at ALS Centre Moscow were generally reluctant to accept psychotherapy services, a music therapist was often able to establish a working relationship with patients and, through live music making, non-verbal interaction and meaningful conversation, to increase motivation, enhance mood, decrease apathy and create a safe emotional space – a "container" for the overwhelming feelings and reactions, thus freeing up mental energy and focus necessary for treatment planning and adherence.

Similarly, music therapy sessions provided a psychologically safe environment for persons with ALS and their caregivers to explore the changing dynamics of their relationship, and the peak experience of cooperative music making provided opportunities for positive socialization and communication. Interactive music improvisation utilizing simple instruments or adaptive music technology became a way of non-verbal communication, self-expression and playful, though meaningful, relating to others. Other techniques, such as free associative singing and musical life review, can facilitate deeper psychodynamic work with ALS patients and their families.

Active music making, such as playing simple musical instruments to the beat, and moving to music also served as a form of moderate physical exercise for persons with ALS who were not able to engage in a physical therapy program. This first clinical evidence also suggested that structured, individualized breathing and vocal exercises had the potential to sustain bulbar and respiratory functions in early and mid-stage ALS.

The principal researcher and another music therapist worked with patients at the ALS Centre Moscow intermittently from 2014 to 2016. In 2017, following the increased demand for the service, two specialists formally trained in music therapy applications for neurological clinical practice and supervised by the principal researcher were added to ALS Center Moscow multidisciplinary team. These specialists were regularly referred by the medical team to patients at various stages of the disease progression and worked with a wide spectrum of psychological and physical goals. Positive feedback received from the persons with ALS who participated in the program in the years 2014 – 2017 and their families supports our tenet that introducing music therapy as a supportive modality of multidisciplinary ALS care has the potential to increase quality of life and wellbeing, as the following quotes reflect:

- "I feel lighter and happier after we do music" – Person with ALS
- "I can relax, I cry less and feel less nervous after a (music therapy) session" – Person with ALS "Unless I do my (music therapy) exercises, it is difficult for me to start speaking in the morning. I notice that after the exercises speech is easier for me, and my family understand me better" – Person with ALS
- "My swallowing improved, I can again take water with my lips and I have almost stopped gagging when I eat – something I constantly experienced in the past" – Person with ALS
- "Music therapy was very important for mom. She always smiled when she spoke about the sessions" – Caregiver

NEED FOR CONTINUED RESEARCH

In the absence of a curative treatment, a wider range of rehabilitation options must be considered for persons with ALS, enabling them to reach their fullest potential and best quality of life, delaying the disease progression and prolonging the lifespan (Paganoni *et al.*, 2015). Music therapy provides a unique combination of psychological, physical, social and communicative benefits for patients with neurodegenerative conditions. Although the physical and psycho-emotional needs of people with ALS that music therapy can potentially attend to are many and varied, existing literature (see Chapter 1. Amyotrophic lateral sclerosis: clinical presentation and care) and clinical evidence suggest that researching the role of an individualized, carefully monitored music therapy program to support the respiratory and bulbar functions of people with ALS currently constitute the highest priority, as these functions directly affect survival.

It is not possible to conduct music therapy treatment for bulbar and respiratory rehabilitation during outpatient clinics, because regular, frequent meetings are required in order for persons with ALS to learn the new respiratory and voice skills. The group setting has been reported to be effective for respiratory muscle training of persons with spinal cord injury (Tamplin, 2011). However, the heterogeneity of ALS presentation, limited mobility in an urban environment due to lower limb involvement and psychological vulnerability of persons with ALS associated with rapid disease progression are important factors to consider when planning the intervention for this clinical population. One-to-one in-home therapy may be a safer, less burdensome and more effective option.

Community services are a relatively new way to deliver rehabilitative music therapy treatment. Previous research has explored the feasibility of home-based music therapy interventions (Kim, 2010; Yang, 2016; Street *et al.*, 2018; Holden *et al.*, 2019; Schmid and Ostermann, 2010). There is limited existing research for home-based MT for ALS (Schmid, 2016). Furthermore, music therapy interventions conducted through ALS Moscow Centre since 2013 have not been examined through formal research. This study contributes to the important body of research in home-based neurorehabilitative music therapy, the latter being an efficient, person-centered and community-oriented model of care for various clinical populations. Applied music therapy research in a multidisciplinary clinical context allows the collection of quantitative and qualitative data essential to assessing safety, tolerability and feasibility of the suggested protocol, while the objectivist case study design (as defined in Chapter 3. Study aims and design) allows scrupulous analysis of individual responses to treatment in this heterogeneous population (Wheeler and Murphy, 2016). This feasibility study responds to the need for continued research in order to understand the role of exercise in bulbar and respiratory rehabilitation in ALS (Hanson, Yorkston and Britton, 2011; Plowman, 2015).

CHAPTER 3

STUDY AIMS AND DESIGN

STUDY AIMS

The main purpose of this research was to determine the feasibility of a home-based music therapy protocol as an intervention to support respiratory and bulbar functions in early and mid-stage ALS. Feasibility studies enable the researcher to determine whether a novel intervention is appropriate for further investigation, if research methods or protocols need modification and how these changes may occur (Bowen *et al.*, 2009). Since this was the first study to examine the role of music therapy in supporting bulbar and respiratory functions of persons with ALS, it focused on the safety and tolerability of the treatment protocol. Additionally, inquiry was made into the most sensitive and feasible tools to assess the treatment effect.

ALS is a complex health condition and its development is poorly predictable in each individual case. It affects most dimensions of everyday life, places great burden on the patient and their family and friends, who acts as caregivers, and presents unexpected challenges constantly. High dropout rates and missing data are common for studies of ALS (Atassi *et al.*, 2013). Assessing feasibility of a home-based music therapy protocol with multiple quantitative and qualitative measurement outcomes is essential before planning a definitive study on effects of music therapy treatment.

STUDY DESIGN: UTILIZING MIXED PARADIGMS

The objectivist case study design, in the form of an ABA mixed methods case series with repeated measures, was employed in this research. The objectivist case study design is one of the designs particularly suitable when developing an innovative research protocol. The term was coined by Ridder and Fachner in (Wheeler and Murphy, 2016) and refers to a research method that bridges objectivity and subjectivity in its inquiry. An objectivist case study is defined as an intensive examination of an individual or a group with the use of a quasi-experimental research design to determine the effect of an independent variable on one or more dependent variables.

The objectivist case study allows the in-depth study of a phenomenon in the real-world practice, where the clinical situation is not manipulated. Similarly to case study research, multiple sources of data are used to investigate the phenomenon from different, perspectives. Specific for the objectivist case study is the inclusion of objective data such as physiological measures or biomarkers, as well as descriptive and observational data transformed to numerical entities. The objective data is thus triangulated or correlated with qualitative data. The risk of bias is reduced through using experimental approaches with comparison to baseline or pre-measurements where the participant serves as his or her own control.

Although beneficial functional outcomes for music therapy with persons with ALS had been observed in the principal researcher's clinical practice, extreme care had to be taken when creating a standardized, uniform treatment protocol that potentially could be applied widely with this clinical population. Disease progression and symptoms are highly variable in each individual care of ALS, and standard rates of decline are not defined. Physical responses and emotional reactions to treatment may be difficult to predict. Complicating the research in this field even further is the absence of standardized outcome measures and tools to assess bulbar function in ALS.

Small number, mixed-method case series design with repeated measures offered the opportunity to pay careful attention to the individual processes of the participants, whilst providing an objective outlook on feasibility of the protocol implementation with this clinical population. Qualitative data in the form of physiological and acoustic measures and numerical observational and self-reported data collected and analyzed, along with the study participants' interviews, music therapist's treatment notes and research field notes. This allowed for a rigorous and systematic exploration of music therapy experience and outcomes.

Including objective measures may help to reduce bias in the situation where most of the data is collected in the field and it is, consequently, not possible to blind participants and research assistants. However, the objective, numerical measures still have the risk of showing changes due to the Hawthorne Effect in a situation when the research participant is aware of being observed and acts accordingly.

CONTROL AND EXPERIMENTAL CONDITIONS

The number of participants recruited for this study (n=8) was defined by availability and limitations of the study host resources (including research assistants, research nurses, volunteers and the funds allocated for transportation expenses necessary to take the participants to and from the laboratory) and of the principal researcher, who conducted the treatment and data analysis. These limitations are discussed in more detail in section Study limitations of Chapter 11. Discussion.

All participants started the trial simultaneously and served as their own controls across the three phases of the study:

- Run-in phase (weeks 1 through 6),
- Treatment (therapy) phase (weeks 7 through 12),
- Follow-up (wash-out) phase (weeks 13 through 16).

As discussed previously, patterns of ALS presentation and progression vary significantly. Even the relatively narrow recruitment criteria for this study allow for vast differences between the participants' responses to music therapy treatment and natural disease progression. Reliable predictors of decline in ALS are yet to be found (Ong, Tan and Holbrook, 2017). However, it is largely agreed among clinicians that, as a rule, every patient follows their own pattern of disease progression, and the speed of the past progressive decline is, to some extent, predictive of their future progressive decline. It makes sense, therefore, to regard the treatment (therapy) phase as the experimental condition, whilst viewing the run-in phase and follow-up phase as control conditions for this study, rather than to recruit a larger group in order to randomize the participants into treatment and control arms.

The duration of the follow-up phase was planned to be shorter than the run-in and the treatment. In the summer most people who are unemployed move temporarily to their country houses ("dachas") and extending the follow-up period to six weeks could prevent full follow-up data collection. This cultural context had to be taken into consideration when planning a study in the spring going into the summer. The shorter follow-up period was factored in when calculating the biomedical data trends (see Chapter 8. Biomedical data analysis results) and presents a limitation to this study, as discussed in the Unequal phase durations.

INTERPRETATION OF BIOMEDICAL DATA

Quantitative and qualitative data were collected at multiple time points during the study, as described in Chapter 4. Outcome measures and data collection. It has to be emphasized that, since ALS is a progressive incurable neurodegenerative condition, gradual decline of respiratory and bulbar functions is expected, with no improvement possibility. When interpreting the long-term data outcomes, it is understood that the direction and the rate of change observed during the run-in period is expected to stay similar if music therapy treatment has no effect. If music therapy has been beneficial for a participant, the trend would be reversed. If the trend is unchanged or amplified, the reason could be that music therapy had a negative effect or that participants' condition declined rapidly. The trends are explained and analyzed in detail in Chapter 8. Biomedical data analysis results.

STUDY HOST AND LOCAL RESEARCH TEAM

Study host, ALS Centre Moscow (Russia), is a non-governmental collaboration between three Moscow hospitals providing home-based multidisciplinary care for persons with ALS and their families since 2012. Approximately 110 ALS patients out of roughly 950 persons with ALS residing in the Moscow region are followed by the team at any given time. Music therapy was first introduced at the Centre in 2013 by the principal researcher. Two music therapists currently work at the Centre.

The medical director of the ALS Moscow Centre gave full approval for this study (see Appendix A). Three research nurses and two research assistants helped to collect data. The principal researcher implemented the six-week home-based music therapy treatment for this study and coordinated the research team work and the resulting data analysis.

ETHICAL APPROVAL AND COLLABORATIONS

Clinical research with human subjects required full compliance to research ethics in two countries for this study. Ethics clearance was obtained from Moscow Municipal Independent Ethics Committee (Moscow, Russia) and from the Faculty Research Degrees Sub Committee at Anglia Ruskin University (Cambridge, UK) (see Appendices B and C). This research protocol was developed to comply with international ethics guidelines on research with human participants. The study was conducted in accordance with the Declaration of Helsinki and in accordance with General Data Protection Regulation.

Indispensable for the research process was direct help with pseudonymized data analysis from a statistician from the School of Medicine, Anglia Ruskin University (Chelmsford, UK), speech-language clinicians at Speech and Feeding Disorders Lab, Massachusetts General Hospital (Boston, MA, USA), and Bulbar Function Lab, Sunnybrook Research Institute (Toronto, Canada), and an information technology (IT) specialist from Canopy Education Inc (Cambridge, MA, USA).

As recognized in Acknowledgements, this study would not be possible without generous pro bono advice from many clinicians and leading experts in ALS care across different professional fields. This study is registered with the U.S. National Library of Medicine ClinicalTrials.gov database, NCT03604822.

RECRUITMENT

Consecutive sampling strategy was employed in order to avoid bias in regard to the disease onset: all newly diagnosed patients living in Moscow city limits and meeting the inclusion and exclusion criteria were invited to participate, until the desired sample size (n=8) was achieved or the cut-off date for recruitment was reached.

INCLUSION CRITERIA

- Diagnosis of probable or definite ALS by the revised El Escorial criteria (Brooks *et al.*, 2000) confirmed by the neurologist at ALS Moscow Centre prior to screening for enrollment.
- Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) (Rooney, 2017) bulbar subscore ≥ 9, but ≤ 11, where bulbar subscore=the sum of ALSFRS-R questions 1-3 (maximum score of 12)
- Forced vital capacity (FVC) greater than 60%
- Unimpaired cognition as evidenced by Edinburgh Cognitive and Behavioural ALS Screen (ECAS, Russian version) cut-off scores adjusted for age and education (Chernenkaya *et al.*, 2018; Abrahams *et al.*, 2014)
- Able to consent to treatment
- Native speakers of Russian

The amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) is a common primary outcome measure to assess disease severity in ALS in clinical practice. However, as discussed in Chapter 4. Outcome measures and data collection, earlier studies have found that ALSFRS-R may represent a less insensitive tool for the identification and tracking of bulbar function over time (Green *et al.*, 2013). (Bakker *et al.*, 2017) suggest that ALSFRS-R constitutes a profile of four clinically relevant domain scores (bulbar, fine motor, gross motor, and respiratory function) rather than a total score that expresses disease severity. In the current study, only the bulbar subscore of ALSFRS-R, i.e. the sum of points from questions 1–3 assessing speech, salivation and swallowing, was used as an inclusion criterium for the study, rather than the total score. This allowed to include all the patients with preserved or mostly unimpaired bulbar functioning, regardless of their disease onset type, their motor functioning and their respiratory functioning.

EXCLUSION CRITERIA

- Tracheostomy or mechanical ventilation
- Diaphragmatic pacer
- Significant concurrent respiratory disease
- Allergies to barium
- Receiving any other experimental treatment for dysarthria, dysphagia, dystussia and dyspnoea for the duration of the study
- Receiving any other music therapy treatment for the duration of the study

RECRUITING CAREGIVERS TO PARTICIPATE IN THE STUDY

As discussed in Chapter 1. Amyotrophic lateral sclerosis: clinical presentation and care, caregivers play a crucial role in the care of persons with ALS. Therefore, when researching the feasibility of the music therapy treatment protocol, it is helpful to take caregivers' perspective into account. At the same time, it is of no lesser importance to maintain autonomy and dignity of participants – persons with ALS in their reliance on caregiver's support during the study. If designated by the primary participants, and only with their permission, their main caregivers were contacted and invited to participate in structured interviews before and after the therapy phase of the study. Detailed description and analysis of these interviews can be found in Chapter 4. Outcome measures and data collection.

INFORMED CONSENT

Prospective participants were provided with a participant information sheet in their native language (Russian) (see Appendices D, E, F and G for the Russian versions and English translation). Each participant, including participating caregivers, signed voluntary informed consent. Participants were provided with the withdrawal form to sign, if they chose to withdraw from the study at any point.

PROCEDURE

An ALS-specific, individualized MT protocol was delivered to the participants in their homes twice weekly for the duration of six weeks by the principal researcher – a professional, board certified (USA) music therapist. Facilitating musical structures were composed by the researcher to support cueing, timing and intensity of breathing and vocalization exercises. These structures were regularly adjusted by the music therapist to suit the unique capabilities, actual individual demands and progress of each participant. One familiar song, selected by each participant during the first session, was used in the therapeutic singing exercise, closing each session.

Caregivers and family members had an option to be present during the sessions, according to the preference of each participant – person with ALS. Special care was taken when scheduling music therapy treatment to avoid interference with participant's daily activities.

Printed ALS-specific voice health guidelines, compiled by the researcher, were provided to all participants prior to starting treatment with the aim of promoting healthy voice use habits in daily life (see Appendix H).

The participants were encouraged, but not required, to independently practice breathing, relaxation and voice skills learned in music therapy sessions on the days when no visit from the music therapist was scheduled, using a recorded guide (CD or mp3 files provided via USB flash drive) and corresponding printed instructions.

Rationale for the innovative music therapy protocol used in this study and its full description can be found in Chapter 5. Music therapy treatment protocol.

EQUIPMENT, TRANSPORTATION AND SETUP

Equipment necessary for the music therapy treatment included an acoustic guitar, a melodica, a smartphone (with a music player and metronome apps), a pocket-size speaker for sound amplification and a binder containing visual aids, treatment protocol, assessment scales and data entry forms. This equipment is lightweight, easily transportable by urban public transportation and requires minimal space and time for setup.

Standard portable equipment, including spirometer, respiratory pressure meter and data entry forms, were used by qualified nurses to collect biomedical data during regular home visits. Participants traveled to the laboratory for videofluoroscopic swallowing study (VFSS) by taxi (paid by the study host), with assistance from trained volunteers. Voice samples were recorded by a research assistant with a headset microphone, a tablet computer and an audio interface in the patient's home. Responses to structured interviews were typed by a research assistant verbatim on a tablet computer.

STUDY CONSORT

The study consort is presented below in Table 1.

Table 1. Study consort

Approximately 110 ALS patients in the Moscow region are followed by the ALS Centre Moscow team. All newly diagnosed patients living in Moscow and meeting the inclusion and exclusion criteria were invited to participate, until the desired sample size (n=8) is achieved. Age: 18+; ALSFRS-R bulbar subscore ≥ 9, but ≤ 11; FVC > 60%; unimpaired cognition (ECAS); can consent; native Russian speakers; no diaphragmatic pacer; no tracheostomy; no significant concurrent respiratory diseases; not receiving other music therapy or other experimental treatment for bulbar and respiratory symptoms. Participants started the trial simultaneously. Each participant received treatment and served as their own control.
↓
Week 1 Data collection: home-based – FVC, MIP, MEP, PEF, CNS-BFS swallowing and bulbar subscores, voice samples; lab – VFSS.
↓
Week 5 Data collection: participant interview, caregiver interview (questionnaire)
↓
Treatment: weeks 6 – 12 Music therapy treatment (2 X per week for 6 weeks) and data collection: home-based – NRS respiration and NRS speech scales, attendance, adherence to independent exercises routine (weeks 7 – 12), treatment notes.

↓

Week 6

Data collection: home-based – FVC, MIP, MEP, PEF, CNS-BFS swallowing and bulbar subscores, voice samples; lab - VFSS

↓

Week 12

Data collection: home-based – FVC, MIP, MEP, PEF, CNS-BFS swallowing and bulbar subscores, voice samples; lab – VFSS.

↓

Week 13

Data collection: participant interview, caregiver interview (questionnaire).

↓

Follow-up: Week 16

Follow-up data collection: home-based – FVC, MIP, MEP, PEF, CNS-BFS swallowing and bulbar subscores, voice samples.

↓

Data analysis

Analysis of feasibility and biometric data, thematic analysis of questionnaire data.

CHAPTER 4

OUTCOME MEASURES AND DATA COLLECTION

Quantitative data were collected at multiple time points throughout the study to assess the main feasibility parameters: recruitment, retention and adherence to treatment, as well as additional feasibility parameters: tolerance and self-motivation. Analysis of numerical data outcomes implies a higher level of objectivity and is important if we are to avoid biased outlook on the research process and results. However, gathering qualitative data in the form of structured interviews and therapy notes was instrumental for deeper understanding of the impact the research and the treatment protocol have on the participants, of the physical and emotional burden and benefits it may present for the participants, and of the challenges and scientific inquiry opportunities it poses to the research team.

Biomedical data measurements were obtained at four time points. Collecting these data allowed the identification of the metrics suitable for objective home-based assessment of bulbar and respiratory functioning in persons living with ALS, to understand the individual reactions of participants to the suggested music therapy treatment and to monitor the common trends across the group, and to assess feasibility of systematic bulbar and respiratory assessment in ALS for future research.

FEASIBILITY OUTCOME MEASURES

Recruitment

All newly diagnosed patients at ALS Moscow Centre living in Moscow city limits and meeting the inclusion and exclusion criteria were invited to participate, until the desired sample size (n=8) was achieved or the cut-off recruitment date occurred. Target recruitment over 80% was considered the marker of a successful feasibility trial, as suggested by a recent overview of 30 publicly funded trials (Walters *et al.*, 2017).

Retention

The total number of participants recruited was compared with the total number of participants who completed the study to calculate retention.

When retention was estimated from 49 previously published ALS trials (Atassi *et al.*, 2013), the attrition rate across 49 studies was 33% ± 19%, of which 15% was due to death. Among surviving participants, the two most common reasons for attrition were adverse events (30%) and consent withdrawal for no specific reason (21%).

Based on these data, retention rate over 70% at the end of follow-up period was considered the marker of a successful feasibility trial for this study. Reasons for attrition were analyzed.

Adherence

Adherence to trial protocol, measured for 601 participants of 5 ALS clinical trials conducted by the NEALS Consortium, was assessed as suboptimal (4.7 deviations/participant/year) by the same authors (Atassi *et al.*, 2013). Omitting parts of the protocol, such as outcomes and safety procedures, and out of window visits were the most common form of nonadherence. Adherence to treatment in real-world settings is estimated around 50% - 55.5% (Shiovitz *et al.*, 2016; Fernandez-Lazaro *et al.*, 2019).

The number of music therapy sessions attended by each participant was recorded as an adherence measure for this study. Mean adherence across all participants who completed the study was calculated. Mean adherence for the group calculated at over 75% music therapy sessions delivered was considered the marker of a successful feasibility trial.

Tolerance

Short-term tolerability of the music therapy treatment protocol was assessed by measuring change in ratings on self-reported Ease of Respiration Numerical Rating Scale (see Appendix I) and change in ratings on self-reported Ease of Speech Numerical Rating Scale (see Appendix J) before and after every music therapy session. Answers to the questions: “How easy is it to breathe for you now?” and “How easy is it to speak for you now?”, were recorded as a numerical outcome on the 10-point numerical rating scale, the difference between the self-assessment numerical value received pre-treatment and the self-assessment numerical value received post-treatment was calculated, and the mean of all differences was taken for every participant. Absence of (zero) change in self-assessed condition or improved (higher scored) self-assessed condition were considered markers of the treatment being well tolerated by the participants. The numerical rating scale (NRS) was decided upon the continuous line visual analog scale (VAS) for this regular evaluation because previous research demonstrated that the NRS was a more repeatable measure than the VAS to assess breathlessness (Wilcock *et al.*, 1999).

Self-motivation

Being a psychological construct, motivation cannot be observed or recorded directly, and is usually measured in terms of observable cognitive, affective, behavioral and physiological responses and using self-reports (Touré-Tillery and Fishbach, 2014). Previous research demonstrates that outcome-focused motivation increases the intention to pursue the activity but decreases how persistently individuals pursue it (Fishbach and Choi, 2012). Consequently, process-focused (internal) motivation in relation to participants’ music therapy experience, rather than outcome-focused (extrinsic) motivation was of primary interest for this research.

Self-reported adherence to a suggested, but not required, independent exercise routine was recorded to assess levels of self-motivation that participants demonstrated with regard to music therapy treatment. Any attempt to practice was recorded, even if the exercise set was not fully completed. No fidelity data were collected. No strategies to increase or to control the adherence were employed. The number of independent exercises sets performed, in proportion to the number of days when no visit from the music therapist was scheduled, recorded during the sessions from four to 12 during the six-week treatment phase, was calculated, measured in percent.

Treatment experience of participants – persons with ALS

Participants' perspective is recognized as an important element in assessing the value of medical care interventions. Patient-reported outcome measures provide insight into the quality of life associated with their health condition and allow for the report on the treatment experience that comes directly from participants. They provide the essential information about the participants' perspective, the potential physical and emotional burden and the benefits the protocol presents for them.

Research interview is a scientific research process based on verbal communication aimed at gathering information, where the topic is controlled by the interviewer and where the interviewee has a certain degree of freedom to respond to open-ended questions (Brédart *et al.*, 2014). Interviewees are assured of confidentiality and in that there can be no right or wrong answers. The one-to-one interviews take place in a safe, comfortable environment. The interviewer must have strong interpersonal and active listening skills, and needs to establish a professional, positive, but not overly friendly, trusting relationship with the interviewee.

Structured interviews with research participants – persons with ALS – were conducted prior to treatment (week 5) and at the end of the follow-up period (week 16) to understand the participants' expectations for music therapy treatment and their impressions of the music therapy experience. The interviews included five open-ended questions and a space to share any additional comments at the end of the conversation.

This interview format was chosen because it provides an opportunity to elicit the essential qualitative data, but is succinct enough not to cause voice fatigue in the participants. The latter needs to always be considered when communicating with persons who have ALS (see Chapter 1, section The Role of Exercise in ALS Care, for more detail).

No audio recordings were made. Firstly, the recording process can make persons with ALS self-conscious about their deteriorating speech and may cause them to experience psychological distress. Secondly, it was important to avoid generating, storing and processing additional data in this already data-rich experiment.

Participant's answers were written down verbatim during a home visit by a trained research assistant. After writing down each answer, research assistants read it back to the participants for a fidelity check. The interviews were conducted in

Russian, the language native to the participants and the research assistant, and translated into English and analyzed by the principal researcher, who is fluent in both Russian and English. This arrangement was due to the resources limitations and could contribute to language and cultural bias, as well as a possibility of bias when interpreting the results. The implications of this for future research are discussed in Study limitations section of Chapter 11. Discussion.

Structured interviews with participants – persons with ALS – conducted prior to music therapy treatment included the following questions:

Question 1. How, do you think, may music therapy affect your speech, breathing and swallowing?

Question 2. How, do you think, may music therapy affect you otherwise?

Question 3. What do you expect in music therapy sessions?

Question 4. How, do you think, will it be to independently do the assigned music therapy exercises between the sessions?

Question 5. How, do you think, may these music therapy exercises affect your speech, breathing and swallowing?

Question 6. Other comments.

Structured interviews with participants – persons with ALS – conducted after music therapy treatment included the following questions:

Question 1. Has music therapy affected your speech, breathing and swallowing? In which way?

Question 2. Has music therapy affected you otherwise?

Question 3. How did it feel to participate in music therapy sessions?

Question 4. How was it to independently do the assigned music therapy exercises between the sessions?

Question 5. Have these music therapy exercises affected your speech, breathing and swallowing?

Question 6. Other comments.

Caregiver experience

As discussed previously, physical and emotional burden is significant for caregivers of persons living with ALS. Understanding caregivers' perspectives on music therapy treatment provides essential information for clinical implementation and future research.

Structured interviews with caregivers were conducted prior to treatment (week 5) and at the end of the follow-up period (week 16) to understand their expectations for and impressions of music therapy treatment. Primary caregivers, if identified by participants – persons with ALS – and only with their permission, were approached for the interviews. The same protocol was adopted as for the interviews with research participants – persons with ALS.

The caregivers' answers were typed verbatim on a tablet during a home visit by a trained research assistant. No audio recordings were made. After typing each answer, research assistants read it back to the caregivers for a fidelity check. The interviews were conducted in Russian, the language native to the participants and the research assistant, and translated into English by a person who is fluent in both Russian and English (the principal researcher).

<u>Structured interviews with participants – caregivers of persons with ALS – conducted prior to music therapy treatment</u> included the following questions:

Question 1. How, do you think, may music therapy affect speech, breathing and swallowing of X (person with ALS)?

Question 2. How, do you think, may music therapy affect X (person with ALS) otherwise?

Question 3. How, do you think, X's engagement in music therapy may affect you as a primary caregiver?

<u>Structured interviews with participants – caregivers of persons with ALS – conducted after music therapy treatment</u> included the following questions:

Question 1. Has music therapy affected X's (person with ALS) speech, breathing and swallowing?

Question 2. Has music therapy affected X (person with ALS) otherwise?

Question 3. Has X's (person with ALS) engagement in music therapy affected you as a primary caregiver?

Question 4. Other comments.

Music therapy clinician perspective

Documentation is an essential part of any music therapy treatment (Hanser, 2018). It can be done in many formats, more or less formal, brief or extensive. Quantitative data, objective outlook, observation, ongoing goal-related assessment are the core elements of music therapy documentation. Qualitative data are not of lesser importance. The music therapist directly engages with the treatment process on physical, cognitive, emotional and social levels of the musical and non-musical interaction. The therapist's subjective perspective and personal reflection provide an important ideographic first-person insight into the nature of this experience and the interpersonal aspects of the music therapy process (Chapter 10. Case study sketches). The challenges and the opportunities this research present to the clinician and the whole research team can be meticulously explored (see Exploring music therapy as a complementary treatment for ALS: the researcher's perspective section in Chapter 7. Feasibility data analysis results).

Individual treatment notes taken after each session and generalized "field notes" taken twice a week, after completion of each consequent session by all the participants, were submitted by the music therapist. Using these two formats allowed the principal researcher to pay detailed attention to each participant's response to treatment and to observe the common trends, milestones and synchronicities within the cohort.

Thematic analysis of the qualitative feasibility data

Thematic analysis (TA) is a common method for analyzing qualitative data in various research fields. It primarily focuses on identifying and reporting patterns of meaning (themes) within data. Although the definition “thematic analysis” is used as an umbrella term, the current study employs two particular approaches to thematic analysis – reflexive thematic analysis developed by (Braun and Clarke, 2006) and narrative thematic analysis outlined by (Riessman, 2008).

Reflexive thematic analysis has been employed to analyze the interviews regarding the treatment experience of research participants – persons with ALS and their caregivers. Braun and Clarke (2006) define reflexive thematic analysis as theoretically flexible TA. This method offers a variety of ways to approach the analysis, including:

- an **inductive way** – coding and theme development are directed by the content of the data;
- a **deductive way** – coding and theme development are directed by existing concepts or ideas;
- a **semantic way** – coding and theme development reflect the explicit content of the data;
- a **latent way** – coding and theme development report concepts and assumptions underpinning the data;
- a **(critical) realist or essentialist way** – focuses on reporting an assumed reality evident in the data;
- a **constructionist way** – focuses on looking at how a certain reality is created by the data.

The following “guidelines”, or “tools”, have been suggested for TA procedure:

- **familiarization with the data** – reading and re-reading the data, to become immersed in its content,
- **coding** – generating succinct labels that identify important features of the data that might be relevant to answering the research question,
- **generating initial themes** – examining the codes and collated data to identify significant broader patterns of meaning (potential themes),

- **reviewing themes** – checking the candidate themes against the dataset, to determine that they tell a convincing story of the data, and one that answers the research question,
- **defining and naming themes** – developing a detailed analysis of each theme and deciding on an informative name for each theme,
- **writing up** – weaving together the analytic narrative and data extracts.

It must be noted that these guidelines are not the rules and are to be applied flexibly to fit the research questions and data. Moreover, the analysis is a recursive process where movement back and force is needed throughout the phases (Braun and Clarke, 2006). A **theme** captures an important aspect of the data in relation to the research question and presents a patterned meaning within the data set. The themes may be determined in a number of ways, though the process has to be consistent within each particular TA.

The process of extracting themes and sub-themes from the interviews is described in detail in Chapter 7. Feasibility data analysis results, section Taking part in music therapy: study participants' perspectives. The data-driven **inductive, semantic, realist version of TA** was applied to the participants' interviews for this study.

Narrative thematic analysis was applied to the treatment notes and the field notes submitted by the music therapist – principal investigator, with the purpose to illuminate the subjective perspective of the clinician and the researcher in regards to the treatment process and the research process. Narrative inquiry emphasizes preserving the integrity of a particular individual in the course of the analysis (Riessman, 2008). This is essential when researching a novel treatment protocol realized within an ongoing therapeutic relationship (see Chapter 5. Music therapy treatment protocol, section The biopsychosocial paradigm). However, in the thematic approach the narrative inquiry is focused exclusively on the content (rather than style or associated meanings). Themes emerge from the research questions and the data themselves, and the coherent story is guided by these themes.

While the resulting narrative is inherently subjective, i.e. biased, this subjectivity comprises an essential dimension of the objectivist case study research method, where the qualitative data are triangulated with the objective data to provide the in-depth account of a phenomenon (Ridder and Fachner, 2006).

BIOMEDICAL OUTCOME MEASURES

Choosing instruments to measure the effect of the music therapy protocol on respiratory and bulbar functions of people with ALS has been arguably the most challenging part of this research. Many ALS-specific measurement tools do exist, but, as related research (Rooney, 2017; Jensen *et al.*, 2017) and problem-oriented discussions in the professional community have revealed (e.g. Bulbar Guidelines Development Symposium, 29th International Symposium on ALS / MND, December 2018), these may lack sufficient sensitivity to reliably measure the change, given that ALS is a rapidly degenerating disease and that the rate of deterioration varies greatly from patient to patient. The clinical assessment of bulbar function may be especially challenging, as it “has not yet attained the standard of practice that is universally employed for the assessment of limb musculature and respiratory function” (Smith *et al.*, 2017). Since no standardized diagnostic procedure exists, “clinicians invariably find it challenging to predict the rate of speech and swallowing decline” (Green *et al.*, 2013). Similarly, although the respiratory subscale of ALSFRS-R is routinely used worldwide to monitor symptoms of respiratory involvement, it only provides limited and sometimes misleading information (Pinto and de Carvalho, 2015).

A survey of 38 ALS clinics in the United States (Plowman *et al.*, 2017) revealed significant variability and inconsistency in clinical assessment and management of bulbar dysfunction in ALS. Body weight was routinely measured by 94.7% of sites, forced vital capacity (FVC) – by 89.5% of sites, body mass index (BMI) – by 63.2% of sites, calorie count – by 36,8% of sites, Maximal Expiratory Pressure (MEP) – by 28,9% of sites, speaking rate and the Sentence Intelligibility test – by 18.4% of sites. Only 27% of sites routinely utilized referral to videofluoroscopic swallowing study. The authors concluded that great need existed for the development of a unified metrics system to accurately detect and monitor bulbar dysfunction in ALS clinical care. Recently published “Provisional best practices guidelines for the evaluation of bulbar dysfunction in Amyotrophic Lateral Sclerosis” (Pattee *et al.*, 2019) present the first uniform assessment of speech and swallow function recommended for multidisciplinary ALS teams. Praising this work as a “landmark accomplishment in the field”, the editors (Gwathmey and Berggren, 2019) noted that it is important to consider both the time it required to take the suggested measurements during each clinic visit and applicability of the guidelines to ALS clinics with limited resources.

A minimally burdensome for the participants, inexpensive and reliable assessment battery to measure bulbar and respiratory changes in early and mid-stage ALS was selected. The choice of outcome measurements was based on the following criteria:

- research evidence, including (Andersen *et al.*, 2012; Baker, Wigram and Gold, 2005; Beukelman, Fager and Nordness, 2011; Bowen, 2013; Brédart *et al.*, 2014; Czaplinski, Yen and Appel, 2006b; Donovan *et al.*, 2008; Haneishi, 2001; Lee, 2017; McCullough *et al.*, 2012; Mefferd, Green and Pattee, 2012; Nishio and Niimi, 2000; Pietkiewicz and Smith, 2014; Pinto, 2017; Mendelsohn, 1987; Plowman, 2015; Rong *et al.*, 2016; Strand *et al.*, 1994; Tamplin, 2008; Touré-Tillery and Fishbach, 2014; Wiens, Reimer and Guyn, 1999; Yunusova *et al.*, 2011; Plowman *et al.*, 2019)
- recommendations from international experts in the field,
- local technical means and laboratory capacities,
- local clinical practice standards for measuring respiratory and bulbar functions of ALS,
- for ethical considerations, minimally invasive, least time-consuming, home-based assessment types were preferred.

The biomedical outcome measures used in this study are described below, along with a rationale for the choice of the measurement.

Outcome measures to assess long-term changes in respiration

Maximal Inspiration Pressure (MIP), Maximal Expiration Pressure (MEP) and Forced Vital Capacity (FVC) were measured at four time points, i.e. baseline (week 1), pre-treatment (week 6), post-treatment (week 12), at the end of the follow-up period (week 16), to assess the long-term changes in respiration.

Forced Vital Capacity (FVC) is a standard spirometry test which measures the volume of air that can forcibly be blown out after full inspiration. This non-invasive test is routinely used to monitor ALS patients, allows to predict prognosis and has been established as a recommended test for clinical trials and an important standard of ALS management (Czaplinski, Yen and Appel, 2006b; Pinto, 2017). FVC was measured by a research nurse using a portable spirometer, in the sitting position and expressed as a percentage of the expected value, in accordance with “Guidelines for the use and performance of quantitative outcome measures in ALS clinical trials” (Brinkmann *et al.*, 1997). The best result of three attempts was recorded.

Maximal Inspiration Pressure (MIP) and **Maximal Expiration Pressure (MEP)** are direct measures of respiratory muscle strength. MIP measures the inspiratory pressure generated against a completely occluded airway and is used to evaluate inspiratory respiratory muscle strength. MEP is a measure of the strength of respiratory muscles, obtained by having the patient exhale as strongly as possible against a mouthpiece (Kamat, 2015). MIP and MEP tests are not routinely performed in ALS care, however review of the literature suggests that these measures may be more sensitive in detecting early respiratory muscle dysfunction compared with spirometry and may have high prognostic relevance (Schoser *et al.*, 2017). MIP value has been found to directly correlate with quality of life in ALS patients (Bourke *et al.*, 2006).

MIP and MEP were measured by a research nurse using a respiratory pressure meter, in the sitting position and expressed in cm H_2O. The best result of three attempts was recorded. Participants were allowed to rest between FVC, MIP and MEP measurements to avoid fatigue (Wiens, Reimer and Guyn, 1999).

Outcome measures to assess the long-term changes in cough

Peak Expiratory Flow (PEF) was measured at four time points: baseline (week 1), pre-treatment (week 6), post-treatment (week 12), at the end of the follow-up period (week 16), to assess the long-term changes in cough.

Peak Expiratory Flow (PEF) is the highest flow achieved from a maximum forced expiratory maneuver started without hesitation from a position of maximal lung inflation (Quanjer *et al.*, 1997). It is instrumental at measuring pulmonary function and airway defense capacity and plays an important role in decision-making for feeding tube and tracheostomy tube placements (Pattee *et al.*, 2019).

PEF was measured by a research nurse using a portable peak flow meter in the sitting position and expressed in percentage from normal value as defined by European Respiratory Society (Quanjer *et al.*, 1993). The best result of three attempts was recorded.

Outcome measures to assess the long-term changes in speech

Speech changes in ALS are challenging to measure, due to multidimensionality of speech production, the absence of standard objective assessment tools and dependency of the assessment on the particular language grammar, phonetics and prosody. Generally, speech can be assessed through: 1) in-person voice assessments by a qualified clinician, 2) patient-reported questionnaires, 3) acoustic analysis of recorded speech samples, 4) instrumental evaluations, including acoustic, aerodynamic and kinematic methodologies (Yunusova *et al.*, 2011; Rong *et al.*, 2016), 5) perceptual assessment of recorded speech samples by a qualified clinician.

Examples of perceptual in-person voice assessments include Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS) protocol and Frenchay Dysarthria Assessment (FDA). These assessments are standard for dysarthria evaluation, but they depend largely on the qualification of the speech and language specialist conducting the tests and require a significant amount of time to perform. As there are no speech and language specialists who are qualified to conduct these assessments in Russia, where the study was conducted, the principal researcher decided against these.

Instrumental evaluations of voice acoustics and aerodynamics provide objective assessment of phonatory function, rather than subjective judgments of voice quality, and kinematic studies yield more precise information regarding bulbar decline in neurodegenerative diseases (Green *et al.*, 2013; Kearney *et al.*, 2017; Bandini *et al.*, 2018). However, these instrumental evaluations require a trained specialist's presence, may be invasive and require purchase of specialist expensive equipment and materials (e.g. nasometer, subglottal pressure meter, Phonatory Aerodynamic System (PAS), Electromagnetic Tracking Device (WAVE), etc.). These considerations prevented the team from using instrumental voice evaluations for home-based assessments in this study.

Participant-reported **Center for Neurologic Study – Bulbar Function Scale (CNS-BFS) speech subscore**, **acoustic analysis of recorded speech samples** and **perceptual assessment of recorded speech samples** by qualified clinicians, recorded at four time points (baseline (week 1), pre-treatment (week 6), post-treatment (week 12) and at the end of the follow-up period (week 16)), were used to assess the long-term changes in speech.

Recently developed **Center for Neurologic Studies – Bulbar Function Scale (CNS-BFS)** is a self-report bulbar function scale which interrogates three domains of bulbar function: speech, swallowing and salivation. For each domain, the research patients are asked to rate seven statements or questions on a scale of 1 to 5. Speech domain subscore can range from "7" (best outcome) to "35" (worst outcome). Patients unable to speak are assigned a value of 6 for the speech domain questions.

The validation study reports that CNS-BFS speech and swallowing subscales outperformed both the bulbar component of the ALSFRS-R and speech and swallowing numerical rating scales when correlations were made between these scales and objective measures of timed reading and swallowing (Smith *et al.*, 2018). Reduction in the self-report Center for Neurologic Studies Bulbar Function Scale (CNS-BFS) was used recently as the primary end-point in the randomized, crossover clinical trial to determine whether Nuedexta medication could enhance speech, swallowing and salivation of persons with ALS (Smith *et al.*, 2017).

For the purposes of this research, it was decided to acquire separate ratings for speech and swallowing CNS-BFS domains only. This allowed to keep the quantifiable data reports systematic for respiratory, speech and swallowing function changes throughout the study. Since the participants of this study were Russian speakers, CNS-BFS (Table 2) was translated into Russian (see Appendix K) by the principal researcher, who is a person fluent in both languages, with a consultation from medical professionals at ALS Centre Moscow.

Table 2. Center for Neurologic Study – Bulbar Function Scale, Speech Subscale

CNS-BFS Speech	Does not apply	Rarely applies	Occasionally applies	Frequently applies	Applies most of the time
1. My speech is difficult to understand	1	2	3	4	5
2. To be understood I repeat myself	1	2	3	4	5
3. People who understand me tell other people what I said	1	2	3	4	5
4. To communicate I write things down or use devices such as a computer	1	2	3	4	5
5. I am talking less because it takes so much effort to speak	1	2	3	4	5
6. My speech is slower than usual	1	2	3	4	5
7. It is hard for people to hear me	1	2	3	4	5

Adapted from (Smith *et al.*, 2018).

The following **voice samples** were recorded during a home visit by a trained research assistant:

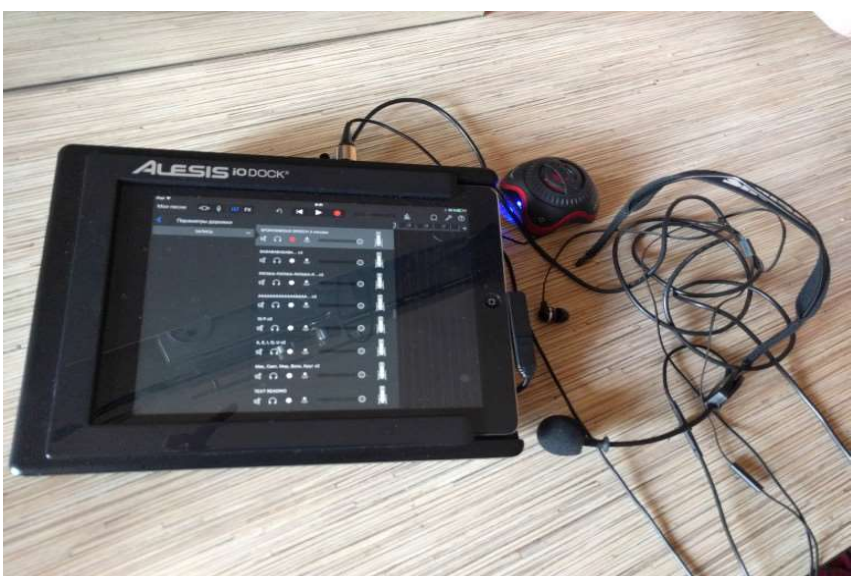
- spontaneous speech (2 minutes),
- passage reading (2 minutes),
- /pa/, /ta/, /ka/ syllables sequence repeated as clearly, as fast, as many times as possible on one exhalation (two attempts, the best is used for calculations),
- /ba/ syllable repeated as clear, as fast, as many times as possible on one exhalation (2 attempts, the best is used for calculations),

- /a/ sound sustained for as long as possible, at participant's most comfortable pitch level, on one exhalation (two attempts, the best is used for calculations),
- separate vowels (A, E, I, O, U) uttered in sequence, with pauses in between, as clearly as possible (two attempts, the best is used for calculations).

Since Russian was the native language for all the participants, The Phonetically Representative Russian Text For Fundamental and Applied Studies of Russian Speech created by (Smirnova and Khitrov, 2013) was substituted for Rainbow passage or Bamboo passage routinely used in speech-language therapy practice in the UK and in the USA (see Appendix L for the full text).

Voice samples were recorded digitally in .wav format, using a Shure WH20XLR Dynamic Headset Microphone, Alesis iO Dock audio interface, Apple iPad 2 tablet and GarageBand software (Figure 5). Participants were encouraged to rest and hydrate between the various recording tasks in order to avoid fatigue and vocal strain. This setup allows control of the sound intensity levels and the distance between the participant's mouth and the microphone head (Tamplin, 2008), thus ensuring high quality and consistency of the recordings.

Figure 5. Equipment for voice samples recording



The following measurement parameters were calculated from the voice samples, recorded at four time points, to assess long-term changes in speech:

- Maximum Phonation Time (MPT), sound /a/, measured in seconds,
- Maximum Repetition Rate – Alternating (AMR), /pataka/ sequence, measured in total number of syllables uttered as fast and as clear as possible on one breath,
- Maximum Repetition Rate – Sequential (SMR), /ba/ syllable, measured in total number of syllables uttered as fast and as clear as possible on one breath,
- Jitter, local, sound /a/, measured in percent,
- Shimmer, local, sound /a/, measured in percent,
- Harmonics-to-Noise Ratio (HNR), measured in Db, sustained /a/
- Vowel Space Area, separate vowels /a, e, i, o, u/, measured in squared Hz,
- Fundamental frequency (F0), oral reading, measured in Hz,
- Speaking rate, oral reading, measured in words per minute,
- Speech-pause ratio, oral reading, measured in seconds per minute,
- Pause frequency, oral reading, measured in number of pauses per minute,
- Hypernasality level, oral reading, measured in points,
- Fundamental frequency (F0), spontaneous speech, measured in Hz,
- Speaking rate, spontaneous speech, measured in words per minute,
- Speech-pause ratio, spontaneous speech, measured in seconds per minute,
- Pause frequency spontaneous speech, measured in number of pauses per minute,
- Hypernasality level, spontaneous speech, measured in points.

Voice samples in .wav format were pseudonymized with the purpose to blind the assessors to the sequence of the samples' recording. Acoustic analysis of the voice samples was conducted using the Praat linguistic computer program – a scientific tool for analyzing speech spectrograms (Boersma and van Heuven, 2001). Compared to perceptual analysis, acoustic speech analysis of sound waveform offers the advantage of describing the voice objectively (Gadesmann and Miller, 2008; Pierce, Cotton and Perry, 2013; Teixeira, Oliveira and Lopes, 2013).

Auditory perceptual (i.e. listening-based) analysis of the same voice samples was performed by three qualified speech-language specialists, native Russian speakers, to assess hypernasality level, since this parameter cannot be reliably assessed using Praat algorithms. Interrater reliability was calculated for the perceptual analysis results (see Hypernasality level section in Chapter 8).

Following is a more detailed overview of speech measurement parameters resulting from acoustic and perceptual analyses of recorded voice samples.

Maximum Phonation Time (MPT) is a standard, simple clinical tool to assess phonatory mechanics. MPT is the longest period during which a patient can sustain phonation of a vowel sound after inhaling maximum amount of air (Maslan *et al.*, 2011; Yunusova *et al.*, 2011). **Maximum Phonation Time (MPT)**, measured in seconds, was calculated to assess long-term changes in speech.

Diadochokinetic syllable rate is a standard assessment tool, used by speech-language pathologists to measure how quickly an individual can accurately produce a series of rapid sounds. Two forms of diadochokinesis typically used clinically are Maximum Repetition Rate – Alternating (MRR-A), which requires the speaker to produce repetitions of the same syllable, and Maximum Repetition Rate – Sequential (MRR-S), which requires the speaker to produce repetitions of a sequence of syllables. Diadochokinetic syllable rate is associated with slower tongue and lower lip movement in persons with ALS and has been found to be one of the most sensitive markers of speech decline in ALS at the early stages when speech intelligibility stays still high (Nishio and Niimi, 2000). **Maximum repetition rate – alternating (MMR-A)**, measured in total number of alternating (/pataka/) syllables uttered as fast and as clear as possible on one breath, and **Maximum repetition rate – sequential (MMR-S)**, measured in total number of /ba/ syllables uttered as fast and as clear as possible on one breath, were calculated to assess long-term changes in speech.

Fundamental frequency, **jitter**, **shimmer** and **harmonics-to-noise ratio** are standard parameters of vocal acoustic analysis. These parameters are essential for speech assessment in ALS, as it is known from previous research on speech-language pathology in ALS that perceptible changes in voice quality, including abnormal (too high or low) pitch, instability of vocal fold vibration and high noise-to-harmonic ratios in voice may be among the first symptoms of bulbar involvement, even in spinal-onset disease (Green *et al.*, 2013). **Jitter** is a measure of frequency instability, **shimmer** is a measure of amplitude instability, **harmonic-to-noise ratio** quantifies the amount of noise in the voice signal, and measures of **fundamental frequency** provide information regarding the nature of the periodicity of vocal fold vibration. **Jitter**, local, measured in percent, **shimmer**, local, measured in percent, **harmonic-to-noise ratio**, measured in Db, and **fundamental frequency (F0)**, measured in Hz, were calculated to assess long-term changes in speech.

Vowel space area (VSA) is the two-dimensional area bounded by lines connecting the first and the second formant frequency coordinates (F1/F2) of vowels. F1 roughly relates to the size and shape of the cavities created by the jaw opening, and F2 roughly related to tongue position, making VSA an acoustic equivalent of kinematic articulation assessment (Sandoval *et al.*, 2013). Larger VSA correlates to clearer speech, VSA is decreased in speech of persons with ALS compared to healthy controls (Weismer *et al.*, 2001). **Vowel space area** of the five vowels /a, e, i, o, u/, measured in squared Hz, was calculated to assess long-term changes in speech.

Speaking rate is measured as the amount of words uttered per minute in connected speech. Speaking rate has been observed to gradually slow at early stages of ALS even as speech intelligibility remains relatively high (Beukelman, Fager and Nordness, 2011; Nishio and Niimi, 2000), with statistically significant difference between the healthy controls and the ALS participants with normal speech intelligibly" (Green *et al.*, 2013). **Speaking rate**, measured in words per minute, was calculated to assess long-term changes in speech.

Speech-pause analysis evaluates pauses in connected speech. Respiratory and articulatory muscle weakness results in more frequent inspirations during speech in ALS, and, consequently, in longer and more frequent pauses (Green *et al.*, 2013;

Nishio and Niimi, 2000). **Speech-pause ratio**, measured in seconds per minute, and **pause frequency**, measured in number of pauses per minute, were calculated to assess long-term changes in speech. The minimum speech threshold value was set at 100 msec and the minimum pause threshold value was at 100 msec in Praat speech analysis software.

Increased nasalance (hypernasality) is a prominent characteristic of speech decline in ALS and directly affects speech intelligibility when it coincides with articulatory imprecision. Aerodynamic measurement of nasal airflow allows for the most reliable assessment of velopharyngeal valving efficacy (Rong *et al.*, 2016), but such measurement required expensive specialized equipment and software, which was unavailable at the study host organization. Acoustic analysis of voice samples does not offer consistent assessment of nasality level. Perceptual analysis of **hypernasality level** was conducted by three qualified speech pathologists, native Russia speakers, measured in points on the scale from “1” (severe hypernasality) to “4” (normal resonance), to assess long-term changes in speech. Voice samples in .wav format were pseudonymized with the purpose to blind the assessors to the time order of recording. Interrater reliability was calculated (see Hypernasality level section in Chapter 8).

Outcome measures to assess the long-term changes in swallowing

There several ways to assess swallowing function, and they vary in their level of objectivity and technical complexity: 1) in-person swallowing assessment by a qualified speech-language clinician, 2) patient-reported questionnaires, 3) instrumental evaluations, such as videofluoroscopic swallowing study (also known as modified barium swallow test) and fiberoptic endoscopic evaluation of swallowing. Whilst ALSFRS-R scale bulbar subscale score was used among other inclusion criteria for recruitment, it was not used as a measurement outcome. It has been previously found that ALSFRS-R may represent an insensitive tool for the identification and tracking of bulbar function over time (Green *et al.*, 2013), a consideration especially important for the study of a relatively short duration.

Self-reported measures of swallowing provide the participants' perspective on the disease progression, which is essential to consider. However, this outlook is subjective and does not provide the full clinical picture. Additionally, it has been noted that persons with ALS tend to underreport swallowing impairment at early stages of the disease due to progressive adaptation to subtle changes in swallowing function (Solazzo *et al.*, 2014). Swallowing assessment by a qualified speech-language clinician was not a feasible option for this study, since there are no practitioners in Russia who are trained and qualified to conduct such assessment. Moreover, this kind of assessment depends largely on qualifications and experience of a speech-language clinician, and, thus, is, to a certain degree, subjective and cannot replace for laboratory-based videofluoroscopic swallowing study assessment (Pattee *et al.*, 2019).

Center for Neurologic Study Bulbar Function Scale (CNS-BFS) swallowing subscore and numeric measurement parameters resulting from videofluoroscopic swallowing study (VFSS) were decided upon to assess changes in participants' swallowing function for this study.

Participant-reported **Center for Neurologic Study Bulbar Function Scale (CNS-BFS) swallowing subscore**, recorded at four time points (baseline (week 1), pre-treatment (week 6), post-treatment (week 12) and at the end of the follow-up period (week 16)), and VFSS, conducted at three time points (baseline (week 1), pre-treatment (week 6) and post-treatment (week 12)), was used to assess the long-term changes in swallowing (Table 3). Since the participants of this study were Russian speakers, CNS-BFS was translated into Russian (see Appendix K) by the principal researcher, who is fluent in both languages, with a consultation from medical professionals at ALS Centre Moscow. It is understood that using the scale which was not yet validated constitute a study limitation (see section Study limitations, Chapter 11. Discussion).

Table 3. Center for Neurologic Study – Bulbar Function Scale. Swallowing.

CNS-BFS Swallowing	**Does not apply**	**Rarely applies**	**Occasionally applies**	**Frequently applies**	**Applies most of the time**
1. Swallowing is a problem	1	2	3	4	5
2. Cutting my food into smaller pieces makes it easier to chew and swallow	1	2	3	4	5
3. To get food down I have switched to a soft diet	1	2	3	4	5
4. After swallowing I gag or choke	1	2	3	4	5
5. It takes longer to eat	1	2	3	4	5
6. My weight is dropping because I can't eat normally	1	2	3	4	5
7. Food gets stuck in my throat	1	2	3	4	5

Adapted from (Smith *et al.*, 2018).

Videofluoroscopic swallowing study (VFSS), also known as a modified barium swallowing examination (MBSE), is an x-ray-based method of evaluating a person's swallowing safety and efficiency. Various volumes and textures of food and liquid are administered by a trained specialist during a patient’s visit to a laboratory. Resulting radiographic images allow for visualization of bolus flow and swallowing physiology (Martin-Harris and Jones, 2008). Although there are health risks associated with x-ray exposure, these are minimal: it would take more than 40 VFSSs annually to exceed the annual radiation exposure dose limit (Kim, Choi and Kim, 2013).

It is recognized that silent aspiration presents a major risk for persons with ALS: patients tend to aspirate during swallow, with no attempt to expectorate aspirated material. High rates of silent aspiration in ALS prompted The Northeast ALS (NEALS) bulbar subcommittee to recommend VFSS among the most reliable means of swallowing assessment, as suggested by “Provisional best practices guidelines for the evaluation of bulbar dysfunction in Amyotrophic Lateral Sclerosis” (Pattee *et al.*, 2019).

Videofluoroscopic swallowing study (VFSS) was recorded by a trained specialist during a visit to a laboratory using a BV Pulsera Mobile C-arm fluoroscope, pulsing at 30 pulses per second and recorded on built-in Medical DVD Recorder at 30 frames per second, to assess the long-term changes in swallowing. Each participant swallowed 10mL of liquid, nectar and pudding-thick liquid boluses, thickened with a xanthan gum-based thickener (i.e., Nestle Thicken-Up Clear®) and mixed to 40% weight-to-volume concentration with BarVIPS powder. VFSS video clips were reviewed and scored by a trained speech-language pathologist, using frame-by-frame analysis following operational definitions outlined by (Steele *et al.*, 2019).

Degree, timeliness and completeness of airway closure are among the main factors contributing to swallowing safety (Vose *et al.*, 2018). The following measurement parameters were calculated from videofluoroscopic swallowing study video clips to assess the long-term changes in swallowing:

- Time-to-Laryngeal Vestibule Closure, liquid 10 mL, measured in ms
- Time-to-Laryngeal Vestibule Closure, nectar 10 mL, measured in ms,
- Time-to-Laryngeal Vestibule Closure, pudding 10 mL, measured in ms,

- Maximum Pharyngeal Constriction Area, liquid 10 mL, measured in % $C2\text{-}4^2$,
- Maximum Pharyngeal Constriction Area, nectar 10 mL, measured in % $C2\text{-}4^2$,
- Maximum Pharyngeal Constriction Area, pudding 10 mL, measured in % $C2\text{-}4^2$,
- Peak position of the Hyoid Bone, liquid 10 mL, measured in % C2-4,
- Peak position of the Hyoid Bone, nectar 10 mL, measured in % C2-4,
- Peak position of the Hyoid Bone, pudding 10 mL, measured in % C2-4,
- Penetration-Aspiration Scale Score (worst), liquid 10 mL, measured in points,
- Penetration-Aspiration Scale Score (worst), nectar 10 mL, measured in points,
- Penetration-Aspiration Scale Score (worst), pudding 10 mL, measured in points,
- Total Pharyngeal Residue C24area, liquid 10 mL, measured in % C2-4,
- Total Pharyngeal Residue C24area, nectar 10 mL, measured in % C2-4,
- Total Pharyngeal Residue C24area, pudding 10 mL, measured in % C2-4,
- Laryngeal vestibule closure, liquid 10 mL, described as complete, partial, or incomplete,
- Laryngeal vestibule closure, nectar 10 mL, described as complete, partial, or incomplete,
- Laryngeal vestibule closure, pudding 10 mL, described as complete, partial, or incomplete.

Pixel-based measures were anatomically-referenced, and expressed as a percent relative to the height of cervical vertebrae C2 to C4 (i.e., % C2-4). Hyoid peak position (x,y,xy) was calculated at frame of peak xy, using online calculator downloaded from Swallowing Rehabilitation Research Lab at https://steeleswallowinglab.ca. Swallow rest was taken within 30 frames of onset of pharyngeal relaxation, prior to any additional bolus spill from mouth or preparation for subsequent swallow (for residue tracing only). For cases who swallowed sequentially (no relaxation between swallows, three bolus trials) the amount of residue was rated at first available relaxation (amount of residue confounded by the additional swallow). The video clips in .mp4 format were pseudonymized with the purpose to blind the assessor – a qualified speech-language specialist – to the time order of the video records.

Ethical considerations for data collection

The defined battery of outcome measures to assess bulbar and respiratory functions for this feasibility study is extensive and requires coordinated effort of research team members, participants with ALS and their caregivers, as well as external qualified assessors. Among this intense data collection process, participants' wellbeing remained the priority. For ethical considerations, it was agreed that data collection would be cancelled or postponed in any case where participant experienced moderate to significant physical or psychological discomfort as a result of data being obtained. The ways to minimize the burden on the participants during the data collection process is discussed in section Data collection and analysis, Chapter 11. Discussion.

The overview of outcome measures used in this study is presented in Appendix M: Outcome measures and data collection summary table.

CHAPTER 5

MUSIC THERAPY TREATMENT PROTOCOL

THERAPY APPROACH AND PRIMARY THERAPY GOALS

ALS-specific, individualized music therapy protocol was developed by the primary researcher, who is a board-certified music therapist (USA) and certified neurologic music therapist, and has over five years of experience working with this clinical population. This treatment protocol was informed and inspired by theory and clinical evidence of neurologic music therapy and by the biopsychosocial paradigm of healthcare.

Neurologic music therapy

Neurologic music therapy is a standardized system of clinical techniques that use the functional perception of all properties of music to train and retrain brain and behavior function. These interventions are directed by functional therapeutic goals according to assessment results and patient's actual needs (Thaut and Hoemberg, 2016). Supported by vast published evidence and clinical outcomes, neurologic music therapy programs are now widely used in the USA and other countries in rehabilitative medical settings, special education settings and by private music therapy practitioners. Voice and wind-playing techniques based on active music-making and supported by external rhythm, such as Oral Motor and Respiratory Exercises (OMREX) and Therapeutic Singing (TS), were found beneficial for research participants in neurorehabilitation. Oral Motor and Respiratory Exercises (OMREX) utilize structured sound vocalization and wind instrument(s) playing in order to enhance articulatory control, respiratory strength and function of speech apparatus (Canga *et al.*, 2015; Eley and Gorman, 2010; Haas, Distenfeld and Axen, 1986; Thaut and Hoemberg, 2016). Therapeutic Singing (TS) involves use of singing activities to facilitate initiation, development and articulation in speech, and to increase functions of the respiratory apparatus (Haneishi, 2001; Jungblut *et al.*, 2012; Thaut and Hoemberg, 2016; Tamplin *et al.*, 2013; Wan *et al.*, 2010).

The biopsychosocial paradigm

The biopsychosocial paradigm introduced by George Engel in 1977 (Engel, 1977) entails a holistic, person-centered approach to biomedicine and requires clinicians to attend simultaneously to the biological, psychological and social dimensions of illness. Biopsychosocial-oriented clinical practice includes (1) self-awareness; (2) active cultivation of trust; (3) an emotional style characterized by empathic curiosity; (4) self-calibration as a way to reduce bias; (5) educating the emotions to assist with diagnosis and forming therapeutic relationships; (6) using informed intuition; and (7) communicating clinical evidence to foster dialogue, not just the mechanical application of protocol. These principles allow to effectively tailor existing medical knowledge to the unique needs of each patient (Borrell-Carrió, Suchman and Epstein, 2004).

Developing the goal-oriented music therapy protocol

Upper motor neurons and lower motor neurons deterioration in ALS results in dysarthria and dysphagia of spastic-flaccid type. Generally, lower motor neurone (LMN) involvement, characteristic of bulbar onset, leads to flaccid presentation, whilst degeneration of upper motor neurone (UMN), characteristic of spinal onset, results in spasticity of bulbar muscles. However, both spasticity and flaccidity are normally present, although actual presentation varies in each patient and changes with the disease progression (Beukelman, Fager and Nordness, 2011). For this reason, muscle relaxation and moderate exercise, as well as learning efficient breathing (Plowman *et al.*, 2019) and voice production techniques, voice care techniques and ALS-specific communication strategies may be helpful, rather than rigorous strengthening oral motor exercises.

Based on extensive literature review (Chiao, Larson and Yajima, 1994; Matsuo and Palmer, 2009; Palovcak *et al.*, 2007; Plowman, 2015; Baker, Wigram and Gold, 2005; Cohen, 1992; Hanson, Yorkston and Britton, 2011; Pinto, 2012; Plowman *et al.*, 2016b; Tabor *et al.*, 2016; Ashworth, 2012; Green *et al.*, 2013; Rong *et al.*, 2016; Plowman *et al.*, 2019) , the following therapy goals for this protocol were decided upon:

1) to increase breath support,

2) to increase muscle relaxation,

3) to maintain speech rate,

4) to prevent or decrease hypernasality,

5) to maintain swallow coordination.

The treatment was delivered to study participants in their homes twice weekly for the duration of six weeks. This study duration is analogous to the duration of the other two recent innovative treatment studies examining respiratory training (Plowman et al, 2015) and active music therapy (Raglio et al, 2016) for persons with ALS.

Since music therapy constitutes a new treatment modality for bulbar and respiratory dysfunction in ALS, safety and tolerability were the main focus of the treatment protocol. Duration of each visit was approximately one hour, including the session opening and closure. The protocol was designed to allow for ample rest and relaxation possibilities between short exercises involving active muscle work, in order to prevent voice overuse and fatigue (Welham and Maclagan, 2003). The patients were advised to be well rested and hydrated, and to wear comfortable clothes allowing for unrestricted movement and breathing. The patients were encouraged to participate to their comfort level in all the exercises suggested and modeled by the music therapist, and to pause, rest and hydrate as needed. The exercises were skipped or modified if the patient felt uncomfortable or tired, or if the exercise did not meet the patient's actual clinical needs. Caregivers and family members could be present during the sessions, according to the preference of the participating person with ALS.

The protocol consists of a series of music-based breathing, gentle stretching, relaxation and singing exercises tailored to the rehabilitative needs of persons with early and mid-stage ALS and constitutes, in a rough approximation, an adaptive voice lesson oriented towards ALS-specific nonmusical (rehabilitative) goals. The principal researcher's professional experience as a singer, vocal coach, phonetician and music therapist working with persons who have ALS informed this protocol. Visual guides and verbal descriptions necessary for understanding anatomy and physiology of voice production were adopted from (Peckham, 2010), breathing and singing exercises were mostly adopted from McClosky vocal technique (McClosky, 2011). Speech-language techniques recommended for persons with ALS, published music therapy protocols for bulbar rehabilitation of patients affected by various neurological conditions were considered, including (Kim, 2010; Haneishi, 2001; Tamplin and Grocke, 2008; Wiens, Reimer and Guyn, 1999; Baker, Wigram and Gold, 2005).

MUSIC THERAPY PROTOCOL

Described in detail below is the basic music therapy treatment protocol for respiratory and bulbar rehabilitation at early and mid-stage ALS that was used in this study. An abbreviated version of the protocol is presented in the table in Appendix N. Experimental music therapy treatment protocol to support bulbar and respiratory functions of persons. Please note that the instructions are provided in the present tense, to simplify the description for the reader.

I. Session opening and assessment

Time (approximately): five minutes.
Therapy objective: assessment.
Materials and equipment: numerical rating scale (NRS) (respiration) and numerical rating scale (NRS) (voice) sheets (see Appendices I and J); NRS data entry sheet (Appendix O); notebook for note taking; two sturdy chairs situated facing each other, approximately 1.5 m apart. Optional: wheelchair, small table, pillow for participant's comfort.

Music therapist and participant exchange salutations. Music therapist assesses participant's physical and emotional state through observation and conversation, and reestablishes the rapport through a brief conversation to ensure psychological comfort of the participant entering the session. The following information is recorded: 1) NRS for current perceived ease of respiration, 2) NRS for current perceived ease of voice production, 3) information about the adherence to the assigned independent exercises routine: frequency, duration, difficulties, comments (starting at session four).

Participant is reminded that they are going to be guided through all the exercises and is welcome to participate to their comfort, to ask clarifying questions and make comments, to stop doing an exercise at any point if they feel uncomfortable or tired, and to pause, rest and hydrate as needed.

II. Body alignment exercise

Time (approximately): three minutes.
Therapy objective: to learn the proper body alignment and its role in respiration, voice production and swallowing.
Materials and equipment: visual aids (see Appendix P, Figures I and II).

Participant is informed (or, at consequent sessions, reminded) that the goal of this initial set of exercises is to learn the proper body alignment and its role in respiration, voice production and swallowing. The anatomy and physiology of respiration, voice production and swallowing are briefly explained to the patient during these and following exercises in order to increase the patient's awareness and sense of control over these processes. The music therapist verbally describes and models every exercise before inviting the patient to participate.

II.1. Body awareness

Participant is encouraged to become aware of the physical sensation of his/her body, to pay close attention to any muscle tension, strain or stiffness and to gently move, stretch or self-massage to release those.

II.2. Body alignment

Participant is encouraged to become aware of their body alignment and to find a good sitting posture by maintaining the spinal alignment from the hips up (Appendix P, Figure I). Suggested steps to achieve this are:

1. both feet are on the ground, shoulder-width apart, forming a 90-degree angle with the thighs;
2. the pelvis is adjusted so there is slightly less curve in the lower back, and the spine feels extended both upwards and downwards;
3. the rib cage is now more upward and "open" (not collapsed);
4. the shoulders are suspended exactly over the rib cage (rather than pulled back or rolled forward);
5. the head is balanced at the top of the spine and feels almost weightless, with the front half of the skull is balanced in front of Altanto-occipital joint, and its hind half is balanced behind Atlanto-occipital joint (Appendix P, Figure II);
6. the upper body is poised and aligned, yet flexible and ready to move: the images of the whole body as a marionette suspended by a rope extending from the top of the skull, or of the head as a water lily flower resting on water surface may be helpful;
7. to check for the proper spinal alignment: stretch arms above the head and bend them down so that fingertips of one hand touch the elbow of the opposite arm; sustain this position for several seconds, then let the arms drop down gently to the sides of the body, but keep the posture.

III. Diaphragmatic breathing exercises

Time (approximately): four minutes.
Therapy objective: to become aware of diaphragmatic action, its role in respiration and benefits of diaphragmatic breathing.
Materials and equipment: visual aids (see Appendix P, Figures III, IV, V).

Maintaining the aligned sitting posture and keeping the rib cage comfortably suspended, the patient is guided through a series of breathing exercises with the goal to become aware of diaphragmatic action, its role in respiration and benefits of diaphragmatic (deep) breathing. Appendix P, Figures III, IV, V may be used as visual aids. No background music or music accompaniment will be used, as this will allow the participants to fully concentrate on the physical sensation of diaphragmatic breathing. During the first several sessions the participant may experience slightly uncomfortable pulling sensation around posterior abdomen wall: this sensation is due to this group of muscles being more intensively worked than usual and will subside. When it becomes habitual, diaphragmatic breathing may reduce the effort necessary for breathing.

III.1. Silent long diaphragmatic breathing (5-10 repetitions)

Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way, and no rib action should occur. Participant is encouraged to place one hand on their abdomen and the other on their chest as they practice diaphragmatic breathing. The front and the side of the abdominal wall expand as the diaphragm contracts and pulls down during breath in, while no visible movement of the chest or shoulders occurs.

III.2. Audible diaphragmatic breathing on /s/ sound (three repetitions)

Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth making a continuous /s/ sound until they run out of air. The sound should not be forced, and no rib action should occur.

III.3. Silent long diaphragmatic breathing (three repetitions) – same as III.1.

III.4. Diaphragmatic breathing with audible sigh (three repetitions)

Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth making an audible, very breathy sigh on a vowel sound (for example, /a/). The sound should not be forced, the throat should be relaxed, and no rib action should occur.

IV. <u>Controlled breathing and lip seal exercise</u>

Time (approximately): four minutes.

Therapy objective: to practice controlled breathing in order to create sustained airflow necessary for speech; to improve oxygen and carbon dioxide exchange; to maintain lip seal (necessary for swallowing and for decreasing salivation).
Materials and equipment: 37-key melodica; individual tube mouthpiece; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification). Optional: a small (approx. 15 cm x 15 cm) piece of lightweight fabric.

Participant is advised to maintain the aligned sitting posture and to practice diaphragmatic breathing during these exercises.

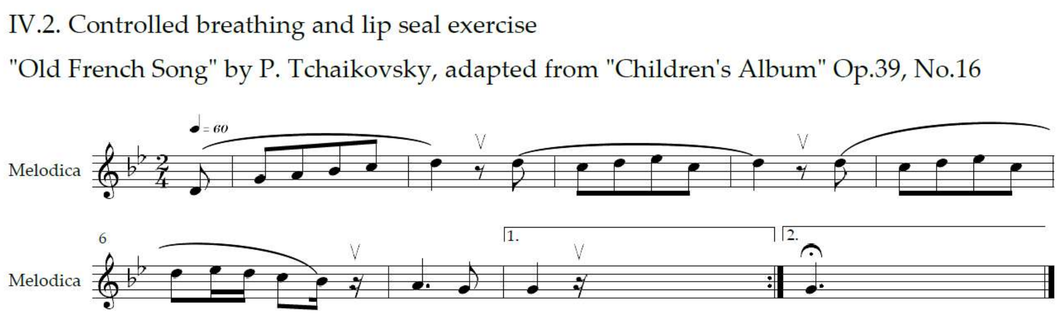
IV.1. Pursed lip breathing (three repetitions)

Participant is instructed to take a diaphragmatic breath in through the nose and to breathe out very slowly through pursed lips ("as if blowing on a fire"). A piece of lightweight fabric held by music therapist in front of the participant can be used for visual feedback.

IV.2. Controlled breathing and lip seal exercise

Participant is instructed to blow into the tube mouthpiece of the melodica while MT plays on the keys of the melodica the first 16 measures from "Old French Song" from "Children's Album" (Op.39, No.16) by Tchaikovsky, at 60 bmp, with accompanying audible metronome click. Participant is advised to breathe in through the nose as necessary between the phrases, MT may provide conducting cues for inhale as necessary. The tempo is adjusted as needed (decreased for a longer exhale) to match participants' ability. See Figure 7.

Figure 7. Transcription of exercise IV.2. Controlled breathing and lip seal exercise



Melodica with replaceable tube mouthpiece (Figure 8) has been selected over other simple wind instruments, such as ocarinas, whistles, harmonicas, kazoos and alike, for several reasons:

- standard design provides quality sound and consistency necessary for reproducible protocol implementation,
- the replaceable tube mouthpiece allows for easy disinfection (each participant keeps their own mouthpiece),
- same instrument with individual mouthpiece can be provided for each participant (reducing the costs of the study),
- the music therapist can adjust phrasing and tempo as necessary while the patient places all the effort on exercising his / her respiratory and bulbar functions,
- the exercise routine can continue even as the patient's limb function declines.

Figure 8. Sprill 37-key melodica used for this study, shown here with replaceable tube mouthpieces

V. Music assisted relaxation for voice production

Time (approximately): eight minutes

Therapy objective: to elicit the relaxation response through music assisted visualization technique (V.1) and to relax and stretch the muscles involved in voice production (V.2 – V.8).

Materials and equipment: Android smartphone; default music player for Android; Spotify application for Android (with subscription); Kinivo ZX120 Mini Portable Wired Speaker for amplification). Optional: lotion or oil for massage; Purell for hands disinfection (if music therapist touches participant's face).

For this protocol McClosky's "Six Exercises in Relaxation" for singers and speakers (McClosky, 2011) were adopted and complemented with techniques for dysphagia treatment, such as chin tuck, jaw thrust, tongue and lip range of motion exercises (NFOSD, 2018). Relaxation response facilitation is especially important in speech rehabilitation treatment, since intonation is affected by the emotional state of the individual and relaxation directly increases vocal fold flexibility (Welham and Maclagan, 2003).

Providing rationale for choosing recorded music for music assisted relaxation appears necessary here. Live music is generally preferred for most clinical situations, as it is more engaging and can be adjusted to immediate responses of the patient, but predictability and the possibility to practice relaxation in the absence of a music therapist is essential for the purposes of this protocol. A few studies discuss the implication of music use to increase relaxation (Thoma *et al.*, 2013; Burns *et al.*, 1999; Khalfa *et al.*, 2003; Nater *et al.*, 2006). Accounting for the music preferences of the client is essential for participant's motivation in music therapy, however a meta-analysis of 22 studies conducted by Pelletier (Pelletier, 2004) demonstrated that researcher-selected music had a greater effect on decreasing stress than listener-selected music. Both perspectives were taken into consideration for this study.

Before starting the treatment phase of the study, each participant is invited to choose one music piece to accompany their relaxation routine out of the three suggested by music therapist. Tracks vary by theme, genre and instrumentation (string orchestra, piano and cello, guitar and electronics), but are similar in character (calm, without abrupt harmonic, rhythmic or dynamic changes) and tempo (slow) (Bernardi, Porta and Sleight, 2006). Choice from the following music tracks is offered to each participant before the start of music therapy treatment:

- "Spiegel in Spiegel" by Arvo Pärt, arranged for cello and piano (from "Pärt: Spiegel im Spiegel" CD by Benjamin Hudson, Sebastian Klinger and Jürgen Krause)
- Orchestral suite No.3 in D Major, BWV 1068: II.Air by J.S.Bach (from "My Classical Life" CD, performed by Karl Münchinger and Stuttgarter Kammerorchester)
- "Autumn colors" (from "Sounds of Life" CD by Windrage Music)

Participant listens to each of the tracks in advance and chooses the preferred one. Special care is taken to make sure that the track does not present an emotional trigger to the patient. If none of these tracks suites the participant, another composition is sought; this composition needs to meet the following criteria:

- moderate, consistent tempo,
- well defined, consistent, but non-intrusive, straight (not syncopated) rhythmic structure,
- legato articulation,
- preferably, triple meter,
- mild, cohesive instrumentation,
- sustained dynamics,
- gradual thematic development,
- no lyrics.

The chosen track will be played on repeat from the smartphone through a Kinivo ZX120 Mini Portable Wired Speaker as a background for Exercise V. Music assisted relaxation for voice production, and provided to each patient as an audio track in their preferred format for the independent exercise routine. Since the same analysis (Pelletier, 2004) found that repeated music and relaxation practice was associated with a greater relaxation response, the same track will be used for all 12 music therapy sessions and will be suggested for the independent practice.

Participant is reminded to maintain the aligned sitting posture, and to be gentle rather than forceful in releasing muscle tension.

V.1. Music assisted visualization and relaxation (about four minutes)

The recorded relaxing music is started in the background at the level allowing for a live narrative to be clearly heard. Maintaining the aligned sitting body position, participant is advised to close their eyes and to breathe deeply, as they are led by the music therapist through a brief (about three minutes) music assisted visualization for relaxation (see English translation of a sample narrative, Appendix Q). At the end of the exercise, as the background music continues, participant is invited to gently open their eyes, first looking downwards and then gradually orienting themselves to the surroundings. The background music continues through the rest of the exercise sets.

V.2. The head and the neck muscles relaxation (two repetitions)

Maintaining the body alignment, participant is advised to let his/her head slowly fall forward under its weight, to feel the stretch on the spine, and then to bring the head back to the balanced position at the top of the spine. Participant may also sway the head gently side to side during this exercise, if it feels appropriate.

V.3. The facial muscles relaxation

Participant is advised to rub his/her hands together or to warm them otherwise and to place the palms over closed eyes for several seconds, then to gently massage the face with circular motions of the pads of the fingers, using both hands, moving from hairline downwards to cheeks, lips and chin, spending more time on areas that feel tight. When the cheeks are being massaged, participant is advised to let their jaw hang slack. Face massage may be performed by music therapist or a care provider if the participant's hand function is impaired.

V.5. The tongue muscles relaxation and stretch (three repetitions)

Participant is encouraged to let the tongue relax and fall forward slightly out of the mouth by releasing its muscles, then to gently stretch the tongue out of the mouth down toward the chin, and to release again allowing the tongue to rest on the lower lip. Participant is further advised to pull the tongue back into the mouth as far as possible, hold for a few seconds, and release.

V.6. The mandible (jaw) relaxation and stretch

Participant is assisted in finding their temporomandibular joints. With the fingers placed over the joints, the patient allows the jaw to drop without resistance. Participant is encouraged to take their jaw between the thumb and forefinger and to gently move the jaw up and down, at first slowly, then faster. The movement will be unrestricted if the jaw is relaxed. Participant is then advised to move the jaw as far forward as possible, hold, then release; then to move the jaw as far back and upwards as possible (chin tuck), hold, then release. This stretch may be repeated two or three times.

V.7. The suprahyoid muscles relaxation

Participant is assisted in finding his/her suprahyoid (digastric and mylohyoid) muscles under their chin (the muscles responsible for elevating the larynx during swallowing). Participant is advised to gently massage these muscles with their thumbs in slow, “kneading” motions, pushing vertically up and releasing down.

V.8. The infrahyoid (strap) muscles relaxation

Participant is assisted in finding their larynx by placing fingers flat against the front of their neck and swallowing, thumb and forefinger of one hand are used to gently move the larynx side to side several times.

VI. “Ping pong” soft palate exercise

Time (approximately): one minute.
Therapy objective: to tonicize the soft palate muscles involved in velopharyngeal function (Woo, 2012) and to practice the proper soft palate position for phonation.
Materials and equipment: none.

The patient is asked to “yawn politely” (half yawn) in order to find the proper position for relaxed sound production. It may help to imagine there is a ping pong ball in the back of the mouth and to hold this position for several seconds. Repeat five times.

VII. Phonation exercises

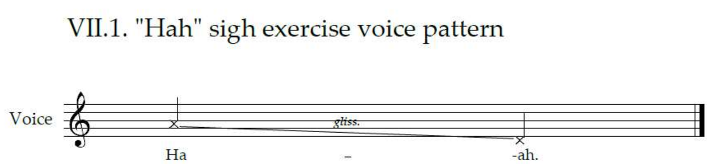
Time (approximately): five minutes.
Therapy objective: To facilitate proper engagement of arytenoid cartilages and vocal folds (VII.1 – VII.3), to increase the speech rate (tongue movement speed) (VII.3).
Materials and equipment: visual aids (see Appendix P, Figures IX and X).

This set of exercises is designed to facilitate healthy phonation (voicing), i.e. proper engagement of arytenoid cartilages and vocal folds, which is essential not only for voice production, but also for efficient swallowing (McClosky, 2011; Matsuo and Palmer, 2009). Relaxed Russian consonant articulation adapted from the voice skills workshop taught by Valentina Georgievskaya is then explained and practiced, with the goal to improve the speech rate (tongue movement speed). The participant is once again advised to maintain the aligned sitting posture and to practice diaphragmatic breathing during the exercises. Music therapist describes and models the exercises for the patient to follow.

VII.1. "Hah" sigh exercise (two repetitions)

Participant is instructed to take a breath, to expel about half of it, then to add a light, "lazy" sigh ("hah"), starting in the voice midrange and inflecting downwards. The tongue rests in the limp position, the jaw is relaxed (Figure 9). Arm motion may be added to this and following exercises to visually represent the unrestricted sound flow: as the sound descends, the arm raised above the head fluidly descends drawing a semicircle in the air.

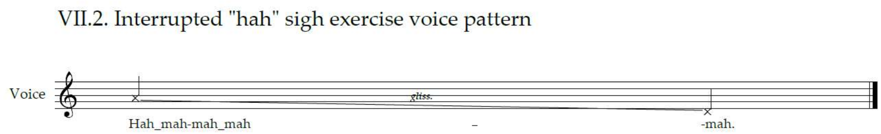
Figure 9. Transcription of exercise VII.1 "Hah" sigh exercise



VII.2. Interrupted "hah" sigh exercise (two repetitions)

Participant is instructed to repeat the previous exercise, allowing the lips to close and open several times at the beginning of the sigh, resulting in light humming sound ("hah-mah-mah-mah-mah"). The lips are not pressed firmly together like in the regular /m/ sound. The tongue rests in the limp position, the jaw is relaxed (Figure 10).

Figure 10. Transcription of exercise VII.2 Interrupted “hah” sigh exercise



VII.3. Voiced consonant sigh exercise (two repetitions for each consonant)

Maintaining relaxation of facial and laryngeal muscles, participant is instructed to take a diaphragmatic breath, then to expel the air while making a continuous consonant sound, starting in the voice midrange and inflecting downwards. An accompanying short vowel sound has to be added to the stop consonants (/b/, /d/,/g/), e.g. “ba-ba-ba-ba-ba”. The sound should not be forced. The jaw and tongue are relaxed. The sequence of the consonants for this exercise is: /v/, /z/, /z</, /l/, rolled /r/, /j/, /b/, /d/, /m/, /n/, /g/. Rolled /r/ may present a challenge for some people. This is not related to ALS and should not discourage the patient from attempting this exercise.

VIII. Consonant range cantillation exercise

Time (approximately): two minutes.
Therapy objective: to facilitate the tongue movement ease and speed, to improve velopharyngeal function, to prevent (reduce) hypernasality.
Materials and equipment: none.

The sequence of tongue movements required for this exercise involves fast progression from the resting position (/m/) to hard palate (/n/), to soft palate (/g/) (McClosky, 2011). Besides facilitating the tongue movement ease and speed, this exercise has the potential to improve velopharyngeal function and, thus, to prevent (reduce) hypernasality, which also contributes to speech intelligibility (Rong *et al.*, 2016).

Participant is instructed to take a diaphragmatic breath and say “Mah-nah-ng-ah” in cantillation once, then proceed saying “Mah-nah-ng-ah” three times on one exhalation, next – saying it six times on one exhalation, then nine times on one exhalation, and, finally, 12 times on one exhalation. Participant is encouraged to maintain and note the freedom of tongue and jaw movement as they do this exercise.

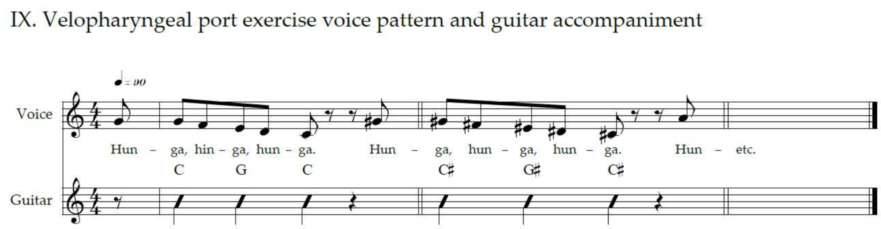
IX. Velopharyngeal port exercise

Time (approximately): three minutes.
Therapy objective: to improve velopharyngeal function, to prevent hypernasality.
Materials and equipment: Visual aids (see Appendix P, Figure X). Acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

This exercise is adapted from (Lyle, 2014). It involves timed upward-and-backward movement of the soft palate alternated with its relaxation. Hypernasality on voiced segments (i.e. vowels and voiced consonants) and excessive nasal emission during production of high pressure sounds such as stops and fricatives are two main consequences of velopharyngeal dysfunction. Proper velopharyngeal closure is essential for healthy swallowing (Matsuo, 2008) and plays important role in speech intelligibility by preventing hypernasality (Rong *et al.*, 2016; Eshghi *et al.*, 2019c).

Starting in the lower mid-range of their voice, participant is instructed to sing the syllables “Hun-ga” three times as a scale from *sol* to *do*. “Hun” corresponds with the offbeat, and “ga” falls on the beat. The exercise is then modulated gradually up by semitones, until it reaches the limit of the participant’s comfortable range. After that it modulated down by semitones until it is three semitones below the starting key. The therapist models the exercise and provides the guitar accompaniment, and sings together with the participant. The patient is encouraged to notice the switching between nasal (“hun”) and non-nasal sound (“ga”). Audible metronome click is set up. The tempo of the accompaniment can be adjusted to the ability of the patient. Gradual increase to up to 90 bpm is advisable in later sessions. See figure 11 for notation.

Figure 11. Transcription of exercise IX. Velopharyngeal port exercise



X. Impulse diaphragmatic breathing exercise

Time (approximately): two minutes

Therapy objective: to increase the efficiency and speed of relaxed diaphragmatic inhalation.

Materials and equipment: acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

The patient is reminded to keep the aligned sitting posture and relaxation of facial and laryngeal muscles during this exercise.

X.1. Impulse breathing with short “hah” exhale (two repetitions)

The exercise starts with participant listening to eight beats of audible metronome click initially set at 4/4, 64 bpm. Participant is instructed to fully relax abdominal muscles, letting the air effortlessly enter the lungs, then to abruptly expel the air with a short, though deep and strong (“barking”) “hah” sound and to immediately let the abdominal muscles relax again, letting the air into the lungs. Suggested sequence: 1) listen and rest for eight beats, 2) eight ”hah” utterances for eight beats, 3) listen and rest for eight beats, 4) eight ”hah” utterances for eight beats, 5) stop. The tempo should be slightly faster that the tempo most comfortable for the participant and may be increased gradually in subsequent sessions if the patient is ready.

X.2. Impulse breathing with sustained “hah” exhales (four repetitions)

As in the previous exercise, participant is advised to fully relax the abdominal muscles, letting the air effortlessly enter the lungs. Then the air is expelled three times following the pattern: “Hah-hah-haaaaaaaah” (short-short-long), where /a/ vowel is very open, strong and deep, but is not forced. After each syllable, the abdominal muscles should relax again, letting the air into the lungs.

XI. Sustained vowels production exercises

Time (approximately): five minutes.
Therapy objective: to practice full diaphragmatic breathing and healthy vocal folds coordination for sustained, supported vowel production.
Materials and equipment: Acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

The patient is reminded to keep the aligned sitting posture and muscle relaxation during this exercise. In case of excessive perceived nasality, participant may be advised to “adopt a pleasant facial expression”, slightly lifting the zygomatic muscles (“lifting the cheeks”).

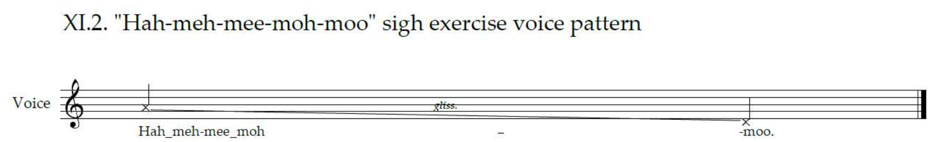
XI.1. Vowel shaping exercise (three repetitions)

With the mouth fully closed, participant is instructed to silently form vowel shapes in the following sequence: /a/, /e/, /i/, /o/, /u/, paying attention to position changes in tongue and facial muscles. Music therapist models the vowels (with sound).

XI.2. “Hah-meh-mee-moh-moo” sigh exercise (three repetitions)

Similar to exercise VII.3, participant is encouraged to take a breath, then expel it on a light, “lazy” sigh, starting in the voice midrange and inflecting downwards. During this exhale, participant forms the vowel shapes /a/, /e/, /i/, /o/, /u/ in a relaxed manner and allows the lips to close and open several times, resulting in light humming sound: “Hah-meh-mee-moh-moo” (Figure 12). The lips are not pressed firmly together like in the regular /m/ sound, and the jaw is relaxed.

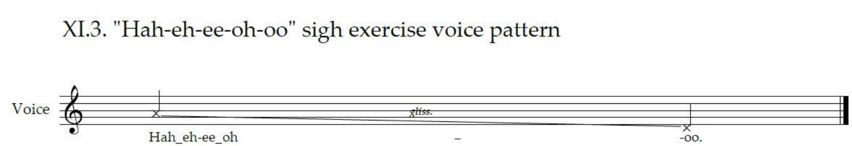
Figure 12. Transcription of exercise IX.2 “Hah-meh-mee-moh-moo” sigh exercise



XI.3 “Hah-eh-ee-oh-oo” sigh exercise (three repetitions)

The instructions for this exercise are the same as for the exercise IX.2., but the lip movement resulting in the light /m/ sound is now omitted: “Hah-eh-ee-oh-oo”. See Figure 13.

Figure 13. Transcription of exercise IX.2 “Hah-eh-ee-oh-oo” sigh exercise



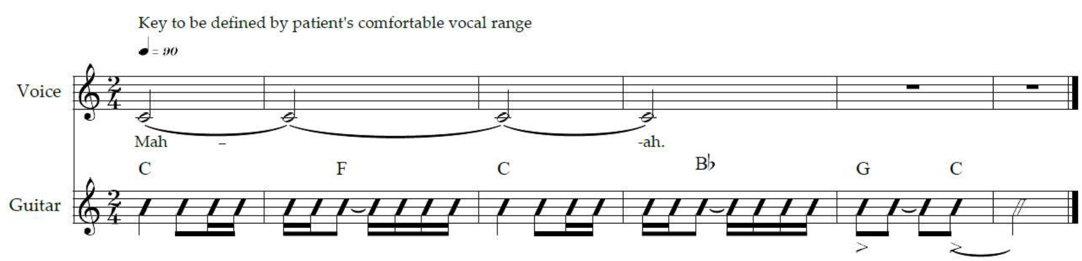
XI.4. Sustained vowels exercise (two repetitions, if tolerated well)

Comfortable tone from participant’s midrange is chosen for the exercise and becomes the tonal center (*do*). The patient sustains *do* for four measures (2/4, 90 bpm) on “mah” syllable, then rests for 2 measures. The next syllable (“meh”) is then sustained in a similar manner, then “mee”, “moh” and “moo”. The therapist provides the guitar accompaniment, and sings together with the participant.

Accompanying audible metronome is set up at 2/4, 90 bpm. The tempo is adjusted as needed (decreased for a longer exhale) to match participants' ability. The exercise may be performed twice, if tolerated well. See Figure 14.

Figure 14. Transcription of exercise IX.2 Sustained vowels exercise

XI.4. Sustained vowels exercise voice pattern and guitar accompaniment



XII. Laryngeal elevation through vocalization (gliding vowels) exercise

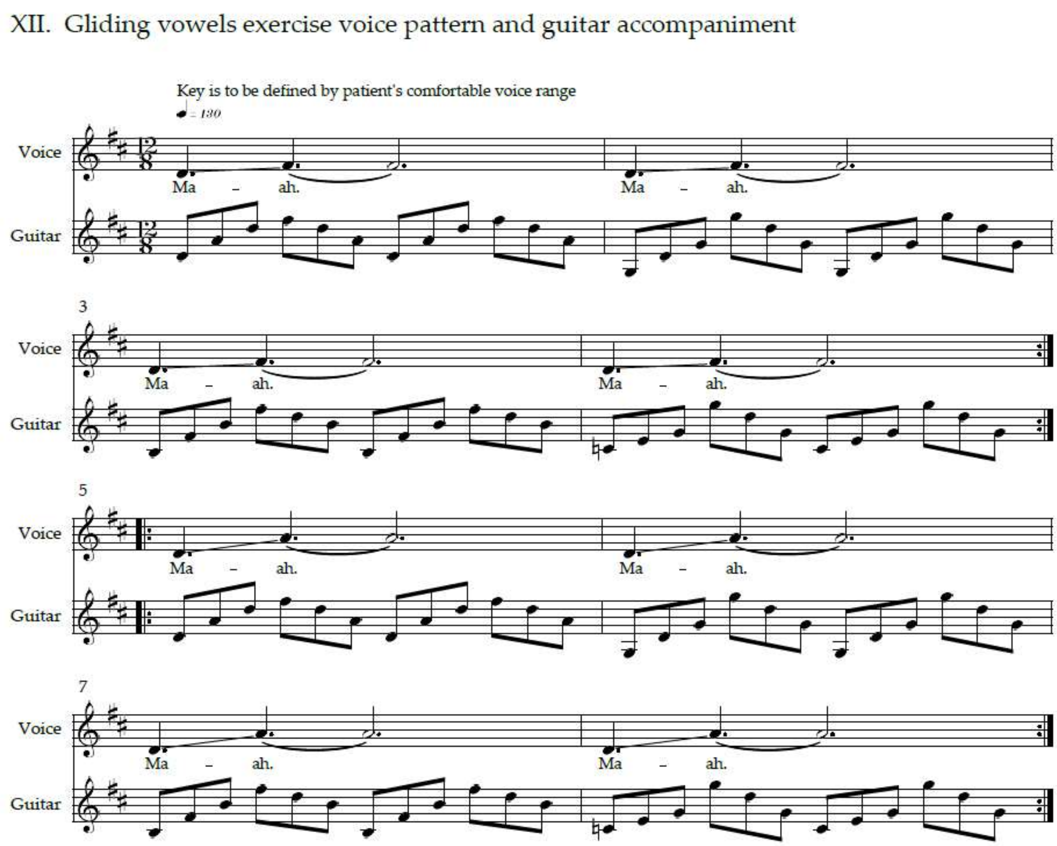
Time (approximately): five minutes.
Therapy objective: to facilitate sustained laryngeal elevation.
Materials and equipment: Acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

This exercise was adapted from (Kim, 2010) protocol for stroke patients with dysphagia and is designed to improve swallowing function by facilitating sustained laryngeal elevation. Vowels /a/, /i/, /u/ are used because they represent the extremes of vocal tract configuration (Ramig, 1988), and /m/ is added for easier sound onset.

The patient is reminded to maintain the aligned sitting posture and face and extrinsic laryngeal muscle relaxation during these exercises.

Music therapist models the exercise and sings together with the participant. A comfortable tone from the participant's midrange is chosen for the exercise. Starting from this tone on "mah" syllable, participant is instructed to slide up a major 3rd interval by beat four (the second dotted quarter) of the measure and to sustain this tone until the end of the measure. This singing pattern is repeated for three more measures, as the harmony changes. Four measures on “mee” and then four measures on “moo” follow. If tolerated well, the whole exercise may be repeated once and major 3rd interval may be increased to perfect 5th for increased laryngeal elevation. Live guitar accompaniment is provided by music therapist, in 12/8, 130 bmp, one harmony per measure, with accompanying audible metronome click. Repeat two times if tolerated well (Figure 15).

Figure 15. Transcription of exercise XII. Gliding vowels exercise



XIII. <u>Vocal cords relaxation exercises</u>

Time (approximately): two minutes

Therapy objective: to relax vocal cords following the singing exercises.

Materials and equipment: none.

Participant is instructed to use diaphragmatic or mixed type of breathing during these relaxation exercises.

XIII.1. Vocal fry exercise

Participant is instructed to take a deep breath and to make vocal fry sound for the duration of the exhale. Can be repeated.

XIII.2. Deep breathing (three repetitions)

Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way. Participant can choose to use a diaphragmatic or mixed (diaphragmatic and chest) type of breathing.

XIII.3. Exhale on hard /h/ (three repetitions)

Participant is instructed to continue deep breathing and then to exhale of a "lazy", long, uninterrupted hard /h/ sound.

XIV. Preferred song performance

Time (approximately): five minutes
Therapy objective: to reinforce all the voice skills practiced in previous exercises (body alignment and posture, diaphragmatic breathing, proper phonation, soft palate elevation, relaxed consonant articulation, etc.), to provide a motivating reward at the end of the session.
Materials and equipment: Acoustic guitar. Optional: song lyrics printout.

Participant is invited to sing their preferred song in a comfortable range, at a comfortable tempo, with live guitar accompaniment provided by music therapist. Music therapist may choose to sing together with the participant to encourage participation and to model healthy singing technique. Both the participant and music therapist provide brief feedback on the performance at the end of the song.

Selection of the song for this exercise occurs as follows. At recruitment, each participant is asked to provide the list of their three to five favorite songs to sing. Music therapist chooses one of these songs to include into the protocol, giving preference to the songs with simple melodic and harmonic structure, enough pauses for proper phrasing, moderate tempo, and emotionally neutral or "positive".

XV. Session closure and assessment

Time (approximately): five minutes.
Therapy objective: assessment.
Materials and equipment: NRS (respiration) and NRS (voice) sheets (see Appendices I and J); NRS data sheet (Appendix O); notebook for note taking.

Music therapist closes the session, acknowledges the patient's effort and reminds of the upcoming session(s) if any are left. The following information is gathered and recorded into the participant's individual data sheet (see Appendix O): NRS score for current perceived ease of respiration, NRS score for current perceived ease of voice production.

Music therapist instructs (or reminds) the patient to practice the recommended daily exercises (see sample exercises set in Appendix R), if possible, and always taking precautions to avoid strain and exhaustion (to "stop if something doesn't feel right"). The music therapist instructs (or reminds) the patient to follow the Voice care guidelines (Appendix H).

Recommended exercises for independent practice

Music therapy treatment protocol described above is aimed at teaching the participants new vocal and respiratory skills that may be beneficial in their condition. New skill acquisition is a process that requires practice, feedback and active involvement of the learner (Kaplan, 2010). Whilst our research was primary focused on practitioner-delivered intervention, it is recognized that benefits of the treatment depend, to a large extent, on the level of individual involvement of each participant. Elements of health coaching were introduced during the study, in the form of suggested independent music therapy exercise routine and voice health guidelines. Health coaching is a relatively new concept in health care that emphasizes a person-centered process that is based upon behavior change theory and encourages patient's active participation, self-discovery and accountability in health management (Wolever *et al.*, 2013). Given relevant knowledge and tools, persons with chronic diseases can gain, if partial in case of ALS, autonomy and control over their condition.

Printed ALS-specific voice health guidelines, compiled by the researcher and based on general vocal health guidelines (McClosky, 2011; Peckham, 2010; Roman, 2014) and ALS-specific speech-language therapy recommendations (Roman, 2014), were provided for participants prior to start of the treatment with the aim of promoting healthy voice use habits in daily life (see Appendix H).

The participants were encouraged, but not required, to independently practice breathing, relaxation and voice skills learned in music therapy sessions on the days when no visit by the music therapist was scheduled. A recorded guide (CD or mp3 files provided via USB flash drive) and corresponding printed instructions for the independent practice were provided to each participant at the end of the 3rd session. The individualized exercises set consisted of abbreviated (approximately 15 minutes long) versions of music therapy treatment protocol used in therapy sessions, with adjustments for the tempo, vocal range, preferred music accompaniment and imagery for relaxation, capabilities and clinical needs unique to each participant, as assessed by music therapist during the first two sessions. See Appendix R for the English translation of Sample recommended daily exercises instructions.

New, modified for best tolerance, version of the exercise set was provided to the participants before the end of music therapy treatment, at the 11th session, and further independent practice was encouraged. Contacts of two local music therapists experienced with the ALS population, who could be helpful with later adjustments of the protocol, were provided.

Audio recording the post-intervention exercises for independent practice for each participant (in Russian), with music accompaniment, can be found among the Supplementary materials to this thesis.

CHAPTER 6

RECRUITMENT DATA ANALYSIS RESULTS

RECRUITING PARTICIPANTS – PERSONS WITH ALS

Recruitment of the study participants occurred over a 20-day period, starting on the 14th of March, 2018, upon receiving ethics approvals from Anglia Ruskin University (Cambridge, UK) and Moscow Municipal Independent Ethics Committee (Moscow, Russia) (see Appendices B and C), and ending on the cut-off date, the 4th of April, 2018, to accommodate the working schedule of research assistants and nurses at ALS Moscow Centre and the principal researcher.

All newly diagnosed patients at ALS Moscow Centre living in Moscow city limits and meeting the inclusion and exclusion criteria were invited to participate by the clinical coordinator via a phone call, until the desired sample size (n=8) was achieved. The coordinator used the online medical database at ALS Moscow Centre to check each potential participant's match to the inclusion and exclusion criteria. If the information necessary to make the decision was missing, the candidate received a tentative invitation. If they were interested, the necessary data was obtained. All the selected participants completed Edinburgh Cognitive and Behavioural ALS Screen (Russian version) (Chernenkaya *et al.*, 2018) with the results above the cut-off score for their age and education level.

Trained research assistants visited at home the pre-selected candidates who were interested to become study participants, provided Participant Information Sheet and Participant Consent Form (see Appendix D) for them and answered their questions regarding the upcoming study.

DEMOGRAPHICS

Since this study was designed as applied clinical research with consecutive sampling recruitment strategy, no special efforts were made to balance the group for gender, age or type of disease onset. No questionnaires were used to gather ethnic or socio-economic data, as these inquiries could potentially present psychological triggers for the research participants, all of whom were former Soviet Union citizens. Some social data (such as occupation) were collected organically, when the participants chose to disclose.

Six females and two males were recruited (Table 4). Seven presented with spinal ALS onset type, one participant presented with bulbar onset. Mean age of the participants was 58.1 years.

As explained in Chapter 3, only the bulbar subscore of Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) – was used as an inclusion criterium for the study. For demographic purposes only, the total ALSFRS-R scores of the participant were collected. Total ALSFRS-R scores of the participants ranged from 31 to 42 points at recruitment, representing a range of motor and respiratory abilities of the participants.

Table 4. Demographics of the study participants – persons with ALS

	Age	Gender	ALS onset type	ALSFRS-R
Pt 1	62	Female	Spinal	37
Pt 2	45	Female	Spinal	41
Pt 3	53	Female	Spinal	42
Pt 4	81	Male	Spinal	39
Pt 5	43	Female	Bulbar	38
Pt 6	62	Male	Spinal	37
Pt 7	49	Female	Spinal	31
Pt 8	70	Female	Spinal	39

RECRUITING PARTICIPANTS – CAREGIVERS OF PERSONS WITH ALS

If designated by the primary participants, and only with their permission, their main caregivers were contacted and invited to participate in the study. Trained research assistants visited the identified caregivers who were interested in becoming study participants, provided them with the Participant Information Sheet (for caregivers) and the Participant Consent Form (for caregivers) (see Appendix E) and answered their questions, if any, regarding their role in the upcoming study.

Six caregivers were recruited, in addition to the seven participants who completed the study. The relations of the participating caregivers to the participants – persons with ALS – were as follows: four were spouses (two wives, two husbands), two were adult children (daughters in both cases). Five caregivers lived in the same household (city apartment) with their relative who had ALS.

REFLECTIONS ON THE RECRUITMENT PROCESS

ALS Moscow Centre is a community-oriented, nongovernmental organization that provides cutting edge, world-class services free of charge for persons living with ALS. The patients' level of trust toward the providers at the Centre is high, and the communication within the community is immediate. Many patients at the Centre reached out to the coordinators and expressed interest in participating in the study. Since most of them did not match inclusion and exclusion criteria, the coordinators put them in contact with the two music therapists at the Centre, who were previously trained in the same protocol by the principal researcher.

Two factors can be named among the main obstacles for recruitment. The first was the candidates deeming themselves "unmusical" and therefore not being able to engage into singing in music therapy. Even those who entered the study appeared very self-conscious about "performing" well enough. Having worked as a vocal coach and music therapist with many clients around the world, the principal researcher trusts that being "unmusical", "tone-deaf" or lacking previous music experience is rarely an issue for achieving therapeutic effect from singing. The participant's motivation to actively engage in music therapy and strong working rapport between the therapist and the client usually define therapy success.

The second obstacle was scheduling the sessions. Persons with early and mid-stage ALS often continue to work outside their homes. Consequently, only those who did not work or had flexible schedules could participate in the study. Another, culturally significant, scheduling issue was the seasonal tradition kept by many urban dwellers in Moscow: during the warm time of the year (starting June) many people move from city apartments to their “dachas” (country cottages) for prolonged periods of time. This makes music therapy session arrangements particularly challenging for a music therapist or a research assistant relying on public transportation. This cultural context had to be taken into account when planning this home-based music therapy protocol research.

CHAPTER 7

FEASIBILITY DATA ANALYSIS RESULTS

Primary data analysis was completed to assess the feasibility of the suggested music therapy treatment protocol. Recruitment rate, retention and adherence to treatment constituted the main numerical outcomes.

Analysis of other quantitative and qualitative feasibility data allowed to gain perspective on tolerance, motivation, participants' treatment experience, caregiver perspective, music therapy practitioner experience and the feasibility of systematic bulbar and respiratory assessment in ALS for future research.

PRIMARY FEASIBILITY DATA ANALYSIS

Recruitment

Recruitment of study participants occurred over 20-day period in March and April, 2018. All newly diagnosed patients at ALS Moscow Centre living in Moscow city limits and meeting the inclusion and exclusion criteria were invited to participate, until the desired sample size (n=8) was achieved. Thus, the target recruitment amounted to 100%. Target recruitment over 80% is considered the marker of a successful feasibility trial (see Chapter 4, Feasibility outcome measures).

The host facility could not provide the exact up-to-date information about the number of patients served; approximate estimation was 110 patients.

Retention

Out of the eight participants recruited, seven participants completed the study. Thus, the retention rate amounted to 87.5%. Retention rate over 70% at the end of follow up period is considered the marker of a successful feasibility trial (see Chapter 4, Feasibility outcome measures).

Attrition

One of the recruited participants died during the course of the study due to a cause unrelated to ALS progression (diabetes, reported by the family). The death occurred after the cut-off date for recruitment, after the consent was signed, but prior to the first data collection. Since any experimental data from this participant was missing, only the data obtained from the other seven participants was used for statistical analysis.

Adherence to treatment

12 music therapy sessions (two sessions per week, for the duration of six weeks) with the principal researcher – board certified music therapist – were scheduled with each participant during the experimental phase of the study. Participants were encouraged, but not required, to independently complete brief, 15-minute individualized exercises set on the days when they had no music therapy session. Only the number of music therapy sessions, and not the number of independent exercises sets completed, was used to calculate adherence. Mean adherence across the seven participants who completed the study amounted to 95.4%. Adherence calculated at over 75% music therapy sessions delivered is considered the marker of a successful feasibility trial (see Chapter 4, Feasibility outcome measures). Adherence to treatment individual data is presented in Table 5.

Table 5. Adherence to music therapy treatment.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Mean
% of MT sessions delivered	100	92	92	92	92	100	100	95.4

Summary of feasibility numerical outcomes

Primary data analysis provides first evidence that it is feasible to use the suggested study protocol for home-based music therapy as an intervention to support respiratory and bulbar functions in early and mid-stage ALS. The numerical outcomes for feasibility of this study protocol are summarized in Table 6.

Table 6. Feasibility numerical outcomes

	Actual	Marker of feasibility success
Recruitment, %	100	80
Retention, %	87.5	70
Adherence, %	95.4	75

SECONDARY FEASIBILITY DATA ANALYSIS

As discussed in Chapter 5. Music therapy treatment protocol, the theoretical framework of an objectivist case study research informs, if partially, the structure of this study (Wheeler and Murphy, 2016). Though this framework highlights an element of objectivity, ideographic first-person insight, prolonged engagement, and therefore subjectivity remain core features in objectivist case study research. Bridging objective and subjective perspectives appears especially useful when analyzing the feasibility of this innovative applied music therapy research in home environment, given the heterogeneity of this clinical population. Additional data collected to assess feasibility of this study protocol included:

- change in ratings on Ease of Respiration Numerical Rating Scale before and after every music therapy session (self-reported) (see Appendix I),
- change in ratings on Ease of Speech Numerical Rating Scale before and after every music therapy session (self-reported) (see Appendix J),
- adherence to the suggested, but not required independent exercises routine (self-report, measured in %),

- structured interviews with research participants – persons with ALS conducted prior to treatment (week 5) and at the end of the follow-up period (week 16),
- structured interviews with caregivers, if identified by persons with ALS, conducted prior to treatment (week 5) and at the end of the follow-up period (week 16),
- brief narrative accounts of individual music therapy sessions submitted by the principal researcher after every treatment session.

Tolerability of the treatment protocol

Change in ratings on Ease of Respiration Numerical Rating Scale (see Appendix I) before and after every music therapy session (self-reported) and change in ratings on Ease of Speech Numerical Rating Scale (see Appendix J) before and after every music therapy session (self-reported) were used to assess the short-term tolerability of the music therapy treatment protocol.

In the beginning and at the end of every music therapy session each participant was invited to answer two questions: “How easy is it to breathe for you now?” and “How easy is it to speak for you now?”. Their answer was recorded as a numerical outcome on the 10-point numerical rating scale, and the difference between the self-assessment numerical value received prior to treatment ("pre") and the self-assessment numerical value received immediately after treatment ("post") was calculated, and the mean of all differences was taken for every participant. Absence of (zero) change in self-assessed condition or improved (higher scored) self-assessed condition were markers of the treatment being well tolerated by the participants.

There was no difference between pre and post values of Ease of Respiration Numerical Rating Scale for three participants, mean post values were higher for three participants, mean post value was lower for one participant (see Table 7).

Table 7. Individual pre and post values of Ease of Respiration Numerical Rating Scale

	Mean Pre, points	Mean Post, points	Mean Pre-Post Difference, points
Pt 1	8.92	9.08	0.17
Pt 2	7.83	8.33	0.5
Pt 3	9.17	9.17	0
Pt 4	8.25	8.25	0
Pt 5	8.25	8.25	0
Pt 6	5	5.83	0.83
Pt 7	8.83	8.5	-0.33

There was no difference between pre and post values of Ease of Speech Numerical Rating Scale for one participant, mean post values were higher for five participants, mean post value was lower for one participant (see Table 8).

Table 8. Individual pre and post values of Ease of Speech Numerical Rating Scale

	Mean Pre, points	Mean Post, points	Mean Pre-Post Difference, points
Pt 1	8.08	8.5	0.42
Pt 2	7.42	7.92	0.5
Pt 3	7.75	7.42	-0.33
Pt 4	8	8	0
Pt 5	4.5	4.67	0.17
Pt 6	4.83	5.83	1
Pt 7	8.33	8.08	-0.25

To assess the statistical significance of changes across all participants, the value differences have been subjected to the Student's two-sample paired *t*-test (Last, 2007). The calculations were performed using the standard library provided by the R language.

Following are the hypotheses used to calculate the statistical significance of changes across all participants for Ease of Respiration Numerical Rating Scale numerical outcomes.

- Null hypothesis: There will be no difference between respiration assessment numerical value received prior to treatment ("pre") and respiration assessment numerical value received immediately after treatment ("post").
- Alternative hypothesis 1: Respiration assessment numerical value received immediately after treatment ("post") will be lower than respiration assessment numerical value received prior to treatment ("pre").
- Alternative hypothesis 2: Respiration assessment numerical value received immediately after treatment ("post") will be higher than respiration assessment numerical value received prior to treatment ("pre").

The results of the Student's two-sample paired *t*-test comparing the pre-treatment ($M = 8.04$, $SD = 1.42$) and post-treatment ($M = 8.2$, $SD = 1.11$) numerical outcomes indicate that the treatment did not have an effect on ease of respiration, $t(7) = 1.15$, $p = 0.296$.

Following are the hypotheses used to calculate the statistical significance of changes across all participants for Ease of Speech Numerical Rating Scale numerical outcomes.

- Null hypothesis: There will be no difference between speech assessment numerical value received prior to treatment ("pre") and speech assessment numerical value received immediately after treatment ("post").

- Alternative hypothesis 1: Speech assessment numerical value received immediately after treatment ("post") will be lower than speech assessment numerical value received prior to treatment ("pre").
- Alternative hypothesis 2: Speech assessment numerical value received immediately after treatment ("post") will be higher than speech assessment numerical value received prior to treatment ("pre").

The results of the Student's two-sample paired *t*-test comparing the pre-treatment (M = 6.98, SD = 1.61) and post-treatment (M = 7.2, SD = 1.41) numerical outcomes indicate that the treatment did not have an effect on ease of speech, $t(7) = 1.22$, $p = 0.27$.

The overall trends point upwards for both Ease of Respiration Numerical Rating Scale or Ease of Speech Numerical Rating Scale, indicating that the protocol was generally tolerated well by the study participants. However, as expected in a feasibility study with a small sample size (n=7), the change was not statistically significant for either Ease of Respiration Numerical Rating Scale (p-value = 0.296) or Ease of Speech Numerical Rating Scale (p-value = 0.270). The desired statistical power needs to be considered for any follow up studies and the sample size needs to be calculated accordingly.

Tolerability data were additionally analyzed in the format of individual case studies (see Chapter 10. Case study sketches).

Self-motivation

The participants were encouraged, but not required, to independently practice breathing, relaxation and voice skills learned in music therapy sessions on the days when no visit by the music therapist was scheduled. A recorded audio guide (CD or mp3 files provided via USB flash drive) and corresponding printed instructions for the independent practice were provided to each participant at the end of the third session. Adherence to this suggested, but not required independent exercises routine (self-report) was considered a measure of self-motivation participants demonstrated in regards to music therapy treatment. Any attempt to practice was recorded, even if the exercise set was not fully completed. The number of independent exercises sets performed, in proportion to the number of days when no visit by the music therapist was scheduled, recorded during the sessions from 4 to 12 during the 6-week treatment phase, is presented in Table 11 (measured in %).

Table 11. Adherence to suggested independent exercise routine

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Mean
% of days between MT sessions when participants engaged in independent exercise routine (self-reported)	68	89	33	39	33	64	45	53

There was no set target for adherence to suggested independent exercise routine. The participants engaged in the independent practice at their own pace and only if they chose to do so. Nonetheless, this data set provides an important insight into self-motivation of the research participants to independently follow the suggested treatment routine. It is indicative that all the participants attempted the independent exercise routine.

Qualitive data in the form of therapy notes was obtained along with the numerical data for adherence to the suggested independent practice routine. In the beginning of every music therapy session, starting at session 4, the research participants were invited to comment briefly on their experience performing the independent exercise routine.

Common reasons for not engaging into the independent practice routine included:

- not feeling well (e.g. due to high blood pressure, menses),
- being too busy to exercise (due to work, healthcare or other commitments),
- being too tired to exercise.

No participants mentioned the provided individual set of exercises being too challenging among the reasons for not engaging into independent practice routine.

Several participants mentioned using music therapeutically outside the suggested independent exercises protocol, e.g. singing favorite songs, using music to cue rhythmic movement, dancing to music for fun. Presumably, this can be viewed as a positive, though unplanned, outcome of music therapy treatment.

Taking part in music therapy: study participants' perspectives

The following sections outline subjective perspectives of the research participants – persons with ALS and the research participants – caregivers of persons with ALS. A total of 14 interviews were conducted with the participants – persons with ALS (see Appendices S, T). A total of 12 interviews were conducted with the participants – caregivers, as identified by the participants with ALS (see Appendices U and V).

The methodological framework of reflexive thematic analysis (Braun and Clarke, 2006) was applied to find common themes across the structured interviews with research participants (see Chapter 4, section Thematic analysis of the qualitative feasibility data). Data-driven inductive, semantic, realist approach to TA was chosen. The process of the analysis included the following steps.

Step 1. All the interview transcripts were collected into four data sets, in separate Word documents:

- Interviews with research participants – persons with ALS, conducted prior to treatment (week 5),
- Interviews with research participants – persons with ALS, conducted at the end of the follow-up period (week 16),
- Interviews with research participants – caregivers of persons with ALS, conducted prior to treatment (week 5),
- Interviews with research participants – caregivers of persons with ALS, conducted at the end of the follow-up period (week 16).

Step 2. All four data sets were translated from Russian into English by the principal researcher. The content and the individual style of each participant were prioritized when translating.

Step 3. The principal investigator familiarized herself with each data set by reading and re-reading the interviews several times during one week.

Step 4. Initial coding occurred within each data set. Succinct labels (e.g. “communication”, “challenge”, “improved mood”, “breathing”) were assigned to the interview phrases, color codes for various labels were establishes.

Step 5. Broad areas of inquiry (meta-themes) were defined within each data set.

Step 6. Six areas of inquiry were refined after a review. They included: 1) Music therapy process as anticipated by the participants – persons with ALS, 2) Music therapy outcomes as anticipated by the participants – persons with ALS, 3) Music therapy process as perceived by the participants – persons with ALS, 4) Music therapy outcomes as perceived by the participants – persons with ALS, 5) Music therapy outcomes as anticipated by the participants – caregivers of persons with ALS, 6) Music therapy outcomes as perceived by the participants – caregivers of persons with ALS.

Step 7. Themes within each area of inquiry were established, based on of repeated patterns (themes) across each the data set.

Step 8. Themes were refined after a review.

Step 9. Based on the number of theme repetitions within each data set, frequency (intensity) characteristic was assigned to each theme. If the same theme emerged in the narrative of two or three interviewees, it was described as the perception that “some participants” had. If the theme emerged in the narrative of four or more interviewees, it was described as the perception that “most participants” had.

Step 10. The analytic narrative with data extracts was written up for the six areas of inquiry.

Following common themes and perceptions were identified as the result of the reflexive thematic analysis of the participants’ interviews.

Music therapy process as anticipated by the participants – persons with ALS

Music therapy process was anticipated by some participants as challenging and requiring additional effort, but most participant were motivated to actively engage in music therapy treatment (translated from Russian):

1) Some persons with ALS expected singing during music therapy to present a challenge, as evident from the following statements: “I will not be able to sing, will not be able to manage” (participant 1), “I am not going to learn how to sing”, “I will do my best to complete everything” (participant 4), “if I will be asked to sing, I will feel inhibited” (participant 7).
2) Some persons with ALS anticipated that consistent engagement in music therapy may require additional organizational effort, as evident from the following statements: “I will have to set aside the time” (participant 3), “I need to find the time and the energy and to work with the tenet that this will help me” (participant 5), “the regularity of the sessions will trouble me”, “I will endeavor to organize myself, not to laze” (participant 7).
3) Most persons with ALS reported being motivated to participate in music therapy treatment, as evident from the following statements: “Will it work out or not? I will try, will see what comes from it”, “when I succeed, it will be joy” (participant 1), “I will try to make a hobby of it and to use it as an opportunity to prolong active living” (participant 2), “Positive expectations. I am ready to orderly perform all the exercises” (participant 3), “I regard these with interest, curiosity and anticipation. I will try to exercise conscientiously” (participant 4), “I am ready for everything” (participant 6).

Music therapy outcomes as anticipated by the participants – persons with ALS

Most participants anticipated music therapy to have a positive effect on their bulbar and/or respiratory functions, as well as on their psychological state. Some participants anticipated increased communication and/or decreased isolation and improved relationship with other family members as a result of the treatment.

1) Most persons with ALS anticipated music therapy to have a positive effect on their bulbar and / or respiratory functions, as evident from the following statements: "In a positive way", "breathing exercises… are beneficial", "exercises will do nothing for my speech, they can only help the lungs" (participant 2), "these sessions will slow down the disease progression", "the muscles will strengthen, will become more elastic, and will be able to function longer" (participant 3), "I hope that any kinds of training – swallowing, breathing, speech – are useful for me when I have this disease", "I hope that decline will slow down" (participant 4), "I hope, beneficially", "breathing exercises help to keep the speech", "one may convince oneself that the exercises will affect the disease course, practice this mindset" (participant 5), "possibly, they will improve speech; don't think they will affect breathing" (participant 7).
2) Most persons with ALS anticipated music therapy to have a positive effect on their psychological state, as evident from the following statements: "Emotional tuning (is) beneficial", "way out of depression", "I would like to have positive emotions and to learn how to support myself emotionally" (participant 2), "mood improvement" (participant 3), "the music itself has positive emotional effect" (participant 4), "positive emotions related to singing", "joy (awaits) because of music" (participant 5), "emotional support" (participant 7).
3) Some PALS stated they anticipated increased communication and/or decrease isolation as a result of music therapy, as evident from the following statements: "To extend my communication circle", "I hope to extend my communication opportunities" (participant 2), "the rescue is in not staying alone, otherwise bad thoughts come" (participant 3), "music, literature, communication with people <…> always encourage me, and through music therapy there will be more opportunities for that" (participant

4), “I am ready to sing together with the children”, “new experiences” (participant 5), “fine pastime”, “let us sing, my friends” (participant 6).

4) Some persons with ALS expected positive change in their relationships with other family members as a result of music therapy, as evident from the following statements: Participant 2 (“I would like to learn how to support myself emotionally, and to support my loved ones more”), Participant 5 (“Because of cooperative work with the children, the time spent together, the relationship with the children will develop positively”).

Music therapy process as perceived by the participants – persons with ALS

Most participants reported being able to self-monitor their progress, whilst being moderately challenged by music therapy experience. All participants reported music therapy to be a pleasurable experience and perceived the suggested independent music therapy exercises as easy to perform. Most persons with ALS reported being motivated to continue performing independent music therapy exercises after the treatment ended.

1) Most persons with ALS reported being able to self-monitor their progress, whilst being moderately challenged by music therapy experience, as evident from the following statements: “There were some problems each time, for example I could not pronounce (rolled) R sound. I am able to pronounce lower (register) vowels, there are problems with others. Some exercises worked out, some not so, I can’t roar”, “It was difficult to sustain notes, singing was most difficult” (participant 1), “the root of the tongue got tired” (participant 3), “I could not reach high notes”, ”At first it did not turn out too well, but then I learned how to breathe abdominally. You have to get used to that” (participant 5), “at times it was difficult, because it did not go as I wanted” (participant 7).
2) All persons with ALS reported music therapy to be a pleasurable experience, as evident from the following statements: “Simply pleasant therapy”, “it was very pleasant to work with the music therapist” (participant 1), “positive, pleasant, rewarding”, “communication with (music therapist), in the first place (has been beneficial)” (participant 2), “I liked everything”

(participant 3), “practicing was pleasant and comfortable”, “we worked with great pleasure”, “I <…> experienced great pleasure from communication and satisfaction with the accomplishments” (participant 4), “it was very pleasant to practice with (music therapist)”, “it was good, comfortable, I liked it very much” (participant 5), “communication was pleasant. Everything else as well” (participant 6), “It was very pleasant to meet and communicate with (music therapist)”, “overall, I enjoyed sessions with (music therapist)” (participant 7).

3) All persons with ALS reported the suggested independent music therapy exercises being easy to perform, as evident from the following statements: “You have to practice, that’s all <…> I have everything that I need for that, the set of exercises on a CD” (participant 1), “it was easy to incorporate (music therapy) into my everyday routine”, “I practiced every day. If I was not feeling well, I shortened the exercise set” (participant 2), “practicing was fine. Everything on the CD is accessible, like with a teacher. I experienced no difficulties” (participant 3), “performing exercises independently in between therapy sessions was made easy by the very detailed instructions which we used all the time. <…> It has been easy to exercise with (the CD), like with a teacher” (participant 4), “I practiced, it takes half an hour. I felt well” (participant 5), “I practice for an hour every day, under control of my wife” (participant 6), “sometimes it was difficult to perform (the exercises set in its) entirety. I divided (the set) into parts and practiced throughout the day” (participant 7).
4) Most persons with ALS reported being motivated to continue performing independent music therapy exercises after the treatment ended, as evident from the following statements: “I will continue to exercise” (participant 1), “I found motivation” (participant 2), “I plan to continue practicing. Will set an appointment with a phoniatrist” (participant 3), “I think if I continue with the exercises that (music therapist) provided, it (*the disease – AA*) will not progress that rapidly” (participant 5), “of course, I will continue practicing” (participant 6), “I will continue exercising on my own. Not sure that I will do that often, but I will practice” (participant 7).

Music therapy outcomes as perceived by the participants – persons with ALS

Most participants believed that music therapy was beneficial for their speech and respiration and that it helped them learn new breathing and vocal skills, but did not affect their swallowing. Some participants perceived that music therapy improved their communication.

1) Most persons with ALS perceived music therapy to have a positive effect on their speech, as evident from the following statements: "Speech became somewhat better", "When I speak slower, my speech is normal" (participant 1), "speech has become more intelligible", "it has become easier to speak. I have enough air to finish the phrase" (participant 2), "I think it has become easier for my family and conversation partners to hear me, I have started to talk with more clarity. I feel that I have started articulating more thoughtfully" (participant 4), "altogether, it is the same now as it was before the (music therapy) sessions. If it has not worsened, it is a good thing already" (participant 6).
2) Most persons with ALS perceived music therapy to have a positive effect on their respiration, as evident from the following statements: "Breathing – yes, /became better/" (participant 1), "it has become easier to breathe as well" (participant 2), "nose breathing has become better" (participant 3), "I think the two months of practice influenced my attention to diaphragmatic breathing… Specific diaphragm training is very useful when one has this disease" (participant 4).
3) Some persons with ALS perceived music therapy to improve their communication, as evident from the following statements: "My doctor told me that my speech has become better, clearer, more comprehensive. My sister and my friend told me the same thing. I feel it myself" (participant 1), "the ability to communicate again with others stabilized my overall condition", "considering that it has become easier for me to speak and an opportunity emerged to express my thoughts, I now have desire and capacity to communicate with friends. Which has become a motivation for communication. And I can now help my former patients with advice, by answering their phone calls" (participant 2).

4) Most persons with ALS perceived music therapy to have no effect on their swallowing, as evident from the following statements: “Swallowing, it is normal” (participant 1), “my swallowing is unimpaired” (participant 2), “I do not notice other changes” (participant 3), participant 6 (“no”), participant 7 (“no changes”).
5) Most persons with ALS perceived music therapy to help them learn new vocal and breathing skills, as evident from the following statements: “(Music therapist) taught me to use diaphragm and abdomen muscles for talking” (participant 2), “I learned a lot of new and interesting things”, “I learned to breathe diaphragmatically, and to relax the muscles of tongue, face and larynx when they are tired”, “I started to pay attention to myself, learned that it is better to talk softly and in a relaxed manner” (participant 3), “I appreciate the help that therapy sessions brought in terms of breathing and speaking-and-singing skills”, “I familiarized myself with elements of voice training. It is useful for more accurate command of vocal cords (participant 4),”at first it did not turn out too well, but then I learned how to breathe abdominally”, “you have to get used to that” (participant 5).

Music therapy outcomes as anticipated by the participants – caregivers of persons with ALS

Most caregivers anticipated music therapy to consist of exercises which would have a beneficial effect on bulbar and/or respiratory functions of participants with ALS, and to benefit the psychological state of the person with ALS, mostly by providing additional opportunities for communication during music therapy. Most caregivers anticipated participation of their family members affected by ALS in music therapy to have a positive effect on the caregiver’s own psychological state.

1) Most caregivers anticipated music therapy to consist of exercises which would have a beneficial effect on bulbar and/or respiratory functions of participants with ALS, as evident from the following statements: “Muscle stretch and work”, “exercise is beneficial” (caregiver 1), “as an exercise, positively” (caregiver 2), “I think it ought to have a positive effect”, “breathing and swallowing will be freer” (caregiver 4), “I hope that positively”, “muscles will be involved and the exercises will affect their strengthening” (caregiver 6), “as an exercise” (caregiver 7).

2) Most caregivers anticipated music therapy to have a positive effect on psychological state of participants with ALS, mostly providing additional opportunities for communication, as evident from the following statements: “Emotional energy, positivity, mood” (caregiver 1), “communication provides a positive outlook” (caregiver 2), “possibly, there will be benefit from (the participant) singing together with the children”, “that is psychology” (caregiver 5), “joy of communication” (caregiver 7).
3) Most caregivers anticipated participation of their family member affected by ALS in music therapy to have a positive effect on caregiver’s own psychological state, as evident from the following statements: “I will calm down a little bit, will receive emotional support” (caregiver 1), “the person who has the disease feels better, depression goes away, and I feel more joyful” (caregiver 2), “psychologically, we have decided, that (music therapy) would be very useful <…> as a stimulus” (caregiver 4), “there will be a positive influence, because this is something new. I look forward to it” (caregiver 6).

Music therapy outcomes as perceived by the participants – caregivers of persons with ALS

Most caregivers reported that music therapy improved or sustained bulbar and respiratory functions of the participant with ALS. Some caregivers reported that music therapy process and, in particular, communication with the music therapist had a positive effect on the psychological state of the participant with ALS, and that participation of their family members affected by ALS in music therapy had a positive effect on caregiver’s own psychological state.

1) Most caregivers reported that music therapy improved or sustained bulbar and respiratory functions of the participant with ALS, as evident from the following statements: “(These functions have) not worsened, and there is some improvement – yes, rather than no” (caregiver 1), “speech, yes, it is obvious and one can hear that” (caregiver 2), “learning diaphragmatic breathing was helpful. Speech became clearer by the end of each session” (caregiver 4), “it is important that there was no regress” (caregiver 6).

2) Some caregivers reported that the music therapy process and, in particular, communication with the music therapist had a positive effect on the psychological state of the participant with ALS, as evident from the following statements: “Mental impact. Likely, this is how (music therapy) had a positive impact. (My wife) anticipated (music therapy) sessions every time” (caregiver 2), “communication with (music therapist) brought joy”, “every lesson was like a holiday with new positive experiences” (caregiver 4), “communication is very important for him. So, the (music therapy) session affected him positively” (caregiver 6).
3) Some caregivers reported that participation of their family member affected by ALS in music therapy had a positive effect on the caregiver’s own psychological state: “She feels better, and I feel relieved” (caregiver 2), “it was sheer positive emotions. <…> That affected me in a positive way” (caregiver 4), “I love communication. It is important to learn something new”, “all this affected me very much” (caregiver 6).

Exploring music therapy as a complementary treatment for ALS: the researcher’s perspective

Brief narrative accounts of individual music therapy sessions were submitted by the principal researcher after every treatment session, total of 80. Additionally, field notes – generalized reflections on the course of research and tendencies within the group during the treatment phase – were submitted by the principal researcher, total of 13.

The methodological framework of narrative thematic analysis outlined by (Riessman, 2008) was applied to highlight the most prominent themes that emerged from the music therapist’s field notes and individual treatment notes (see Chapter 4, section Thematic analysis of the qualitative feasibility data). The choice of themes was influenced by the purpose of the research and by the data themselves. The process of the analysis included the following steps.

Step 1. All treatment notes and all field notes submitted by the music therapist were copied into one Word document. Some notes were submitted in English and some in Russian. No translations were made.

Step 2. The principal investigator read and re-read through the text data several times during one week to search for recurrent meanings and patterns.

Step 3. Initial coding occurred within each data set. Succinct labels in English (e.g. “song singing”, “relationship”, “yawning”, “boundaries and spaces”, “music therapist’s role”, “audio recording”, “synchronicity”, “exercise adaptation”, “music-assisted relaxation”) were assigned to parts of the text data. Color codes for various labels were establishes.

Step 4. Broad areas of inquiry (meta-themes) were defined.

Step 5. Seven areas of inquiry were refined after a review. They included: 1) Logistics, 2) Essential professional self-care, 3) Treatment protocol implementation, 4) Music-assisted relaxation, 5) Post-intervention exercises for independent practice, 6) Therapeutic relationships, 7) The role of the music therapist.

Step 6. Themes within each area of inquiry were established, based on of repeated patterns (themes) across each the data set.

Step 7. Themes were refined after a review.

Step 8. Based on the defined areas of inquiry and themes, a coherent narrative from the perspective of the principal researcher – music therapist was written.

The following sections contain the narrative perspective of the principal researcher on the music therapy process and the research process in relation to the main research questions.

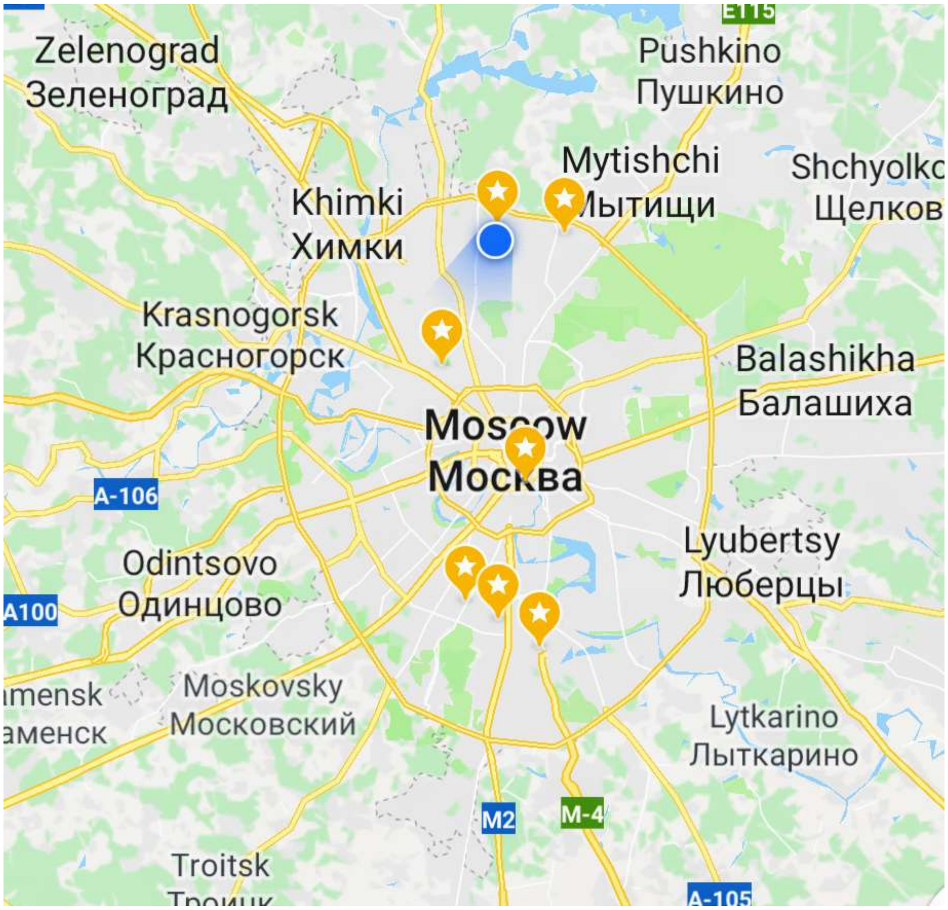
Logistics

The geography of this research has been intricate from the very beginning. I started developing the music therapy protocol for ALS Moscow Centre (Moscow, Russia) in 2013. This was pro-bono work that I conducted as a part of my seven-year long music therapy advocacy, during frequent visits from Boston, USA, where I resided, worked and taught. By 2017, with two professional music therapists and more than 20 volunteers trained in therapeutic applications of music to support persons with ALS and their families in Moscow and Saint Petersburg, enough anecdotal evidence was collected to suggest that the innovative music therapy intervention implemented at the Centre had beneficial effect on both the emotional state and the physical functioning of persons with ALS. The clinical evidence warranted more formal investigation under research conditions, and this brought me to Anglia Ruskin University's Doctoral School in Cambridge, UK.

It felt logical to carry out the field phase of the study at ALS Moscow Centre where the protocol was first implemented and where the medical team and the ALS community knew and readily accepted music therapy as a complementary treatment modality. This also meant more complicated logistics: creating study protocols in two languages (English and Russian), going through Ethics Committees in two different countries, adjusting to national differences in standard clinical measurements, taking into account cultural aspects and changing my therapy style accordingly, arranging childcare for my children in Boston, USA, and finding a long-term accommodation for myself in Moscow. The duration of the study and the sample size were largely predefined by general logistics and the available resources.

This was the first time I consistently worked with any client population in Russia for six weeks. Conducting this work in home environments made the process unpredictable and challenging on many levels. Despite the number of participants being small (n=8, and one participant died before the start of the treatment), the therapy phase arrangements were time-consuming and physically demanding. Moscow is the capital and the largest city in Russia, with over 20 million residents within its metropolitan territory and the official area of 2561,5 square kilometers. Consecutive sampling strategy was used to recruit the study participants, which resulted in a geographically diverse group. Figure 16 demonstrates the relative location of research participants homes on Moscow city map.

Figure 16. Relative location of research participant homes on Moscow city map.



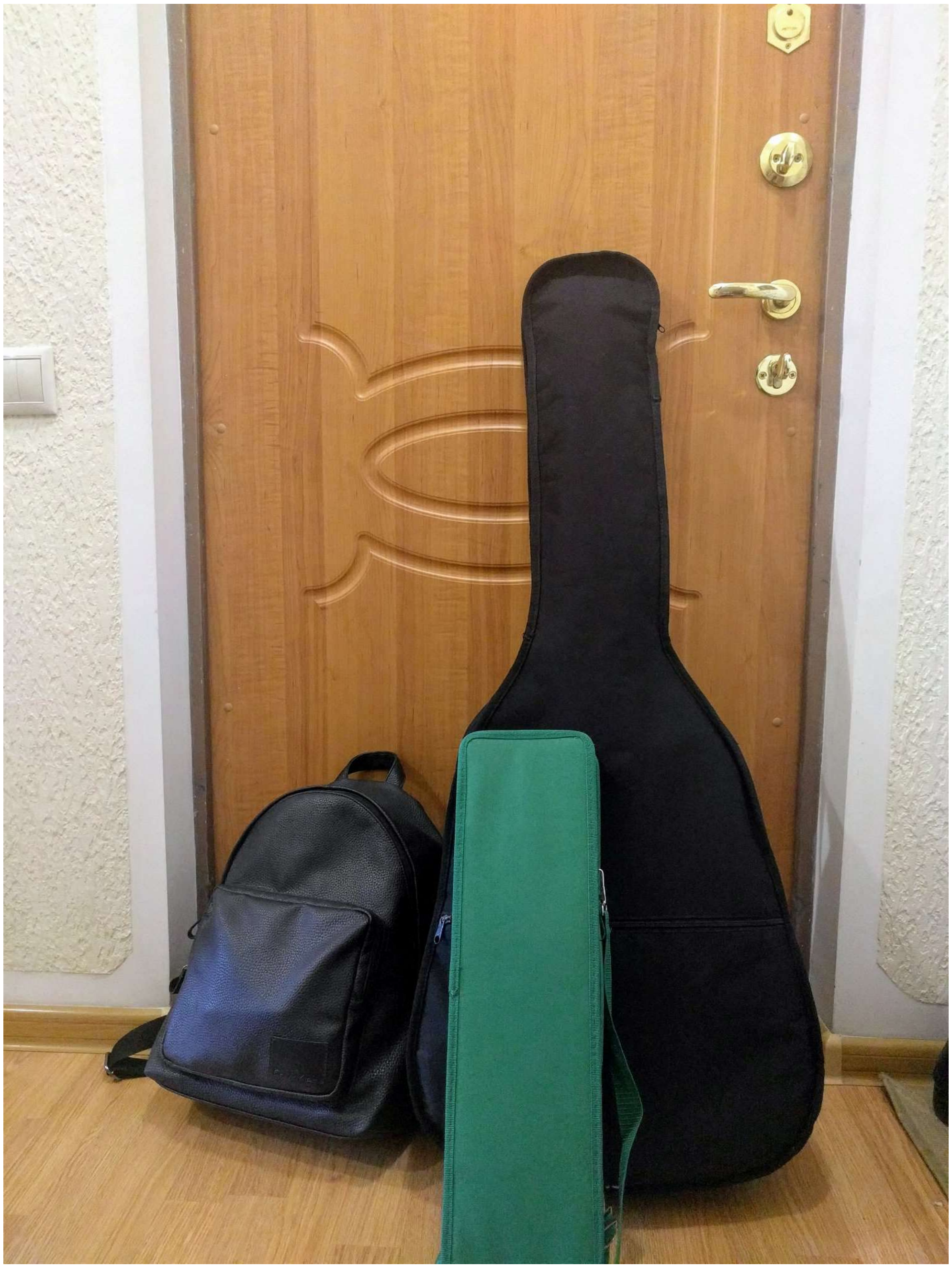
It normally took me from one hour to one and a half hours to get from one participant's location to another, and, similarly, from my Moscow apartment to one of the participants' homes in the beginning of the day and back to the apartment at the end of the day. My weekly working schedule is summarized in Table 12.

Table 12. Weekly schedule of the principal researcher during treatment phase

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
10:00 – pt visit	10:00 – pt visit	Data processing, notes, planning, creating home exercises sets	10:00 – pt visit	10:00 – pt visit	Data processing, notes, planning, creating home exercises sets	Day off
12:30 – pt visit	12:30 – pt visit		12:30 – pt visit	12:30 – pt visit		
15:00 – pt visit	15:00 – pt visit		15:00 – pt visit	14:45 – pt visit		
ALS Centre visit, coordination	18:10 – pt visit			17:00 – pt visit		

The equipment I carried included an acoustic guitar in a case, a melodica in a case, a smartphone with music player app and metronome app, a pocket-size speaker for sound amplification and a binder containing visual aids, treatment protocol, assessment scales and data entry forms (Figure 17). I mostly relied on public transportation (the underground, city buses) and walking to get from one location to another. Occasionally I used taxi: this included times when I was running late or the elements (e.g. heavy rain or wind) made it difficult to walk with the equipment. I have to note that the same logistics would likely present more challenges if the research was conducted in wintertime: the travel times would be longer and additional arrangements would likely be needed to transport the music instruments during snowfall, icy conditions and freezing weather common in Moscow.

Figure 17. Transporting the equipment during the therapy phase



Essential professional self-care

Proper self-care is important for music therapists who provide professional support to people in need, though this aspect is often neglected in practice, which may lead to burn outs and decreased quality of music therapy services (Clemens-Cortez, 2013). As with any music therapy work, I included basic self-care elements into the process.

The long travel time allowed me to make treatment notes using Google voice assistant on my Android phone and to mentally rest and reset between the sessions. When additional inspiration was needed, I engaged in photo-therapy, taking pictures of Moscow streets, city cats, trees, houses, skies. As there was not enough time in the work day for a lunch break, I planned on-the-go snacks to maintain physical energy. Finally, I had opportunities for weekly peer supervision with colleagues from ALS Moscow Centre medical team, which were invaluable and allowed for safe and confidential opportunities to analyze therapy process.

Treatment protocol implementation

Synchronous progress in the cohort

One of the most fascinating observations I made working with this group of seven persons with ALS was the synchronicity that I perceived between their individual treatment processes. With only one exception, all the participants seemed to hit similar milestones at certain consequent sessions. For example, although music therapy exercises initially required significant cognitive effort from the participants and even appeared to cause some frustration, the participants' body awareness and ability to self-monitor gradually increased by sessions 3 and 4. This allowed them to "feel" the desired breathing pattern or vocal position rather than to "imagine" those, making practice more effective and more enjoyable. The skills acquired in music therapy started to generalize around sessions 5, when the participants began to consciously use diaphragmatic breathing to support their speech, and session 6, when most participants discovered "talking as adapted singing" and began to use learned resonance and emphasized articulation to increase intelligibility of their speech. I could safely fade out verbal direction for the exercises at session 9 for all the participants.

The participant, whose development in therapy was different from the rest of the group, was the only one with bulbar onset ALS. Whilst it may seem logical to conclude that this exception to the synchronicity could be accounted for by difference in the disease onset, there are plenty of other factors to consider: for example, this participant was the youngest in the group, she had to take care of her children, the children were regularly present during music therapy sessions, etc. Case study format (see chapter 10. Case study sketches) was used to analyze this case in more depth.

Music preferences and song choice

Using client-preferred music is considered the gold standard in evidence-based music therapy. However, the objectives of this treatment protocol were exclusively in the physiological domain and could not be achieved without precisely structured music-based exercises led by a qualified music therapist. Keys, tempos, rhythmic structures, syllables used for vocalization were specific to each participants' level of functioning and individual vocal range. The two elements of the protocol allowing for somewhat greater freedom of music choice were Exercise V. Music assisted relaxation for voice production, and Exercise XIV. Preferred song performance (see Chapter 5. Music therapy treatment protocol).

For most participants, choosing the song for exercise XV turned into a much-needed opportunity for recollection, emotional reflection, connection to their whole self, and in that – overcoming the "patient" role and taking a proactive position in treatment. For me as a music therapist this process became a cornerstone in the early development of therapeutic relationship with each participant. It allowed me to get to know them on a personal level, and to gain a basic understanding of their vulnerabilities and inspirations. I was happy to get this confirmation of my intuitive idea that the song choice should take place during the first therapy session, as a part of live interaction with the music therapist, rather than alongside the process of signing the informed consent or by either phone or email, prior to the first interaction in person. Additional time, up to 30 minutes, needed to be factored in for this process during the first session. For some participants the song performed together with the music therapist, accompanied by the guitar, became a highlight of the session, especially later in treatment when the participants felt a stronger connection to the therapist and became more confident in their singing skills.

Similarly important for the participants was the opportunity to choose one of the three tracks suggested by the protocol for music assisted relaxation. The three tracks offered varying styles, timbers, textures and time signatures, but were pre-selected to be equally appropriate to facilitate music assisted relaxation. Whilst some participants had difficulty choosing between the tracks, the others experienced strong emotional reactions to the tracks. For example, one of the participants deemed “Spiegel im spiegel” by Arvo Pärt “too grave”, because of the piano timbre, despite the fact that the piece is written in a major key.

Treatment protocol adjustments

The music therapy interventions for the study were conceived as a fixed protocol, with each intervention comprising flexible elements, where tempo, pitch, intensity, instructions, background music or narrative can be adjusted to meet the clinical needs, capabilities and current state of any recruited participant. With every session it became more and more obvious to me that not only were such adjustments, indeed, needed for each participant, but that almost every new session required slight changes.

By the time the participants familiarized themselves with the protocol and felt generally comfortable working through it (around session 7), it proved to be useful to set individual objectives at the beginning of every session. The process was informal: normally, I contemplated the previous session experience and made suggestions at the beginning of the next session, advising each participant on the things to pay special attention to. The focus could be brought to specific areas including deeper diaphragmatic breathing, improving resonance and increasing relaxation. Sometimes a participant would set an objective for themselves: for example, to sustain exhalation longer during melodica exercise.

There were certain “tricks of the trade” I learned from meticulously implementing the protocol with this diverse group of participants. Some of the ideas came as solutions to common challenges in skill acquisition during therapy, some were offered by the participants. Here are several examples.

- A small bright object (such as a pocket mirror) may be used to create a focal point to encourage good posture during the session.
- If a participant presents with severe hypernasality, the music therapist can a) remind them of "ping-pong" soft palate position often throughout the session; b) replace 'm' with 'g' in Exercise VII.2 ("hah-mah-mah" => "hah-gah-gah").
- If tight jaw is an issue, the music therapist may suggest 1) that the participant tries various head positions during singing and choses the optimal (less tense) one; 2) that the participant holds the jaw with their fingers on exercises such as XI.3 ("hah-eh-ee-oh-uh") or XI.4 (long syllable), as needed.
- Simple, vivid images from everyday life may help some participants understand therapy tasks better: the therapist may say that the tongue is moving to the back of the mouth is "like a car backing into the garage" (the root of the tongue moves rather than its tip) or that "mananga" syllable sequence should sound as if a servant in a theatrical play was announcing the arrival of someone important named Mananga (which translates into more resonant sound and good projecting).
- For all the participants, their singing range was more extensive than their speaking range. It appears to be safe and effective to ask participants to sing slightly higher than their normal (as affected by ALS) speaking range. As participants start singing, they discover that they can sing without difficulty in this higher range and experience sensations of pleasant discovery and success. This appears to be very motivating for the participants.
- Body awareness turned out to be something very new for most participants, which may be cultural. Paying close attention to breathing, body posture, muscle tone presented a challenge to the participants, but became easier after regular practice, in most cases – by sessions 6 and 7.
- One participant, for whom mind-body connection presented a great challenge, eventually was able to perform all the breathing and singing exercises, but stayed too self-conscious to engage in the song-singing exercise at the end of the session. I suggested that I sang their favorite song and they could join me whenever they were ready – a strategy that often works with adults in therapy, judging from my experience. However, this was not successful. During session 2 we came up with a solution: I sang, and the participant "pretend-sang" by taking and expelling the air and

articulating as if they were uttering phrases of the song. We used this arrangement until the end of treatment.

Some questions, concerns and controversies arose as well.

- Most of the participants presented with much yawning following breathing, relaxation and stretching exercises. Some tried to conceal the process or apologized for it, commenting that they did not feel bored or tired, and that they could not explain why they felt the strong urge to yawn. Music therapists should comment positively in such cases, affirming yawning as a beneficial sign: it is common knowledge for professional singers that proper singing position is similar, physiologically, to yawning position, and often singing may trigger yawning.
- Some participants were eager to find out about the progress of other treatment group members and asked questions. I believe that the best way to address this is to provide some generalized answers: "Yes, this seems common to…", "Many people are conscious about their…", "This exercise is surely among everyone's favorite", etc.
- An unexpected hazard emerged around session 7. As research participants made progress resulting in stronger breath support, ease and clarity of speech (as noticed by themselves and their friends and relatives), some of them started to overuse their voice in extended conversations, speaking on the phone, singing for fun, and in one case - reading poetry aloud to further "exercise" their voice. Recommendations for vocal health that I provided at the beginning of the treatment were being ignored, as persons with ALS (justifiably so) enjoyed their new ease and clarity of speaking ("I don't have to repeat myself now when I speak on the phone!" – one participant excitedly remarked as I cautiously reprimanded her for her hoarse voice in the beginning of a session).
- At approximately session 9, when the participants had become accustomed to the protocol and their stamina had increased, some of them inquired about enhancing and prolonging the exercise sets – both in sessions and for independent practice. This enthusiasm sometimes led the participants to pushing themselves too hard and overworking in sessions, and it was my job as a music therapist to gently set the safe

limits without discouraging the participants and undermining their motivation.

- Another, related discovery was culture-specific. Poetry is highly esteemed in Russia. For many, poetry presents emotional comfort and intellectual stimulation, brings memories and captures fleeting feelings that cannot be fully expressed without metaphoric imagery. People memorize poetry from childhood and it accompanies them throughout life. Some participants suggested adding poetry recitations to their independent exercise routine as a way to "train speech". When asked, I had to say, unfortunately, I could not attest to safety of these recitations, because I had no understanding of the oral motor or diaphragmatic demands and how they might affect treatment responses within the protocol. Like any exercise in ALS, the uncontrolled poetry recitations potentially carry the risk of overworking the vocal production apparatus, leading to exertion and muscle damage (refer to Chapter 3 for the discussion about the current research about exercise in ALS). Still, I wonder if poetry could, indeed, be a way to bridge singing skills to speaking skills?

Audio and video recording

Audio and video recording were attempted in sessions, for several purposes: 1) to see if the treatment may be video recorded, potentially, during one of the later sessions; 2) upon participant's request; 3) to empower a participant by recording a piece of music they have been proud to successfully perform. However, it appears that audio recording process is psychologically stressful and hearing the result may be discouraging for persons with ALS, rather than beneficial. Partial video recordings of two sessions (with two different participants) were made, with the permission of the participants, for educational purposes and presentations.

Music assisted relaxation

All the patients commented positively about MAR and / or demonstrated relaxation response and positive affect in reaction to the exercise. Suggestions from the music therapist for the "safe places" imagery during the music assisted relaxation (see Appendix Q) are important but only during the first session. In later sessions it was helpful to ask participants in advance if they already knew what their imagery would be for the music assisted relaxation.

Some participants were eager to share their imagery. Listening to and acknowledging their narrative, especially during the first session, was essential for building therapeutic rapport. However, it is important to remember that the main objective of this exercise is preparation for physical relaxation rather than psycho-emotional support, and to proceed to stretching exercises as soon as possible. It felt organic to keep the background track playing on repeat during the stretching exercises, as this provided a sense of continuity and safety.

Post-intervention exercises for independent practice

The first set of individual exercises for home practice was prepared upon the initial meeting with each participant in therapy. Individual audio guides and printed instructions were provided to each participant at the end of the third therapy session (see Appendix R). For some participants this set was adjusted during the treatment phase: exercises were omitted or added, extended or transposed as appropriate.

The adjusted set of exercises was provided to each participant at the end of session 11. The participants were encouraged to try them before our last meeting. During session 12 there was an opportunity for everyone to discuss the new exercises, to ask questions and to practice them in my presence to receive feedback and advice. All the participants found the new exercises comfortable to perform. There were certain changes to the new set, as compared to the first one:

- The ranges and tempos were changed to match actual abilities of each participant. These ranges and tempos were also limited to each participant's "comfort zone", to avoid the risk of overworking muscles and damaging vocal cords.

- Any exercises that proved to be challenging to perform without support from the music therapist (as reported by participants) were excluded: e.g. Exercise VIII (cantillation of the syllable sequence “mananga”) was excluded for all participants; Exercise X (impulse diaphragmatic breathing) was excluded for participants who were easily fatigued, etc.
- Despite participants’ requests to include their favorite song accompaniment into the set, I decided not to include it, since singing a song could trigger a negative emotional response or cause unnecessary fatigue. However, the song accompaniment, in their individual range and tempo, was sent separately to each participant who requested it.
- Some participants decided to acquire a melodica for their personal use. They discussed this with me and asked my advice on a choosing particular model. I did not provide any additional instructions for melodica use.
- Each exercise set included an accompanying track for music assisted relaxation, with basic instructions and imagery narrative.
- Each exercise was presented as a separate track on the audio guide. This arrangement allowed the potential to exclude or (later) change exercises or to use only some of the tracks (for example, to only practice MAR – which, I believe, could be beneficial in the later stages of the disease progression).

Audio recording the post-intervention exercises for independent practice for each participant (in Russian), with music accompaniment, can be found among Supplementary materials. The participants were advised to seek help of the staff who were music therapists at ALS Moscow Centre to adjust the exercise sets as needed in the future. The music therapists were provided with all the information needed for providing these services.

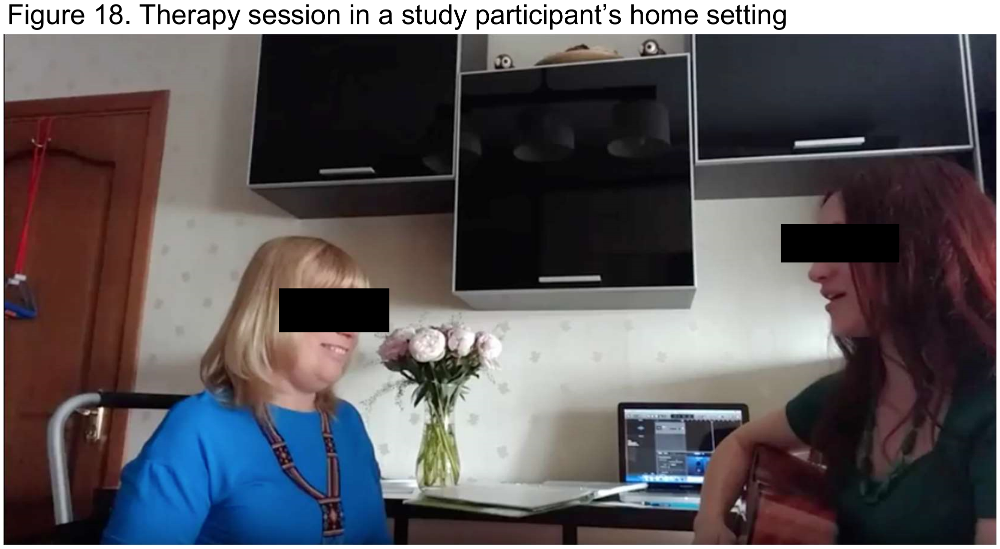
Therapeutic relationships

The therapeutic relationship between a certified music therapist and a client is always at the core of the music therapy process, however structured and prescriptive the therapist-led protocol may be. As someone who grew up in post-Soviet Russia, but spent almost 15 years living, studying and working abroad, I found myself in a beneficial position as an explorer who understands the culture of research participants well enough to "blend in", and who can be sufficiently distanced from that culture to maintain a somewhat objective view.

Home is considered a very private, almost sacred, space in Russia. Entering this space upgrades a relationship to a closer, more personal level almost automatically. My regular home visits to the participants largely overlapped with the cultural concept of "visiting", or "guest-going", traditionally reciprocated by the infamous Russian hospitality. It is considered rude to leave a visitor without a treat: a meal or, at the very least, a drink, complete with a range of snacks. No matter how hard I worked at maintaining professional boundaries and timeframes for therapy sessions, often I had to accept a cup of tea or coffee, or a handful of chocolates not to cause an offense to the "hosts".

It requires skill and work to find the culturally appropriate, professional, yet personable therapeutic relationship with each client in music therapy. Boundaries come into play: the acceptance and the limits of physical touch, the appropriate humor, the timely, weighted personal disclosure, the use of personal space (Figure 18). These boundaries vary from client to client, depending greatly on cultural specifics, on the age and demeanor of a client and a therapist, and on the stage of the therapy process.

Figure 18. Therapy session in a study participant's home setting



This graceful relationship dance manifested itself soundly in the continuously shifting ways the participants and I used the Russian formal “You” and informal “you” throughout the therapy phase. These pronouns are significant markers of boundaries in Russian culture. It is traditional in Russia to use formal “You” (“Вы”) when addressing an adult with whom you are only acquainted. Is also often used when communicating in a professional setting (especially in academia, even if people are close). People who know each other better usually use informal “you” (“ты”); in most cases, mutual agreement leads to a switch from formal to informal address. In some cases, mostly in rural areas, older people use informal “you” to address those who are 15+ years younger, whilst those younger people use formal “You” in the same situation.

Initially all the participants and I used the formal “You”. However, this changed as relationships evolved. The participants who were closer to me in age tended to use formal “You”, but soon it started to feel forced, and I suggested switching to informal “you”, which was readily accepted. Professional boundaries were still kept, but communication became more relaxed and authentic. With the rest of the participants, who were significantly older than me, formal “You” was used, both ways, initially. However, two of them eventually switched to informal “you”, without discussion. I felt comfortable with that, but continued using formal “You” addressing them. In all the situations, the changes felt natural and perfectly reflected the dynamics of therapeutic relationships I had with each participant.

Extreme care had to be taken dealing with ALS-related boundary issues. For example, self-massage of face and neck may be difficult for participants whose upper limbs are affected by the disease. In such cases, the music therapist can offer help, but should not insist if the participant is uncomfortable: neck, lip and tongue stretches all can be done by the participant independently and would suffice. If a caregiver is present, they can perform the massage following the therapist’s instructions.

Most participants chose to share their favorite music with me at some point of their treatment. This process was very distinct from choosing a favorite song to sing at the end of each session. The participants normally shared the music at the beginning of a session, before assessment: they spoke of their favorite artists or songs, and sometimes invited me to listen to the tracks on YouTube. This sharing, though it often required additional work of reinstating timing boundaries, became an important part of forming and developing therapeutic relationships and much-needed safe space of communication and self-expression for the participants.

Keeping the fragile balance of providing just basic psycho-emotional support enough for each participant to work on their therapy goals without switching over to music psychotherapy was the most difficult aspect of therapeutic relationships in this research for me. Most participants' need for authentic communication, validation and open exploration of challenging personal ALS-related topics appeared immense. Only one of the participants enjoyed strong psychological support available from the family. The ethical weight of balancing one type of needs (physical) over another type of participants' needs is significant and may be daunting for a music therapist skilled in attending to both types. In the framework of a study, this task of balancing extends into research skills, where ethical issues are arguably even more scrutinized. Luckily, I had an opportunity to discuss these situations with the medical team and to provide references to psychotherapists experienced with the ALS population.

Therapeutic relationship closure, with most participants, was not easy. As it is standard in professional practice, I started planning it in advance, mentioning it to every participant at the end of the 8th session. As we were approaching the closure, around session 11, some participants switched to more formal communication (in one case, even changing the relaxed informal "you" address to the official "You"). I felt that it was difficult for most participants to accept that therapy was coming to an end and that, by initiating the switch to a more formal style and setting the stricter boundaries in communication, they attempted to protect and distance themselves emotionally in advance.

Saying goodbyes at session 12 was emotional for everyone. One participant commented: "My body is resisting the fact that this is the last music therapy session". Some participants were tearful and very visibly upset. I prepared additional individual songs to sing together with or for the participants at the end of this last session and gave out small presents: cards with personal messages and kazoos – the instruments still somewhat exotic in Russia, though fun and useful for practicing the skills acquired during therapy. Giving such small gifts is within the professional scope of ethics suggested by American Music Therapy Association (AMTA, 2019) and serves to provide comfort to the clients at the time when the therapeutic relationship finishes. Where I sensed it as appropriate, I initiated instrumental improvisation with some participants to contain their strong emotions about saying farewell. The contacts of ALS care centre staff music therapists were provided to all the participants, including caregivers.

Even though, ethically speaking, this had been very “clean” therapeutic relationship closure and all the participants were provided with ongoing support, I still felt disturbed. It was emotionally difficult for me to walk away knowing that, even if quality and quantity of the services I provided could be matched by other music therapists, I could not transfer to the colleagues my unfolding relationship with the participants. I got to know them at earlier stages of the disease progression, when they were freer to express themselves through body and language. I became a witness to their struggle, to their strength, to their evolving personality, I entered their inner circle. Having to close these relationships and to leave felt like a loss, justified and expected for a music therapist working in palliative care, but always new.

The role of the music therapist

Whilst planning and implementing this research, I have been asked the same question over and over. The question came from speech-language therapists, nurses, physical therapists, volunteers, medical doctors, scientists, funders, persons with ALS, musicians. The question found me in Boston, in Glasgow, in London, in Cambridge, in Moscow. I have been pondering the same question myself.

Can this protocol be implemented by someone who is not a music therapist?

I would have loved to give a positive answer. This would mean immediate availability of this treatment to many persons living with ALS around the globe. However, the answer is not straightforward.

Each participant responds to the protocol in their own way. Ongoing in-session assessment and analysis of responses to the treatment lead to on-the-go adaptations of the protocol, individualized adjustments of not only the tempo, pitch, tonality, rhythm, but also modification, exclusion and addition of the exercises to benefit each patient, with consideration for the specifics of their disease progression and changing physical capabilities. Even though psycho-emotional support is not the goal of this treatment, emotional responses of each patient need to be attended to with empathy, tact and professional knowledge of psychodynamic process.

It is absolutely essential that the music therapist performs all the exercises and sings together with participants. The benefits are many: it models the appropriate sound production, provides the structure, encourages participants, and is helpful for finding the resonance (Figure 19). However, it is very important that the music therapist is sensitive enough to changes in participants' voice quality and fades to background at times when a participant's voice is at its best.

Figure 19. The music therapist models the appropriate sound production, illustrated also by an arm motion, whilst working with a study participant in her home

The best position for the music therapist is to be seated directly in front of the participant, on a steady chair, on the same level as the participant. This positioning allows the participant to "mirror" the music therapist's movements, breathing patterns, articulation with minimal effort, which is essential for more effective skill acquisition. If necessary, the music therapist can be seated across the table from the participant. This may be useful if staying upright presents challenge or is fatiguing for the participant.

The music therapist has to be very attentive and sensitive to the smallest changes in the quality of each patients' voice and breath sound. Such attention is crucial and helps, firstly, to prevent damage to patients' vocal cords due to straining and, secondly, to comment immediately on any vocal and breath quality improvements, providing real-time feedback and encouragement to participants. The physical therapist from ALS Moscow Centre who observed one of the sessions, at the request and with the permission of one of the participants, confirmed in a later conversation that the role of the music therapist in implementing this protocol was "essential".

Although independently developing skills acquired in therapy is strongly encouraged for the participants – with the potential for a "music therapy coaching" model (see section Independent music therapy exercise, in Chapter 11. Discussion), - this research demonstrated that the "coaching" itself takes much time and effort. It took significant time to fade verbal directions out: most participants were ready for that only by session 9. Non-verbal prompting and modeling proper breathing and vocal techniques continued to be important for most participants until the last (12th) session.

Participants made comments about how music therapy sessions structured their days and weeks, provided something to be responsible for and to look forward to. When discussing the upcoming therapy closure, one of the patients remarked that it would be difficult to follow the exercise routine without regular encouragement and supervision from the music therapist.

Capacity to attend to the immediate psycho-emotional and physical needs of the client, and to create a safe, no-pressure environment where each client is welcome to gradually learn and build up new skills, understanding aetiology and progression of human neurodegenerative diseases, awareness of recent scientific discoveries, knowledge of anatomy and physiology of respiration and voice production, capacity to adjust music accompaniment in real time as beneficial for the client – these are some of the essential competencies a certified music therapist has to own when implementing the suggested music therapy protocol.

Can this protocol be implemented by someone who is not a music therapist?

My current answer is: unlikely.

CHAPTER 8

BIOMEDICAL DATA ANALYSIS RESULTS

The primary focus of this research was on assessing the feasibility of the study protocol, specific to the clinical population of persons with early and mid-stage ALS in home environments. Relevant outcome measures were defined and extensive biomedical data to evaluate respiratory and bulbar changes were collected at multiple time points to provide a perspective on data collection in a home-based clinical trial. This process allowed to assess the choice of the measurement outcomes and provided a perspective on data collection. This information may be useful for future studies of bulbar and respiratory functions in ALS.

Only descriptive statistics were used to present and analyze the biomedical data, since, due to the small number of participants (n=7) and heterogeneity of the group, any statistical inference would be unreliable. Similar to feasibility data analysis, only the data from the seven participants who completed the study were analyzed.

TIME POINTS, PERIODS AND TRENDS

All the biomedical measurements for this study, with the exception of videofluoroscopic swallowing study, were obtained at **four time points**:

- Time point 1 = baseline (week 1),
- Time point 2 = pre-treatment (week 6),
- Time point 3 = post-treatment (week 12),
- Time point 4 = at the end of the follow-up period (week 16).

The three periods between the time points were marked as "run-in" (weeks 1-6), "treatment" (weeks 7-12), and "follow-up" (weeks 13-16) periods.

A laboratory-based videofluoroscopic swallowing study (VFSS) was conducted only at **three time points**, in order to minimize the burden for the participants, as this test required transportation to the lab. VFSS measurements were obtained at three time points:

- Time point 1 = baseline (week 1),
- Time point 2 = pre-treatment (week 6),
- Time point 3 = post-treatment (week 12).

The two periods between these time points are the same "run-in" (weeks 1-6) and "treatment" (weeks 7-12) periods, with the "follow-up" period omitted.

DATA PRESENTATION: TREND GRAPHS

Each measurement outcome is presented in two ways:

1) a table with individual measurements and group means for all available assessment time points,
2) a trend graph visualizing the relationship between group trends over all available treatment periods.

To assess the change in trends, for each of three (or two, in case of videofluoroscopic swallowing study) periods a trend was calculated as a rate of change of the measurement over time (in weeks):

$$Trend_{run\text{-}in} = (M_{t2} - M_{t1}) / 6,$$

$$Trend_{treatment} = (M_{t3} - M_{t2}) / 6,$$

$$Trend_{follow\text{-}up} = (M_{t4} - M_{t3}) / 4,$$

where M_{tn} is the measurement value at time point *n*. The lengths of “run-in” and “treatment” periods are six weeks, the “follow-up” period is four weeks (the reasons for which are explained in Chapter 3. Study aims and design, section “Control and experimental conditions”). Hence different denominators in the formulas.

The trend graphs have been rendered in R programming language using the “ggpubr” library. Graphs in Figures 20-33 and 35-48 visualize the relationship between trends over three periods: “run-in”, “treatment”, and “follow-up” (omitted for VFSS).

The horizontal axis in each graph is categorical, showing the three periods – “run-in”, “treatment”, and “follow-up”, while the vertical axis is quantitative, showing the measurement trend. Each colored dot on the graph represents a single participant’s trend in a single period, and the gray dot in each period represents the mean of all participants’ trends (i.e. the “mean trend”). Each mean dot also shows vertical brackets representing the 0.95 confidence interval.

Presenting the data in the form of trend graphs allows quick at-a-glance visual assessment. The dots located above zero represent the measurement rising (positive rate of change), while the dots located below zero represent the measurement falling (negative rate of change). The rates of change can be compared across the periods: if the “mean trend” dot in the “treatment” period is obviously higher than mean trends in the “run-in” and “follow-up” periods, it means that the measurement outcome was either rising during the “treatment” period quicker than in the other two (when the dots are above zero), or else was falling slower (when the dots are lower than zero).

For measurements where higher score corresponds to better bulbar or respiratory functioning, positive rate of change translates into improved or sustained physical functioning in respective areas. For measurements where lower score corresponds to better bulbar or respiratory functioning, negative rate of change translates into improved or sustained physical functioning in respective areas.

Line graphs for the patterns of individual and group mean biomedical outcome measurements changes can be found in Appendix W.

ANALYZING THE LONG-TERM CHANGES IN RESPIRATION

Forced Vital Capacity (FVC) (Table 13, Figure 20), **Maximal Inspiratory Pressure (MIP)** (Table 14, Figure 21), **Maximal Expiratory Pressure (MEP)** (Table 15, Figure 22) were measured at the four time points to assess long-term changes in respiration.

Mean trends for all three outcome measures suggest that the respiratory functional parameters of the study participants – persons with ALS were sustained or improved during the treatment period (see Chapter 11. Discussion, section Discussion of the biomedical data for a detailed overview).

Table 13. FVC (%) individual measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	FVC_t1	FVC_t2	FVC_t3	FVC_t4
1	76	75	89	80
2	69	83	85	79
3	121	115	113	113
4	87	83	88	72
5	63	60	61	63
6	82	73	60	64
7	84	63	62	83
Mean:	83.143	78.857	79.714	79.143

Figure 20. Relationship between FVC trends over three periods. Higher score corresponds to better functioning. Brackets denote 0.95 confidence intervals.

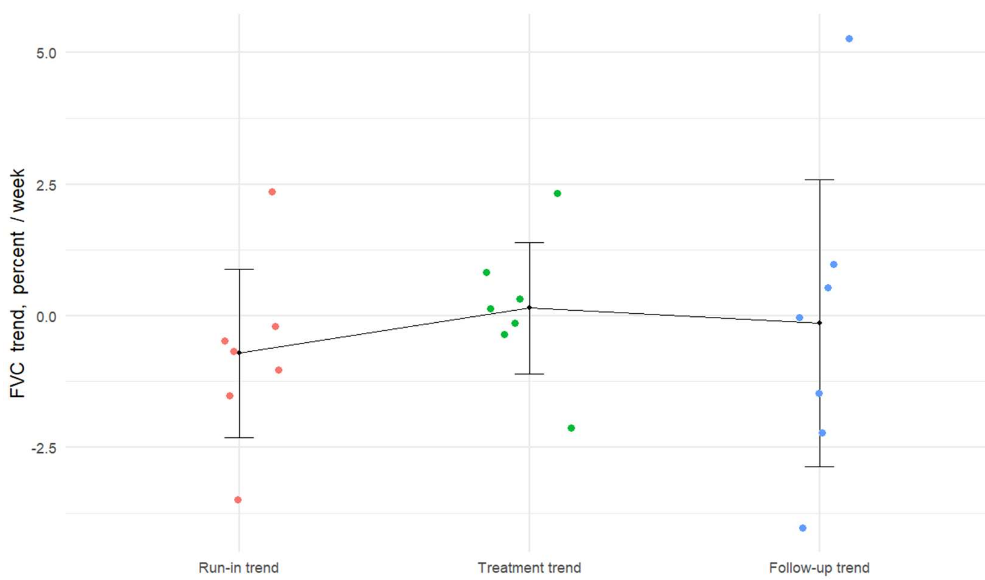


Table 14. MIP (cm H_2O) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	MIP_t1	MIP_t2	MIP_t3	MIP_t4
1	73	69	91	98
2	44	26	57	81
3	41	38	41	42
4	55	62	49	54
5	32	39	33	42
6	70	56	60	58
7	48	40	57	51
Mean:	51.857	47.143	55.429	60.857

Figure 21. Relationship between MIP trends over three periods. Higher score corresponds to better functioning. Brackets denote 0.95 confidence intervals.

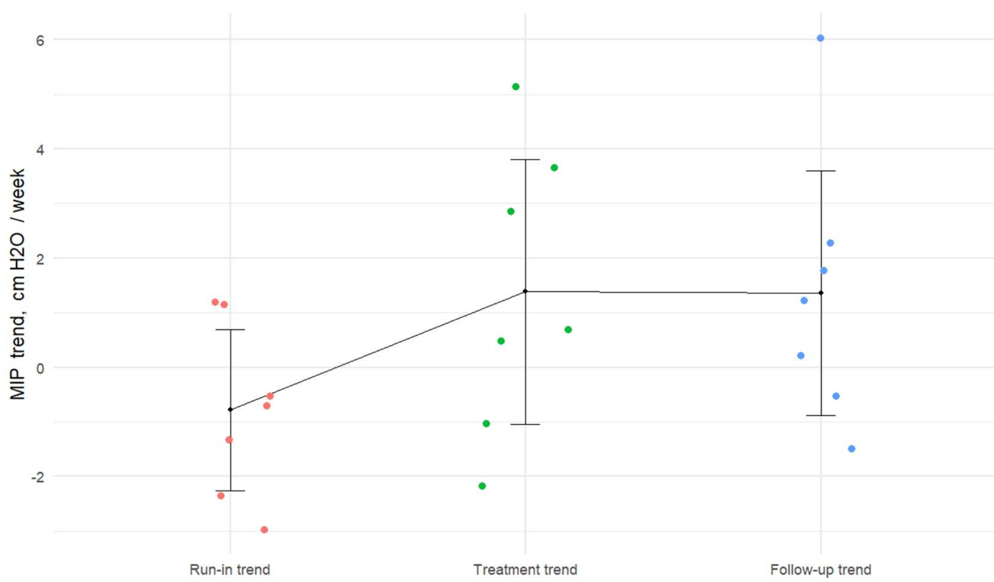
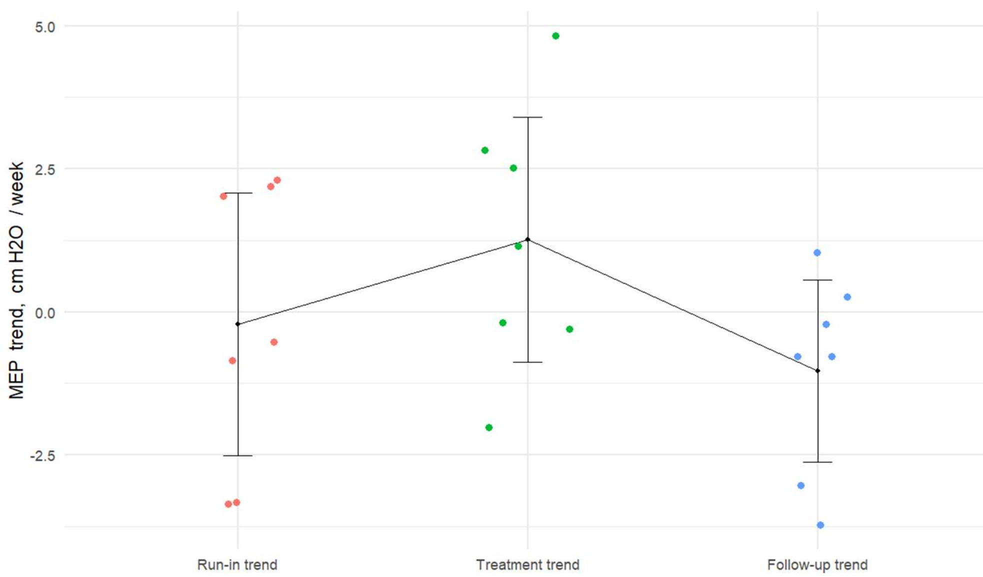


Table 15. MEP (cm H_2O) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	MEP_tp1	MEP_tp2	MEP_tp3	MEP_tp4
1	68	65	94	79
2	63	76	83	87
3	67	81	80	77
4	91	86	103	91
5	35	47	35	34
6	79	59	57	54
7	55	35	50	51
Mean:	65.429	64.143	71.714	67.571

Figure 22. Relationship between MEP trends over three periods. Higher score corresponds to better functioning. Brackets denote 0.95 confidence intervals.



ANALYZING THE LONG-TERM CHANGES IN COUGH

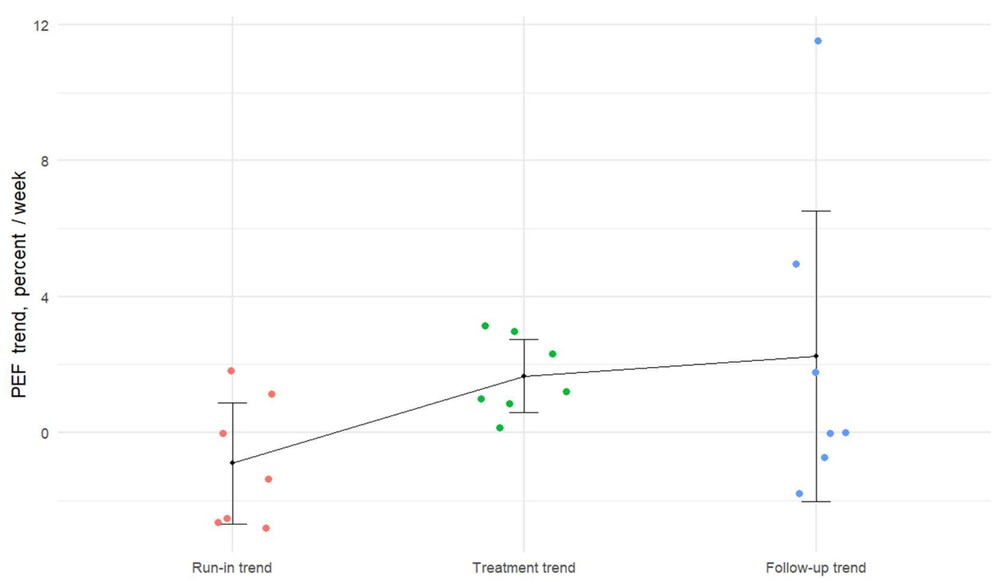
Peak Expiratory Flow (PEF) (Table 16, Figure 23) was measured at the four time points to assess long-term changes in cough.

Mean trends suggest that the cough functional parameters of the study participants – persons with ALS improved during the treatment period (see Chapter 11. Discussion, section Discussion of the biomedical data for a detailed overview).

Table 16. PEF (%) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	PCF_t1	PCF_t2	PCF_t3	PCF_t4
1	30	22	36	82
2	120	103	121	128
3	99	106	107	127
4	109	94	100	93
5	66	50	69	66
6	68	68	75	75
7	64	75	80	80
Mean:	79.429	74.000	84.000	93.000

Figure 23. Relationship between PEF trends over three periods. Higher score corresponds to better functioning. Brackets denote 0.95 confidence intervals.



ANALYZING THE LONG-TERM CHANGES IN SPEECH

Center for Neurologic Study Bulbar Function Scale (CNS-BFS) speech subscore (Table 17, Figure 24) and measurement outcomes obtained from the voice samples: **Maximum Phonation Time (MPT)** (Table 18, Figure 25), **Jitter, local** (Table 19, Figure 26), **Shimmer, local** (Table 20, Figure 27), **Harmonics-to-Noise Ratio (HNR)** (Table 21, Figure 28), **Maximum Repetition Rate – Alternating (MRR-A)** (Table 22, Figure 29), **Maximum Repetition Rate – Sequential (MRR-S)** (Table 23, Figure 30), **Vowel Space Area** (Table 24, Figure 31), **Fundamental frequency (F0)** (Table 25, Figure 32), **Speaking rate** (Table 26, Figure 33), **Speech-pause ratio (pause per minute)** (Table 27, Figure 35), **Pause frequency (number of pauses per minute)** (Table 28, Figure 36), **Hypernasality level** (Table 29 and 30, Figure 37), were calculated at the four time points to assess long-term changes in speech.

Initially two minutes of oral passage reading and two minutes of spontaneous speech were included into the list of recorded voice samples. These tasks presented no issues for most participants. However, some participants were fatigued by the two-minute oral reading, gasping for breath and reading in a quieter or strained voice by the end of the first minute. Yet some became too emotional when recording spontaneous speech, changing the subject very soon from the given neutral theme to a discussion of their disease progression or family issues, and, in some cases, tearing.

For ethical considerations, decision was made to not record spontaneous speech and to shorten the oral reading passage. The following excerpt from the phonetically representative Russian text (Smirnova and Khitrov, 2013) was used for all participants:

Дом, в котором я живу, расположен на окраине маленького городка, у самой подошвы горы. Здесь мягкий климат и редко идут дожди. Ночью небосвод бывает так густо усеян звездами, что кажется, будто все миллиарды их из нашей галактики разбросаны вверху над моей головой. Летним утром, как только я открываю окно, моя большая комната наполняется запахом *цветов. Ветки черешен смотрят мне в окна, и легкий теплый ветер усыпает мой письменный стол белыми лепестками.*

All participants needed more than 30 seconds to complete reading this passage. Fundamental frequency, speaking rate, speech-pause ratio, pause frequency, hypernasality level were calculated for oral reading voice samples only.

To calculate Speech-pause ratio and Pause frequency (the measurement parameter analyzed later in this chapter) in PRAAT speech analysis software the minimum speech threshold value was set at 100 msec and the minimum pause threshold value was set at 100 msec (Figure 34).

Perceptual analysis of the voice samples was conducted by three qualified speech pathologists, native Russia speakers, to assess change in Hypernasality level, measured in points on the scale from “1” (severe hypernasality) to “4” (normal resonance). The interrater reliability between the three raters was calculated and was low at 52% (Table 29).

Mean trends suggesting that the following speech functional parameters of the study participants – persons with ALS were sustained or improved during the treatment period: **CNS-BFS speech subscore, MPT, MRR-A, MRR-S, Jitter (local), Shimmer (local), NHR, Speaking rate, Speech-pause ratio, Pause frequency, Hypernasality level**.

Mean trends suggesting that the following speech functional parameters of the study participants – persons with ALS declined or showed slower rate of improvement during the treatment period were observed for the following outcome measures: **Fundamental frequency, VSA**.

See Chapter 11. Discussion, section Discussion of the biomedical data for a detailed overview.

Table 17. CNS-BFS speech subscore (points) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	CNSBFSsp_t1	CNSBFSsp_t2	CNSBFSsp_t3	CNSBFSsp_t4
1	18	16	14	14
2	8	13	8	10
3	8	10	10	9
4	8	7	10	9
5	24	27	24	29
6	12	13	15	16
7	10	9	9	9
Mean:	12.571	13.571	12.857	13.714

Figure 24. Relationship between CNS-BFS speech subscore trends over three periods. Lower score corresponds to better functioning. Brackets denote 0.95 confidence intervals.

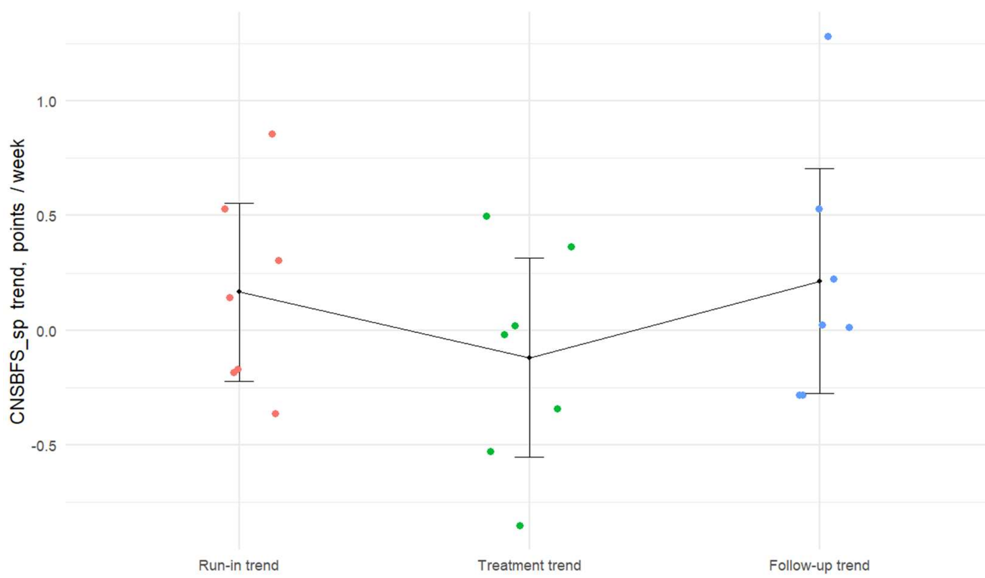


Table 18. MPT (seconds) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning

Participant	MPT_t1	MPT_t2	MPT_t3	MPT_t4
1	15.96	4.66	12.23	6.95
2	19.66	4.62	13.46	8.14
3	8.52	7.13	6.25	8.13
4	11.84	15.7	14.48	11.51
5	6.68	8.48	9.26	9.48
6	17.1	15.3	22.37	18.04
7	3.61	4.34	7.4	3.71
Mean:	11.910	8.604	12.207	9.423

Figure 25. Relationship between MPT trends over three periods. Brackets denote 0.95 confidence intervals.

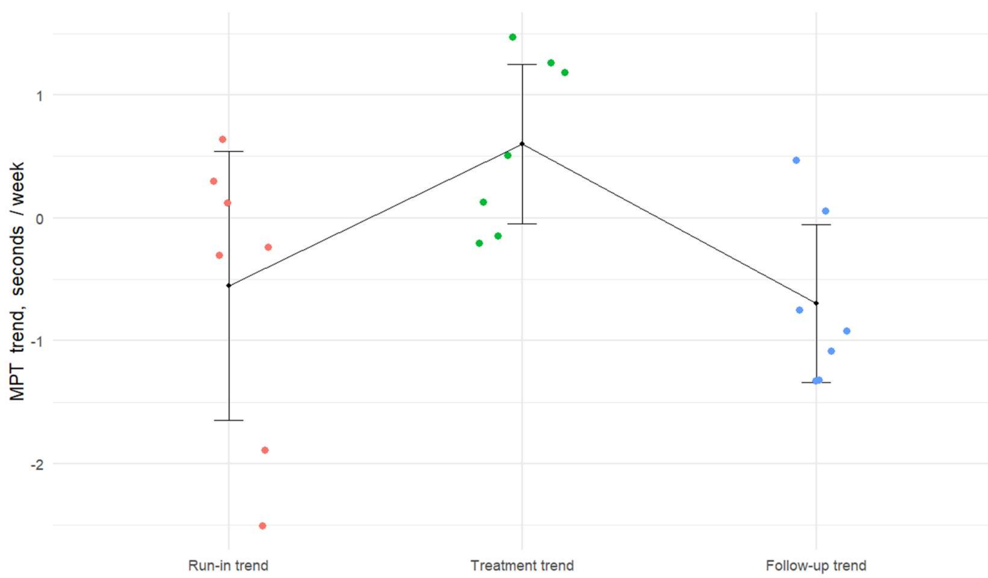


Table 19. Jitter (local, %) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	Jitter_t1	Jitter_t2	Jitter_t3	Jitter_t4
1	0.431	0.302	0.172	0.376
2	0.318	0.609	0.187	0.519
3	0.371	0.377	0.547	0.378
4	0.46	0.701	0.254	0.356
5	0.308	0.366	0.33	0.314
6	0.422	0.597	0.389	0.497
7	0.537	0.306	0.512	0.436
Mean:	0.407	0.465	0.342	0.411

Figure 26. Relationship between Jitter, local, trends over three periods. Brackets denote 0.95 confidence intervals.

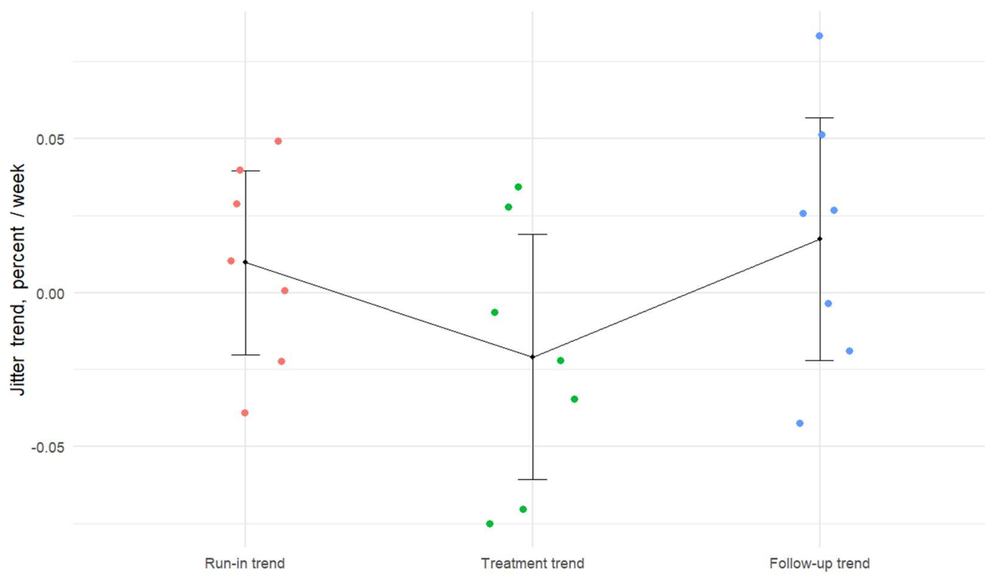


Table 20. Shimmer (local, %) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	Shimmer_t1	Shimmer_t2	Shimmer_t3	Shimmer_t4
1	2.252	3.479	1.031	2.755
2	5.784	3.994	1.275	5.758
3	2.994	2.68	4.526	2.827
4	3.553	3.262	3.225	6.961
5	1.983	2.505	1.285	2.034
6	3.799	8.194	5.643	8.031
7	4.133	2.326	5.545	2.386
Mean:	3.500	3.777	3.219	4.393

Figure 27. Relationship between Shimmer, local, trends over three periods. Brackets denote 0.95 confidence intervals.

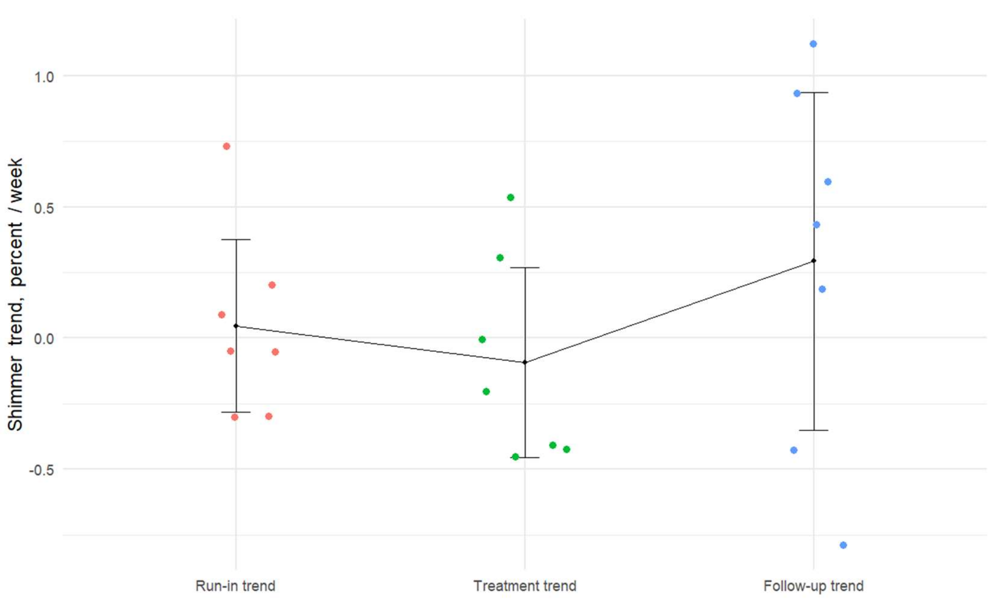


Table 21. HNR (Db) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	NHR_t1	NHR_t2	NHR_t3	NHR_t4
1	18.454	21.141	25.74	21.167
2	21.138	19.715	30.726	18.556
3	20.314	22.39	18.359	19.493
4	20.223	22.081	21.812	17.79
5	23.402	25.091	25.499	23.161
6	20.667	15.408	18.941	15.251
7	18.395	21.538	19.413	20.543
Mean:	20.370	21.052	22.927	19.423

Figure 28. Relationship between HNR trends over three periods. Brackets denote 0.95 confidence intervals.

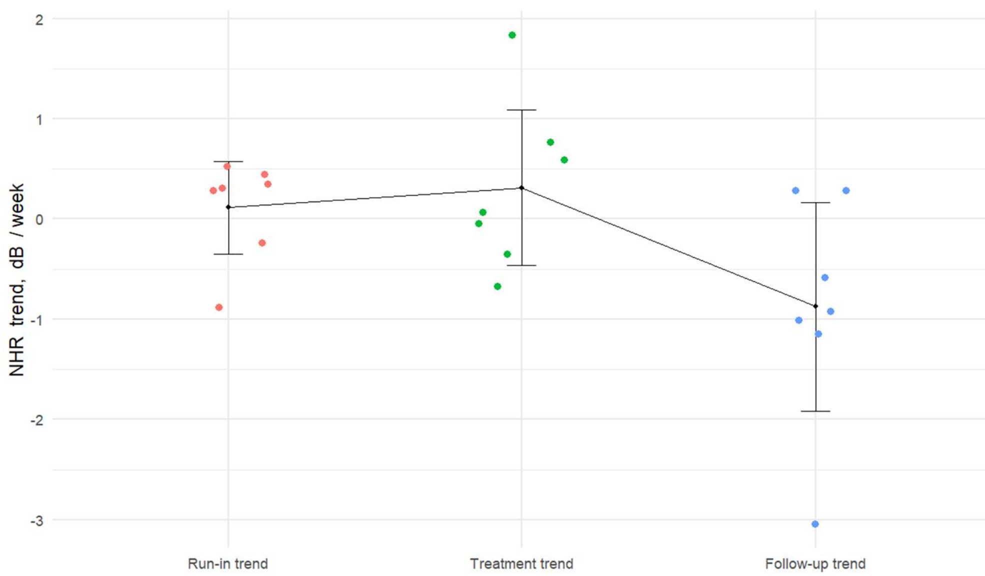


Table 22. MRR-A (syllables, total) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	MRR-A_t1	MRR-A_t2	MRR-A_t3	MRR-A_t4
1	33	33	54	43
2	171	69	108	60
3	108	102	126	93
4	48	87	117	170
5	12	3	21	15
6	66	51	45	45
7	36	30	45	36
Mean:	67.714	53.571	73.714	66.000

Figure 29. Relationship between MRR-A trends over three periods. Brackets denote 0.95 confidence intervals.

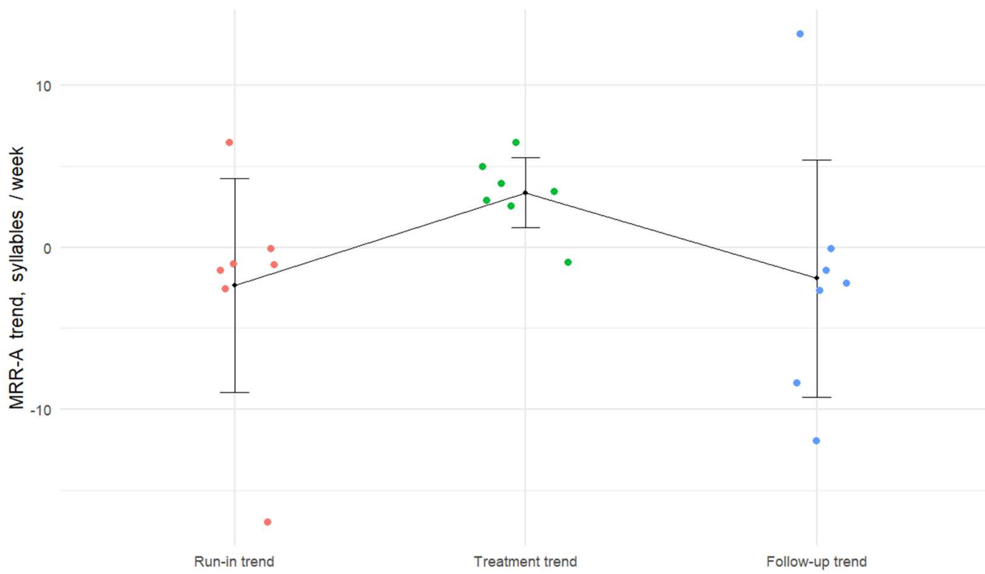


Table 23. MRR-S (syllables, total) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	MRR-S_t1	MRR-S_t2	MRR-S_t3	MRR-S_t4
1	32	29	29	30
2	77	27	81	57
3	89	91	105	101
4	44	20	92	86
5	11	13	21	14
6	39	48	43	47
7	13	16	45	27
Mean:	43.571	34.857	59.429	51.714

Figure 30. MRR-S trends over three periods. Brackets denote 0.95 confidence intervals.

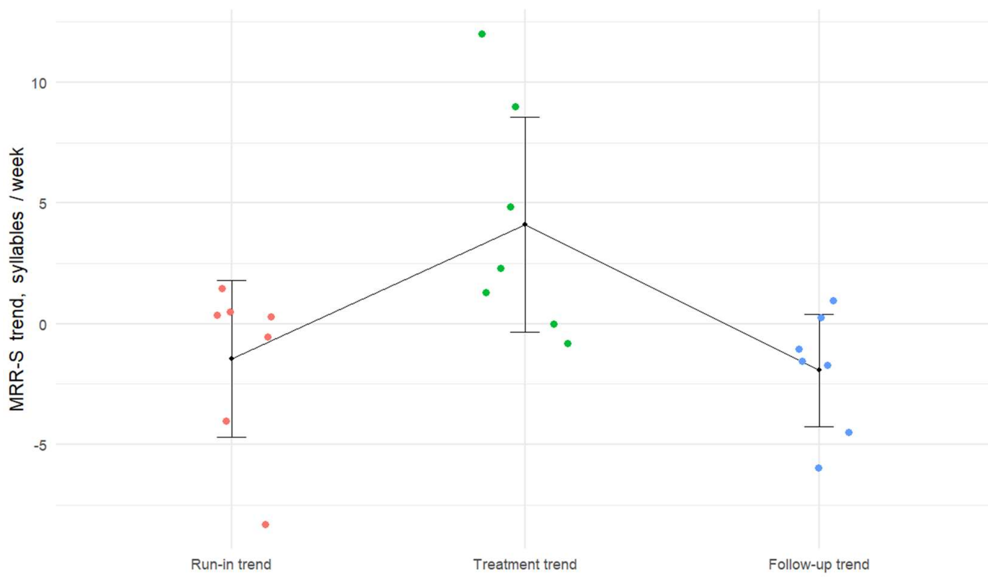


Table 24. VSA (Hertz, squared) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	VSA_t1	VSA_t2	VSA_t3	VSA_t4
1	335474	383408.5	293932.5	399866.5
2	194705	689702.5	615575	774734.5
3	435659	478926.5	394459	422385
4	422040.5	469824.5	479047.5	431202
5	287983.5	116180	340084.5	398212
6	208821	226215	190827	199621
7	430167	242673.5	433381	309478
Mean:	330692.9	372418.6	392472.4	419357.0

Figure 31. Relationship between VSA trends over three periods. Brackets denote 0.95 confidence intervals.

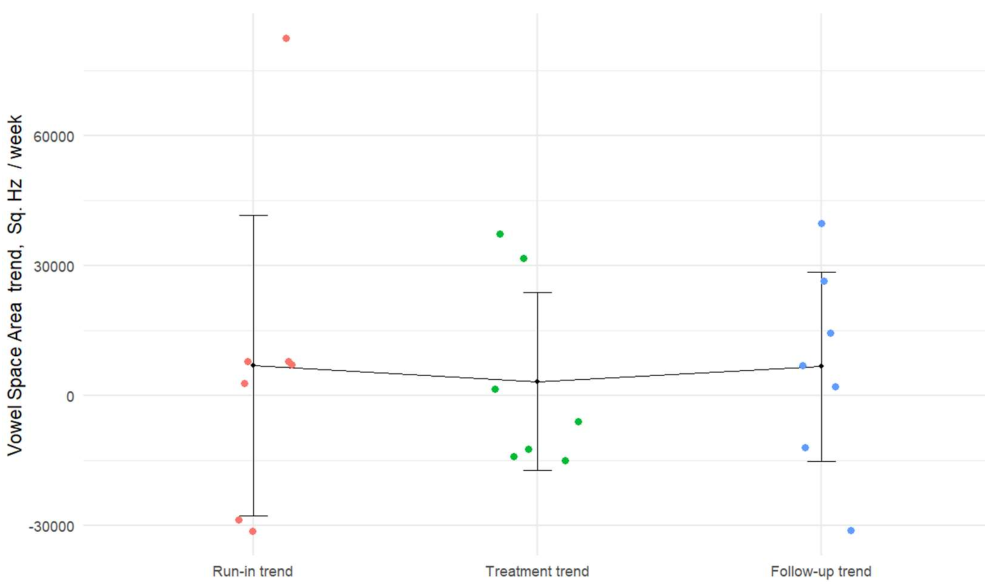


Table 25. Fundamental frequency (Hz) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	Freq_t1	Freq_t2	Freq_t3	Freq_t4
1	162.2	161.8	162.6	179.9
2	232.6	243	231.2	234.9
3	161.1	156.2	177	176.5
4	127.2	129.3	145.7	130.6
5	228.7	224.6	212.8	213.3
6	120.3	143.8	139.4	157.4
7	193.7	194.5	196.2	187.5
Mean:	175.114	179.029	180.700	182.871

Figure 32. Relationship between Fundamental frequency trends over three periods. Brackets denote 0.95 confidence intervals.

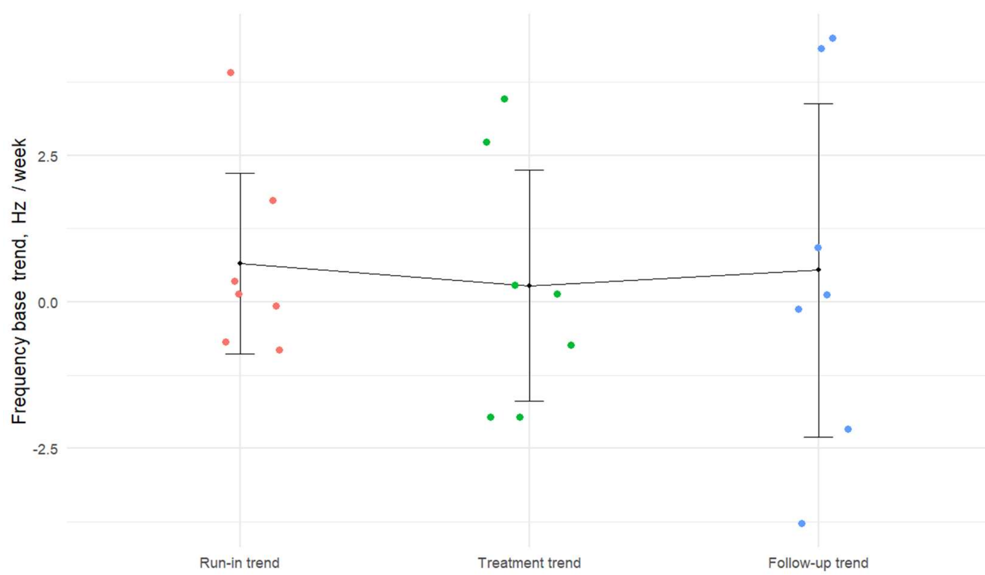


Table 26. Speaking rate (words per minute) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	SR_t1	SR_t2	SR_t3	SR_t4
1	68	60	72	72
2	130	142	136	136
3	138	110	130	114
4	98	106	110	110
5	72	62	52	54
6	84	74	76	76
7	98	76	88	88
Mean:	98.286	90.000	94.857	92.857

Figure 33. Relationship between Speaking rate trends over three periods. Brackets denote 0.95 confidence intervals.

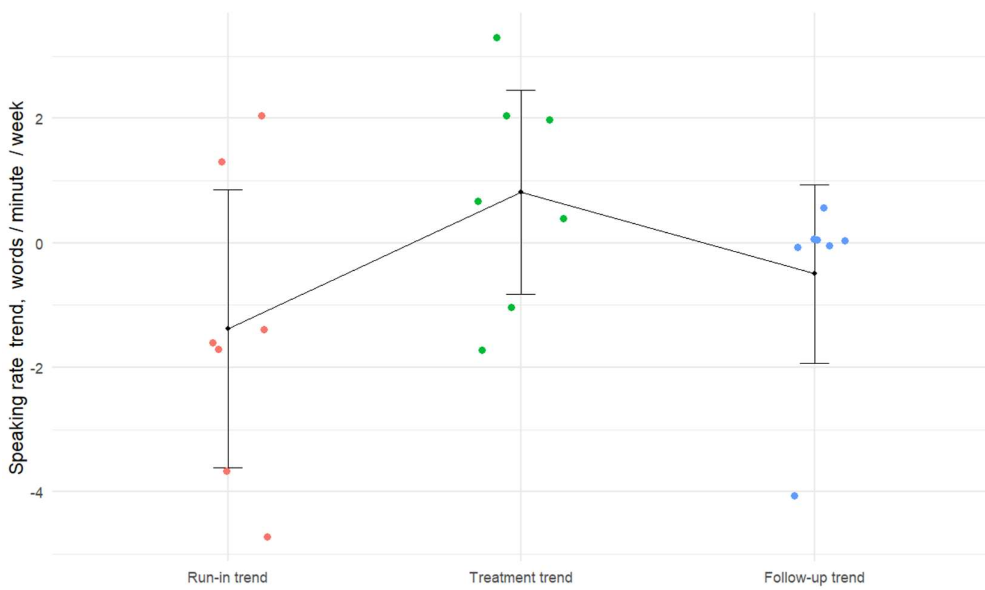


Figure 34. PRAAT parameters for Speech-pause ratio analysis and Pause frequency analysis

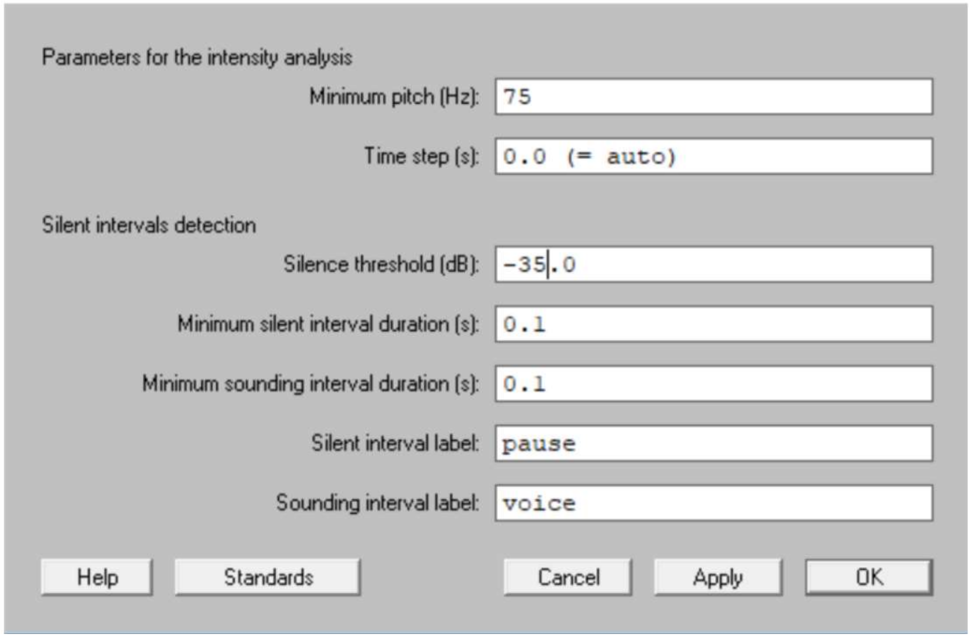


Table 27. Speech-pause ratio (seconds per minute) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	SPAt_t1	SPAt_t2	SPAt_t3	SPAt_t4
1	21	26	17	14
2	9	8	10	10
3	3	8	4	5
4	13	13	11	10
5	15	18	17	15
6	11	11	8	8
7	10	15	12	13
Mean:	11.714	14.143	11.286	10.714

Figure 35. Relationship between Speech-pause ratio trends over three periods. Brackets denote 0.95 confidence intervals.

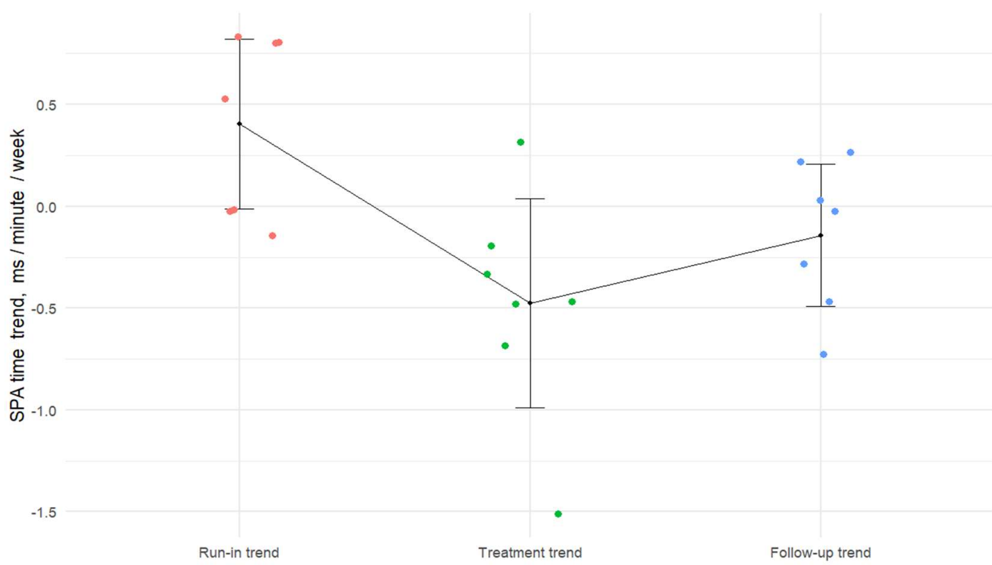


Table 28. Pause frequency (total, per minute) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	SPAq_t1	SPAq_t2	SPAq_t3	SPAq_t4
1	44	54	38	38
2	14	14	18	14
3	10	12	10	12
4	26	24	20	18
5	48	48	50	46
6	16	14	12	16
7	30	34	28	26
Mean:	26.857	28.571	25.143	24.286

Figure 36. Relationship between Pause frequency trends over three periods. Brackets denote 0.95 confidence intervals.

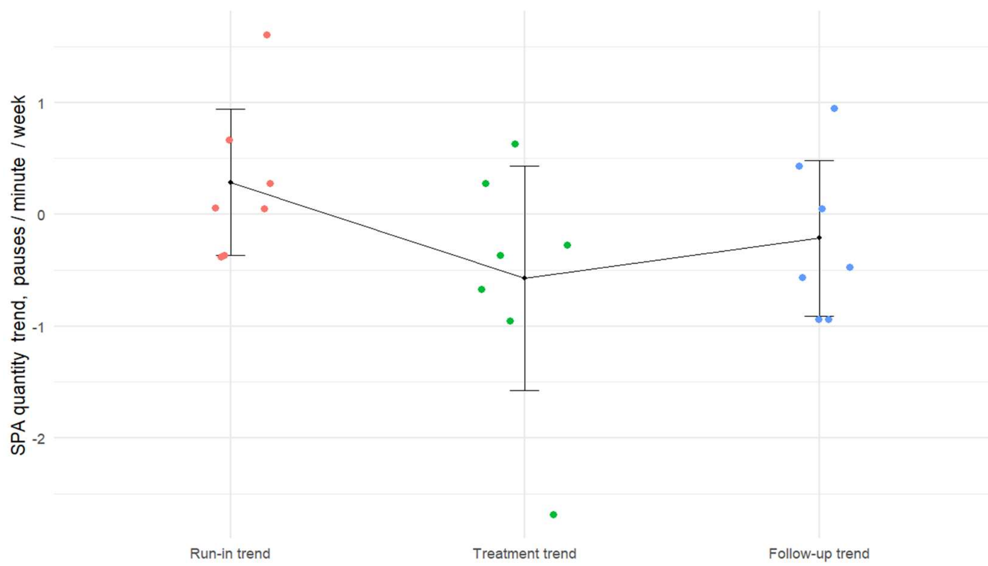


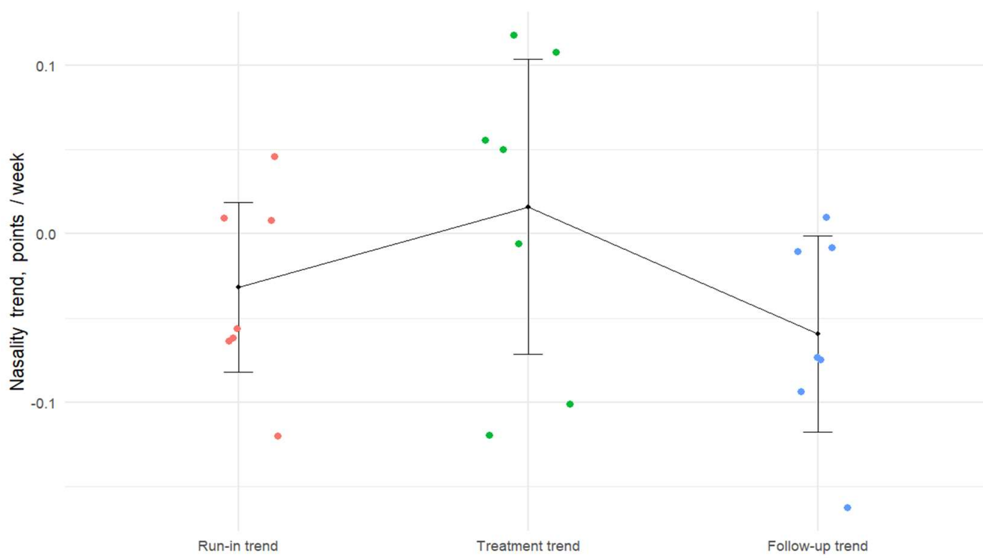
Table 29. Individual rater results and interrater agreement for Hypernasality level (points)

	Rater 1	Rater 2	Rater 3	R1/R2	R2/R3	R1/R3	Agreement
Pt 1 tp 1	1	2	1	0	0	1	0.33
Pt 1 tp 2	1	2	2	0	1	0	0.33
Pt 1 tp 3	2	3	2	0	0	1	0.33
Pt 1 tp 4	2	2	2	1	1	1	1.00
Pt 2 tp 1	4	4	4	1	1	1	1.00
Pt 2 tp 2	4	4	4	1	1	1	1.00
Pt 2 tp 3	4	4	4	1	1	1	1.00
Pt 2 tp 4	4	4	4	1	1	1	1.00
Pt 3 tp 1	4	4	3	1	0	0	0.33
Pt 3 tp 2	3	4	2	0	0	0	0.00
Pt 3 tp 3	3	4	3	0	0	1	0.33
Pt 3 tp 4	3	4	3	0	0	1	0.33
Pt 4 tp 1	4	4	4	1	1	1	1.00
Pt 4 tp 2	4	4	3	1	0	0	0.33
Pt 4 tp 3	4	4	4	1	1	1	1.00
Pt 4 tp 4	4	4	3	1	0	0	0.33
Pt 5 tp 1	2	2	1	1	0	0	0.33
Pt 5 tp 2	2	2	1	1	0	0	0.33
Pt 5 tp 3	1	1	1	1	1	1	1.00
Pt 5 tp 4	1	1	1	1	1	1	1.00
Pt 6 tp 1	3	4	2	0	0	0	0.00
Pt 6 tp 2	2	4	2	0	0	1	0.33
Pt 6 tp 3	1	3	2	0	0	0	0.00
Pt 6 tp 4	1	3	2	0	0	0	0.00
Pt 7 tp 1	3	3	2	1	0	0	0.33
Pt 7 tp 2	2	3	2	0	0	1	0.33
Pt 7 tp 3	3	3	3	1	1	1	1.00
Pt 7 tp 4	2	3	2	0	0	1	0.33

Table 30. Hypernasality level (points) individual and mean measurements at four assessment time points. Higher score corresponds to better functioning.

Participant	Nasality_tp1	Nasality_tp2	Nasality_tp3	Nasality_tp4
1	1.33	1.67	2.33	2.00
2	4.00	4.00	4.00	3.67
3	3.67	3.00	3.33	3.33
4	4.00	3.67	4.00	3.67
5	1.67	1.67	1.00	1.00
6	3.00	2.67	2.00	2.00
7	2.67	2.33	3.00	2.33
Mean:	2.905	2.714	2.810	2.571

Figure 37. Relationship between Hypernasality score trends over three periods. Brackets denote 0.95 confidence intervals.



ANALYZING THE LONG-TERM CHANGES IN SWALLOWING

Center for Neurologic Study Bulbar Function Scale (CNS-BFS) swallowing subscore (Table 31, Figure 38), recorded at the four time points, and measurement outcomes obtained from videofluoroscopic swallowing study (VFSS) video clips, recorded at three time points (see Chapter 8. Biomedical data analysis results, section Time points, periods and trends): **Time-to-Laryngeal Vestibule Closure (LVCrt), nectar 10 mL** (Table 32, Figure 39), **Time-to-Laryngeal Vestibule Closure (LVCrt), pudding 10 mL** (Table 33, Figure 40), **Maximum Pharyngeal Constriction Area (MPCAn), nectar 10 mL** (Table 34, Figure 41), **Maximum Pharyngeal Constriction Area (MPCAn), pudding 10 mL** (Table 35, Figure 42), **Peak position of the Hyoid Bone (PeakXY), nectar 10 mL** (Table 36, Figure 43), **Peak position of the Hyoid Bone (PeakXY), pudding 10 mL** (Table 37, Figure 44), **Penetration-Aspiration Scale Score (PAS) (worst), nectar 10 mL** (Table 38, Figure 45), **Penetration-Aspiration Scale Score (PAS) (worst), pudding 10 mL** (Table 39, Figure 46), **Total Pharyngeal Residue C24area (totC24), nectar 10 mL** (Table 40, Figure 47), **Total Pharyngeal Residue C24area (totC24), pudding 10 mL** (Table 41, Figure 48), **Laryngeal vestibule closure (LVC), nectar 10 mL** (Table 42), **Laryngeal vestibule closure (LVC), pudding 10 mL** (Table 43), were used to assess long-term changes in swallowing.

Mean trends suggesting that the following swallowing functional parameters of the study participants – persons with ALS were sustained or improved during the treatment period: **CNS-BFS swallowing subscore, LVCrt nectar, LVCrt pudding, MPCAn nectar, MPCAn pudding, PeakXY nectar, PeakXY pudding, totC24 nectar, totC24 pudding**.

Mean trends suggesting that the following swallowing functional parameters of the study participants – persons with ALS declined or showed slower rate of improvement during the treatment period were observed for the following outcome measures: **PAS nectar, PAS pudding**.

The results of the analysis were compromised because some VFSS data was missong due to a laboratory technical error (see section Missing VFSS data at the end of this chapter). See Chapter 11. Discussion, section Discussion of the biomedical data for a detailed overview and the implications for future studies.

Table 31. CNS-BFS swallowing subscore (points) individual and mean measurements at four assessment time points. Lower score corresponds to better functioning.

Participant	CNSBFSsw_t1	CNSBFSsw_t2	CNSBFSsw_t3	CNSBFSsw_t4
1	9	7	8	8
2	11	13	10	10
3	11	14	8	7
4	13	12	10	13
5	16	19	18	19
6	13	16	14	20
7	12	12	12	12
Mean:	12.143	13.286	11.429	12.714

Figure 38. Relationship between CNS-BFS swallowing subscore trends over three periods. Brackets denote 0.95 confidence intervals.

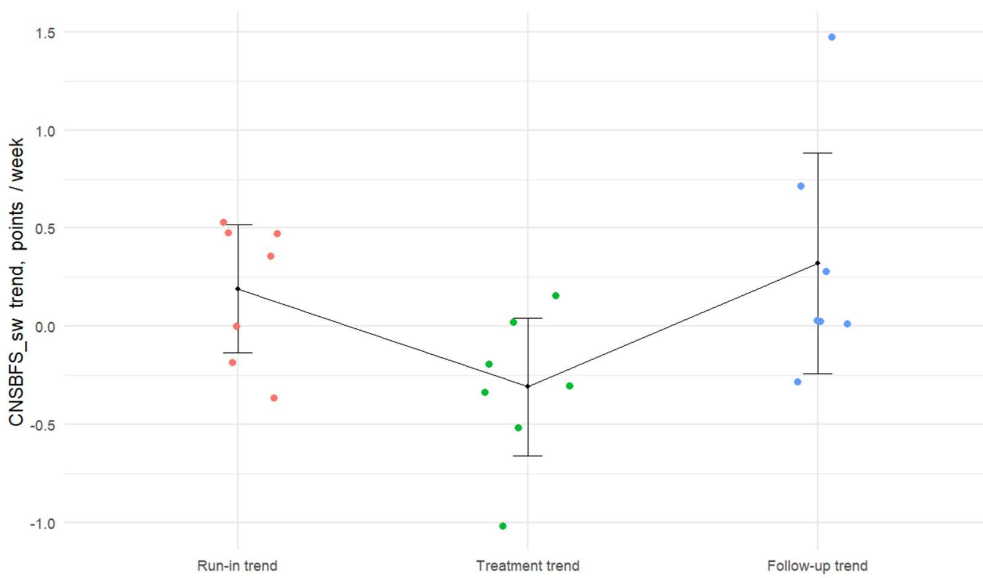


Table 32. LVCrt, nectar 10 mL (ms) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	LVCrtn_t1	LVCrtn_t2	LVCrtn_t3
2	360	400	240
3	240	160	240
4	240	280	280
5	600	440	440
6	440	400	160
Mean	376	336	272

Figure 39. Relationship between LVCrt, nectar 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

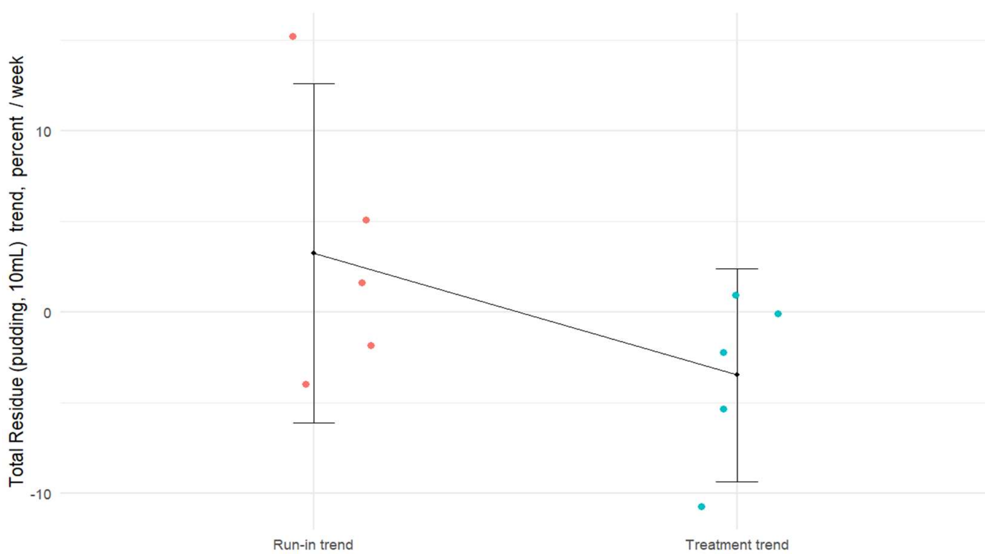


Table 33. LVCrt, pudding 10 mL (ms) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	LVCrtp_t1	LVCrtp_t2	LVCrtp_t3
2	400	240	240
3	360	360	240
4	200	240	120
5	640	360	400
6	280	440	320
Mean	376	328	264

Figure 40. Relationship between LVCrt, pudding 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

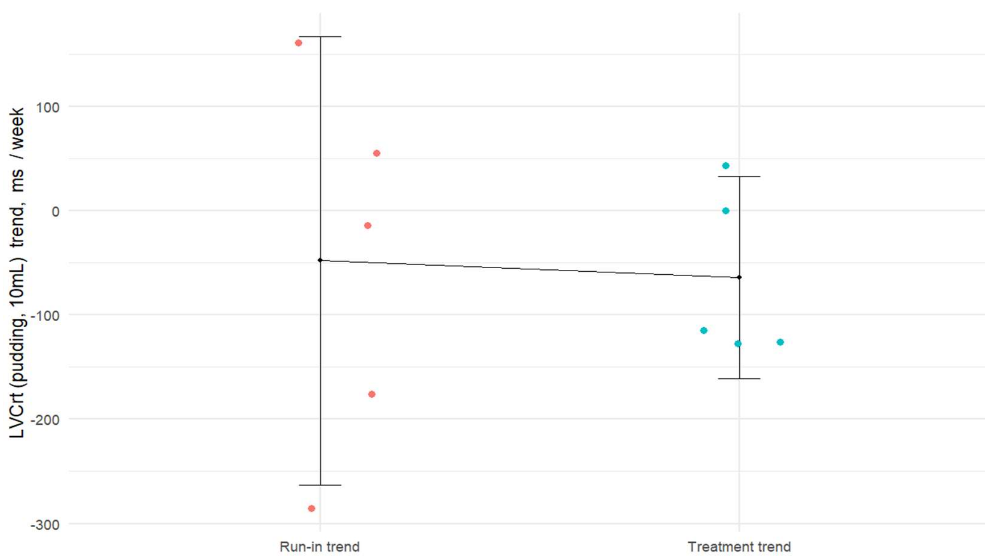


Table 34. MPCAn, nectar 10 mL (% C2-4^2) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	MPCAnn_t1	MPCAnn_t2	MPCAnn_t3
2	3.40941758	10.13944761	2.543253
3	2.9455915	5.710712639	7.754257
4	3.51707662	5.445806512	2.597211
5	9.64075675	6.663143871	3.893648
6	11.639785	14.51433228	15.84521
Mean	6.23052549	8.494688581	6.526715

Figure 41. Relationship between MPCAn, nectar 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

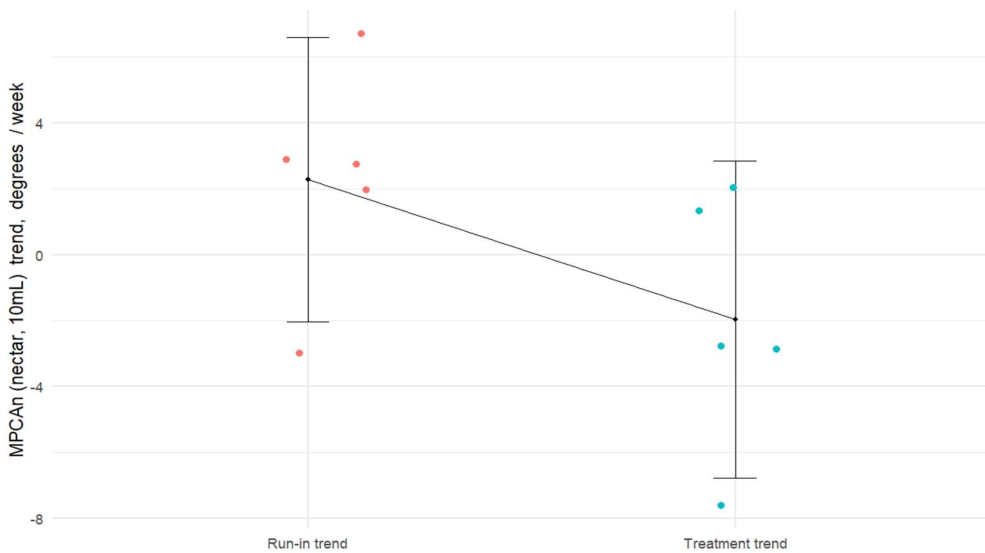


Table 35. MPCAn, pudding 10 mL (% C2-4[2]) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	MPCAnp_t1	MPCAnp_t2	MPCAnp_t3
2	3.079057604	4.330900777	4.025907331
3	4.67484866	7.200453733	6.510919871
4	5.433459744	8.731734229	3.957121688
5	7.909192227	10.0939909	6.568875036
6	16.31579166	40.65572656	33.12445659
Mean	7.482469979	14.20256124	10.8374561

Figure 42. Relationship between MPCAn, pudding 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

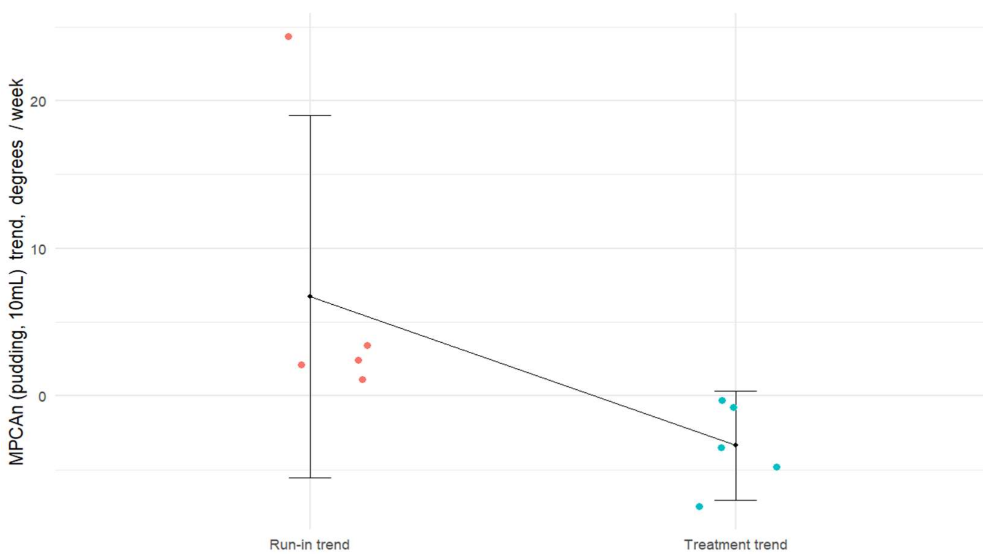


Table 36. PeakXY, nectar 10 mL (% C2-4) individual and mean measurements at three assessment time points. Higher score corresponds to better functioning.

Participant	PeakXYn_t1	PeakXYn_t2	PeakXYn_t3
2	149.1	152.3	156.9
3	150.9	141.2	145.5
4	180.6	184.3	183.9
5	140.9	148	146.2
6	163.9	160.6	160.5
Mean	157.08	157.28	158.6

Figure 43. Relationship between PeakXY, nectar 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

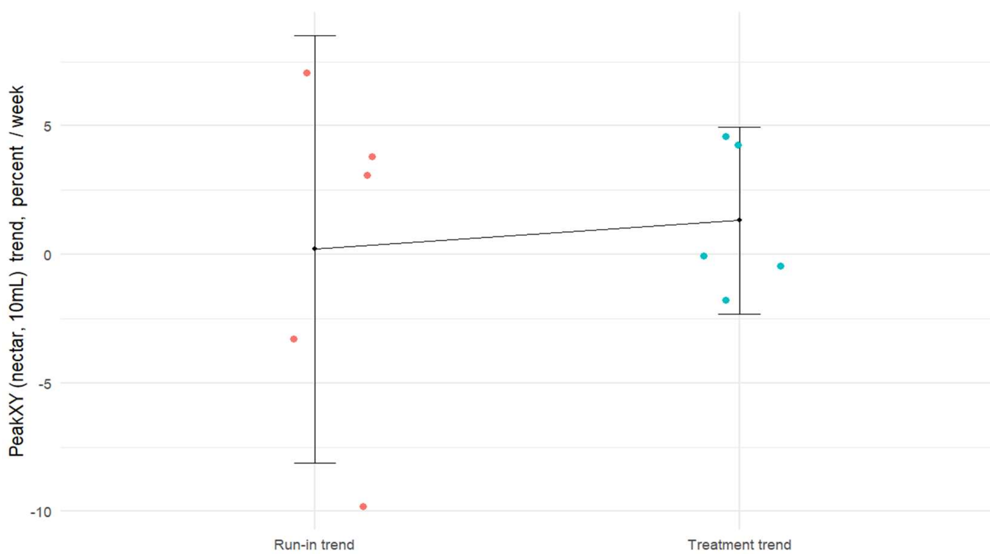


Table 37. PeakXY, pudding 10 mL (% C2-4) individual and mean measurements at three assessment time points. Higher score corresponds to better functioning.

Participant	PeakXYp_t1	PeakXYp_t2	PeakXYp_t3
2	151.5	145.9	149.7
3	148.9	151.1	148.7
4	196.2	181.8	199.9
5	145.3	152.1	148.2
6	172	148.7	165.2
Mean	162.78	155.92	162.34

Figure 44. Relationship between PeakXY, pudding 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

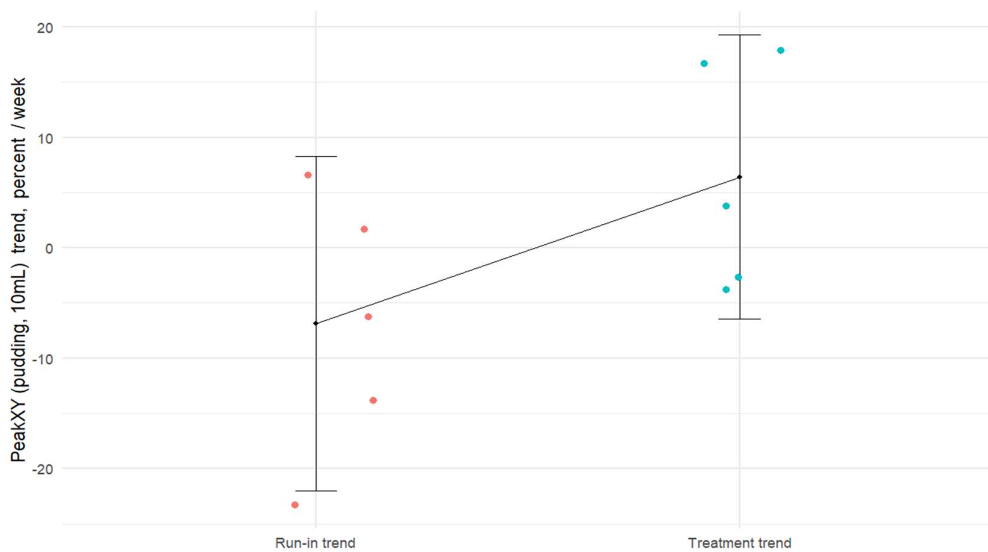


Table 38. PAS (worst), nectar 10 mL (points) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	PASn_t1	PASn_t2	PASn_t3
2	1	1	5
3	1	1	2
4	1	1	2
5	2	6	5
6	1	1	1
Mean	1.2	2	3

Figure 45. Relationship between PAS (worst), nectar 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

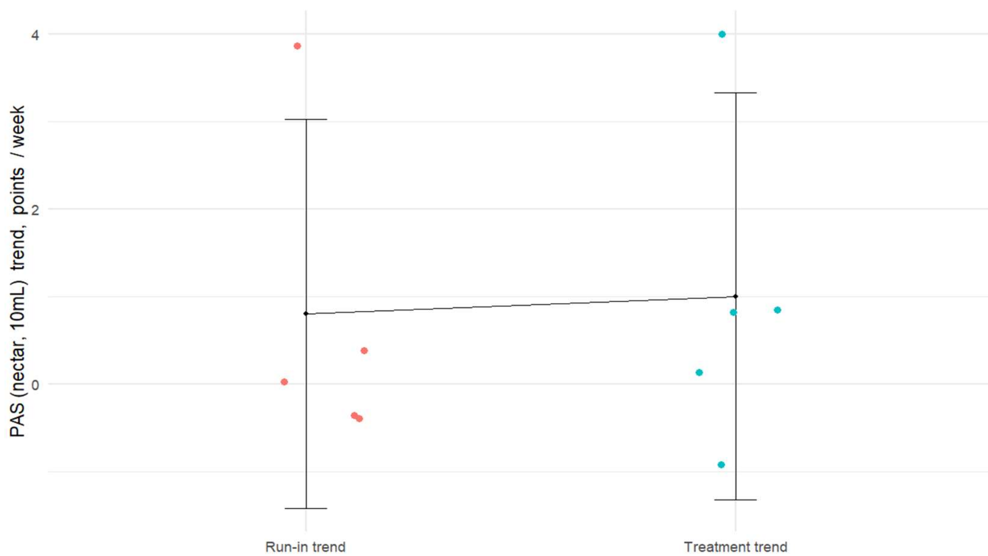


Table 39. PAS (worst), pudding 10 mL (points) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	PASp_t1	PASp_t2	PASp_t3
2	5	1	1
3	1	2	2
4	1	1	1
5	1	5	3
6	1	1	3
Mean	1.8	2	2

Figure 46. Relationship between PAS (worst), pudding 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

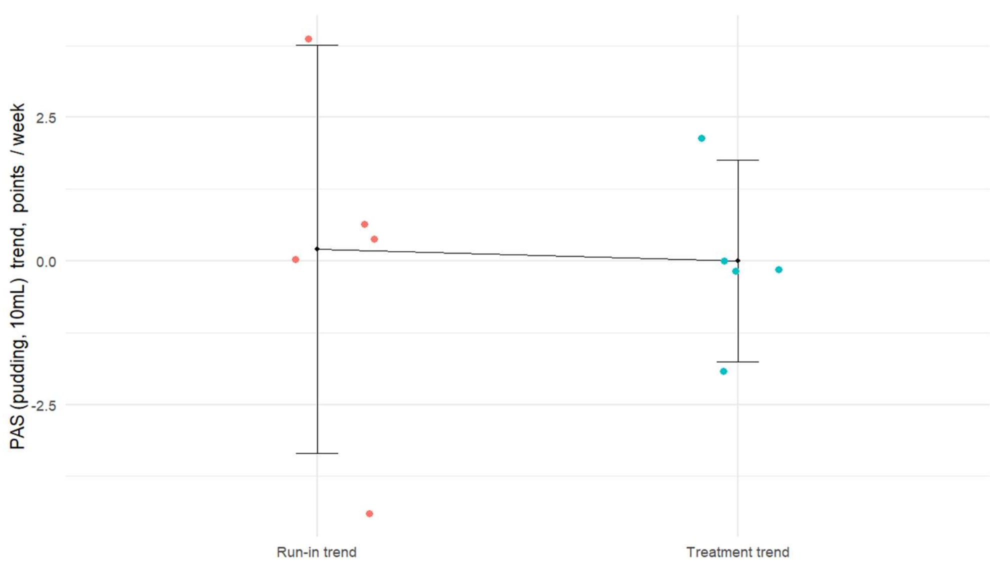


Table 40. TotC24, nectar 10 mL (% C2-4) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	totC24n_t1	totC24n_t2	totC24n_t3
2	1.5114466	6.719501338	1.381531396
3	1.4108957	3.142448902	4.130194898
4	4.8939937	2.953970978	2.907582467
5	8.1621392	4.232066181	1.982200267
6	13.582741	28.79061578	18.01529424
Mean	5.9122432	9.167720635	5.683360654

Figure 47. Relationship between totC24, nectar 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

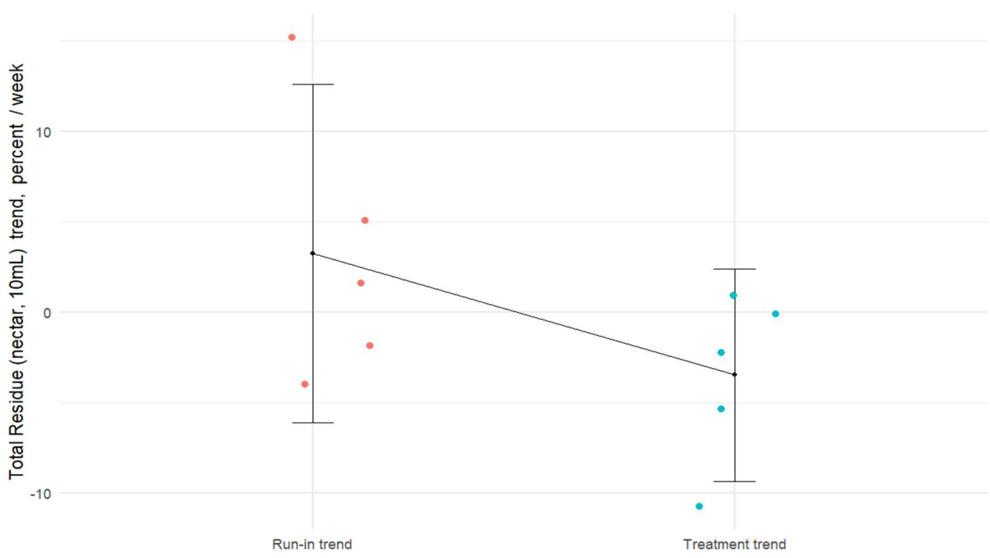


Table 41. TotC24, pudding 10 mL (% C2-4) individual and mean measurements at three assessment time points. Lower score corresponds to better functioning.

Participant	totC24p_t1	totC24p_t2	totC24p_t3
2	1.67565221	4.61141829	3.509672232
3	6.00775756	8.55609461	5.723845175
4	2.91294337	7.47843618	3.484580659
5	3.55738697	6.66928515	4.553890179
6	17.9090241	45.1455462	21.13985385
Mean	6.41255284	14.4921561	7.682368419

Figure 48. Relationship between totC24, pudding 10 mL, trends over two periods. Brackets denote 0.95 confidence intervals.

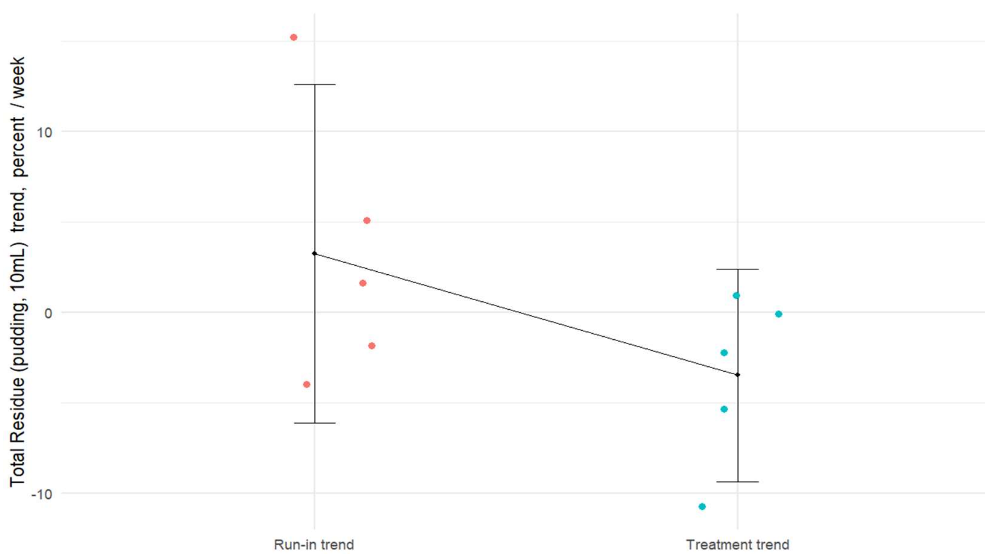


Table 42. LVC, nectar 10 mL, individual descriptions at three assessment time points. LVC described as “complete” corresponds to a safe swallow.

Participant	LVCn_t1	LVCn_t2	LVCn_t3
2	partial	complete	partial
3	complete	complete	complete
4	compete	complete	complete
5	partial	complete	partial
6	complete	complete	complete

Table 43. LVC, pudding 10 mL, individual descriptions at three assessment time points. LVC described as “complete” corresponds to a safe swallow.

Participant	LVCp_t1	LVCp_t2	LVCp_t3
2	partial	complete	partial
3	complete	complete	complete
4	complete	complete	complete
5	complete	partial	partial
6	complete	complete	complete

Missing VFSS data

Although all participants who completed the study made all three visits to the laboratory for videofluoroscopic swallowing study (VFSS) and followed the protocol described in the section Outcome measures to assess long-term changes in swallowing (Chapter 4), consistent data from all three time points is only available for five participants, for two samples (nectar and pudding). The data is missing due to a mistake in video capturing: some clips were only recorded by an external video camera, but not by the built-in Medical DVD recorded of the BV Pulsera Mobile C-arm fluoroscope. Quality of the video from the external camera was sufficient for descriptive clinical swallowing assessment by a speech language specialist, but too poor for the calculations used in this study to take place. For the participants with the missing high-quality video recordings, no VFSS data was analyzed. No VFSS data was analyzed for liquid samples.

All the participants still benefited from free VFSS assessments: qualified speech-language specialist explained the results to all the participants and provided relevant clinical advice regarding their current state, prognosis and care.

Implications for future studies are discussed at Chapter 11. Discussion, section Resources limitations.

CHAPTER 9

SUMMARY OF DATA ANALYSIS RESULTS

SUMMARY OF FEASIBILITY DATA ANALYSIS RESULTS

Primary data analysis provides first evidence that it is feasible to use the suggested study protocol for home-based music therapy as an intervention to support respiratory and bulbar function in early and mid-stage ALS. Recruitment rate (100%), retention rate (87.5%) and mean adherence (95.4%) were above the suggested markers for the protocol feasibility.

Data on short-term tolerability of the treatment protocol indicated that the protocol was generally well tolerated by the study participants, with the overall trends pointing upwards for both Ease of Respiration Numerical Rating Scale (p-value = 0.296) or Ease of Speech Numerical Rating Scale (p-value = 0.270), even though, as expected in a small study with only seven subjects, neither change was statistically significant.

Mean adherence to suggested independent exercise routine constituted 53%. It is indicative that all the participants attempted the independent exercise routine. Common reasons for not engaging into the independent practice routine included: not feeling well (e.g. due to high blood pressure, menses), being too busy to exercise (due to work, healthcare or other commitments), being too tired to exercise. No participants mentioned the provided individual set of exercises being too challenging among the reasons for not engaging into independent practice routine.

As assessed through interviews with the participants – persons with ALS before treatment, the music therapy process was anticipated by some participants as challenging and requiring additional effort, but most participants were motivated to actively engage in music therapy treatment. Most anticipated music therapy to have a positive effect on their bulbar and/or respiratory functions, as well as on their psychological state. Some participants anticipated increased communication and/or decreased isolation and improved relationships with other family members as a result of the treatment. After the treatment phase, most participants reported being able to self-monitor their progress, whilst being moderately challenged by the music therapy experience. All participants reported music therapy to be a pleasurable experience and perceived the suggested independent music therapy exercises as easy to perform. Most persons with ALS reported being motivated to continue performing independent music therapy exercises after the treatment ended. Most participants believed that music therapy was beneficial for their speech and respiration and that it helped them learn new breathing and vocal skills, but did not affect their swallowing. Some participants perceived that music therapy improved their communication.

Most caregivers anticipated music therapy to consist of exercises which would have a beneficial effect on the bulbar and/or respiratory functions of participants with ALS, and to benefit the psychological state of the person with ALS, mostly by providing additional opportunities for communication during music therapy. Most caregivers anticipated participation of their family members affected by ALS in music therapy to have a positive effect on the caregiver's own psychological state. After treatment, most caregivers reported that music therapy improved or sustained bulbar and respiratory functions of the participant with ALS. Some caregivers reported that music therapy process and, in particular, communication with the music therapist had a positive effect on the psychological state of the participant with ALS, and that participation of their family members affected by ALS in music therapy had a positive effect on caregiver's own psychological state.

SUMMARY OF BIOMEDICAL DATA ANALYSIS RESULTS

Although most mean trends in biomedical data suggest that the bulbar and respiratory functions of the group participants were sustained or improved during the treatment period, whilst, in most cases, the same functions declined during the run-in and follow-up periods, no general assumptions should be drawn. Individual participants' trends are varied and the small scale of this study is preventive of calculating statistical significance of the changes.

The summary of mean trend tendencies for respiration, cough, speech and swallowing functional parameters of the study participants – persons with ALS is presented in Table 44. The detailed description and explanation of the biomedical outcome measures used in this study can be found in Chapter 4. Outcome measures and data collection, section Biomedical outcome measures.

Table 44. The summary of mean trend tendencies for respiration, cough, speech and swallowing functional parameters of the study participants – persons with ALS

	Markers of functional parameters sustained or improved during the treatment period	Markers of functional parameters declined or improvement slowed down during the treatment period
Respiration	FVC MIP MEP	None
Cough	PEF	None
Speech	CNS-BFS speech subscore MPT MRR-A MRR-S Jitter (local) Shimmer (local) NHR Speaking rate Speech-pause ratio Pause frequency Hypernasality level	Fundamental frequency Vowel Space Area
Swallowing	CNS-BFS swallowing subscore LVCrt nectar LVCrt pudding MPCAn nectar MPCAn pudding PeakXY nectar PeakXY pudding totC24 nectar totC24 pudding	PAS nectar PAS pudding

Based on this biomedical data analysis, we can conclude that the suggested music therapy protocol is safe to implement with early and mid-stage ALS population. From the analysis of the mean trends we may also infer, with caution, that this innovative treatment protocol may have beneficial effects on respiratory and bulbar functions in early and mid-stage ALS. However, the sample size of this feasibility study is very small, especially considering the partially missing VFSS data, and the individual responses of the participants to treatment vary. A study with the main goal of understanding the effect of the described music therapy protocol on bulbar and respiratory dysfunction in ALS has to be designed with a larger cohort.

RESPIRATORY AND BULBAR ASSESSMENT IN ALS

The total of 34 biomedical outcome parameters were used in this study: three were used to assess the long-term changes in respiration, one was used to assess long-term changes in cough, 17 were used to assess long-term changes in speech and 13 were used to assess long-term changes in swallowing. The combination of the standard instrumental respiratory and cough tests, videofluoroscopic swallowing study (VFSS) with subsequent frame-by-frame analysis of video clips, acoustic analysis of recorded voice samples, along with self-reported scales such as CNS-BFS, appear to be feasible, objective way to assess respiratory and bulbar function in ALS. Nasalance of speech, an important speech marker in ALS, could not be measured reliably using acoustic or perceptual analysis of recorded speech samples. Other ways of measuring nasalance have to be considered. Pertinence of the utilized outcome measurement parameters to the purpose and clinical setting of this study and implication for further research are discussed in Chapter 11. Discussion.

CHAPTER 10

CASE STUDY SKETCHES

As discussed earlier (Chapter 3. Study aims and design), case studies allow to amplify scientific insight into the process and results of music therapy, bridging objective and subjective perspective. Reading case studies is valuable for practitioners as well, as it allows them to understand how theoretical knowledge can be applied in real clinical settings and to expand their repertoire of what is possible in therapy (Wheeler and Murphy, 2016). Most importantly, case studies give the author an opportunity to touch upon the human dimension of protocolized research, to show the personal aspirations, joys and struggles behind the numbers – things that rarely can be forsaken when working in the ALS care community.

Brief overview of profiles, therapy processes and results for each participant are presented in this chapter to give a raw snapshot impression of each case. Feasibility considerations and common themes are discussed in Chapter 7. Feasibility data analysis result. Implications for future research and clinical practice are presented in Chapter 11. Discussion.

PARTICIPANT 1

Profile on recruitment

The participant was a 62-year-old female with spinal onset ALS. Her ALSFRS-R score was 37 at recruitment. She reported that her ALS was progressing very slowly. Her speech was slurred, unclear, labored and difficult to understand. Her voice had features of strong hypernasality, severe creakiness, breathiness. She had a tendency to expel most of the air during the first several syllables uttered, then to gasp for air. The participant coughed often, but reported having no cold or allergies. She complained about tightness in her chest and said she coughed to relieve the tightness. The participant could walk with support, mobility of her arms and hands was not restricted. The participant recently moved to a small city apartment in Moscow from another town. She did not work, lived alone, had a social worker visiting her twice per week to help with the errands, as well as a sister and an adult daughter who visited her often.

Adherence and self-motivation

The participant attended 12 sessions and completed the independent exercise routine in 68% of all opportunities (self-reported).

Therapy process

One obstacle during music therapy sessions with this participant was laughter. Light in character, this participant could find something funny in just about anything, including her symptoms or “mistakes” she made performing an exercise. However, she worked in therapy with intent and concentration.

Losing the timbre and flow of her speaking voice to disease had been especially difficult for this participant. During the first session she commented that her voice used to be “beautiful”, “young”, much higher. She worked as a call center assistant and often got compliments on the sound of her voice. At the beginning of the second session, the participant played a recording of her voice prior to ALS onset. The voice was in a higher range, had no strain and excessive nasality and, indeed, sounded beautiful. The recording provided a powerful reference point for the further music therapy work.

The participant chose "Air" by Bach for music-assisted relaxation. The choice of a song for therapeutic singing presented an issue. The participant was eager to sing a Russian romance ("Динь-динь-динь" – "Ding-Ding-Ding"), difficult for performance and traditionally sung in a very high register. A music piece of this kind would not meet therapy objectives and would likely become a demotivator if used regularly in sessions. However, the participant insisted because the romance had a special meaning for her. It was agreed then to have this piece as a "work in progress", whilst adding another, simpler folk song ("Ой, цветёт калина" - "Oh, Guelder Blossoms") as a "warm up" song. Surprisingly, this arrangement worked out well. The folk song provided the perfect phrasing, tempo and range to practice the vocal and breathing skills acquired during therapy sessions (eventually the song was transposed a minor third up, per request of the participant). The romance was an emotional highlight of the session: the therapist sang the challenging verses, and the participant joined for simpler, but still beautiful choruses (sung on /la-la-la/ during earlier sessions, with the lyrics added later on).

This participant made exceptional progress in therapy regarding increased speech clarity, perceived not only by herself and the music therapist, but, reportedly, by friends, family and medical staff. Starting at session 5, she reported that her speech became clear enough so that she could speak on the phone again, even though it was tiring to talk for extensive periods of time. With further treatment, speech continued to improve, becoming more resonant and more articulate. It was soon discovered that the participant's singing voice range was much wider than her speaking voice range. Strain almost disappeared in singing, especially in higher register, the consonants became distinct. Music-assisted relaxation routine, self-massage of face and neck region, temporary switching to breathy, "airy" sound to relax vocal cords (e.g. switching /m/ onset to /h/ onset in exercise XII. Gliding vowels exercise) and frequent silent pauses for rest between the exercises appeared to reduce the muscle tension and the vocal strain resulting from it. Learning diaphragmatic breathing allowed the participant to use more air support when speaking, which, in turn, was helpful for even breath distribution on exhale. Toning soft palate through exercises, along with finding stronger vocal resonance, perceptually decreased hypernasality of speech. Since the participant commented she experienced no vocal fatigue, a brief open-sound, full-voice traditional Russian singing exercise was added for practicing strong resonance.

Initially, syllables /ga/ and /da/ were the most challenging for the patient and she was not able to pronounce them. Holding the jaw in open position with fingers of both hands during consonant production exercises and performing the jaw and the chin muscles self-massage many times throughout the session were helpful in improving articulation and speech clarity.

The improvement of speech presented an unexpected challenge: the participant enjoyed talking a lot! Once she met the music therapist at the door and reported that her son had just left and that they spent over an hour talking. Excited, she proceeded talking about this visit for another 15 minutes. The danger of voice fatigue and the session time constraints had to be weighed carefully against sharing the enthusiasm of the participant!

Relaxation and breathing exercises became the focus of the sessions at times when the participant experienced high blood pressure. The light in the room was dimmed for such sessions and the sessions were shortened.

Notable was this participant’s increasing self-awareness: even before the music therapist provided any feedback, the participant often commented on a particular detail that needed work (e.g. an exhalation that had to be longer and more even, collapsed posture that needed changing, etc) or something that was a success (e.g. “This was good!”, following exercise IX.2 Sustained vowels exercise). The participant was capable of attentive observation of her body sensations; after a session she once commented: “I feel less tightness under my ribs after our sessions and less strain in my shoulders" (initially she often spoke of experiencing tightness in chest and of the desire to expand chest and expel “something” from it). She was instrumental in setting attainable session-to-session goals for herself and clearly formulating the purpose behind these: "I am not looking to sing that much, it's ok, but I need to save my voice".

At the last session the participant reported she felt that music therapy had been useful for her speech and said that she would continue exercising on her own. She expressed moderate emotions about the therapy closure. Before parting, the participant and the music therapist sang the Russian romance together, then the music therapist sang a gypsy romance for the participant, per her request. The participant recorded both songs to have as a keepsake and to demonstrate to her friends and family. A kazoo was given as a gift to the participant (see Therapeutic relationships section of Chapter 7. Feasibility data analysis results for the rationale behind the gift choice).

PARTICIPANT 2

Profile on recruitment

The participant was a 45-year-old female with very recent, rapidly progressing spinal onset ALS and ALSFRS-R score of 41. Her speech was clear and fast paced, easy to understand. However, the participant described her speaking as “strained” at the beginning of the treatment and complained about the spasticity she felt in the neck region, on the right side. The participant reported no breathing issues. Her gait was slightly compromised, but the participant could walk without support. Her right arm and hand were affected by the disease, with limited mobility; her left arm was affected to a lesser extent. The participant appeared very emotional, was sensitive to language, including assessment test terminology and song lyrics. She worked as a pediatrician and a medical team leader, but had recently decided to retire: it was now difficult for her to get to work and to perform her work duties. Additionally, she reported that she felt social pressure from coworkers to retire because of her health condition. The participant lived in a small city apartment with her husband and adolescent daughter – a very closely knit, loving family.

Adherence and self-motivation

The participant attended 11 sessions and completed the independent exercise routine in 89% of all opportunities (self-reported).

Therapy process

The participant was very sensitive and often emotional. The beginning of the therapy phase coincided for her with leaving her job in medicine, due to a rapid disease progression. She was very motivated to participate in the study not only for possible benefits of the treatment, but also to contribute to scientific research for ALS. It was difficult for her to connect to the ALS community and to attend clinics, since sightings of and conversations with persons with late-stage ALS and their caregivers triggered her fears and brought to her mind ideas she could not yet get comfortable with. She acknowledged her acute need for support and communication about difficult, disease-related issues. The participant was especially grateful for all the information the music therapist provided regarding the physiological mechanics of ALS and the rationale behind the protocol (“I wish the doctors told me all of that”). It was clear that informing this participant about the treatment process in a scientific way somewhat decreased her stress.

As the therapeutic relationship developed, it became a part of the routine to provide the safe space for the participant in the beginning of each session to briefly talk about her disease, adjustments, negative thoughts, coping and family dynamics. Emotional state of the participant directly affected her physical state, including speech production. The participant commented that "emotions got in the way", adding to the strain in the body; she admitted she "could not speak with anyone without crying"; at other times she reported feeling depressed and having anxiety. The participant reported feeling less anxious and more relaxed at the end of some sessions. However, psychological distress prevailed throughout the treatment.

The participant chose “Air” by Bach for music-assisted relaxation. She commented that another track, Arvo Pärt’s “Spiegel im Spiegel”, sounded “too grave”. She spoke about several songs that were meaningful for her, but burst into tears after attempting to sing one of them. A neutral traditional folk song with easy phrasing was agreed upon for the purposes of therapeutic singing (“Ой, цветёт калина” - “Oh, Guelder Blossoms”). Nonetheless, song singing was often an emotional experience for the participant. During the fifth session the music therapist played the song in more upbeat tempo, with more rhythmically subdivided accompaniment, to help the participant with articulation and to, hopefully, avoid becoming upset. The participant noticed the change and commented that it helped her not to get emotional.

The participant’s apartment was very small, and it was not possible to fit two regular chairs facing each other into the space between other pieces of furniture. Consequently, the participant sat in a steady chair, with support (pillow behind the back), whilst the music therapist sat in a lower armchair facing the participant.
Music-assisted relaxation, including shoulder and facial massage, was essential to reduce general muscle tightness and vocal spasticity. The music therapist assisted the participant with the massage, including the trapezius muscles on the right side where spasticity was strongest, as the participant’s arms had limited mobility.

Learning abdominal breathing and finding stronger resonance became the other major goals for the therapy.

The participant analyzed the sessions, often reflected on how exactly each exercise benefited her voice and breathing, added her own suggestions and self-assessment. She repeatedly remarked that, besides exercise, the music therapy routine was helpful in structuring her week and provided her with something to look forward to.

At session six the participant said that she was now capable of “fully using” her voice, and that this change was noted by her friend when she spoke on the phone. She commented on being happy about the restored ability to speak freely and mentioned that her psycho-emotional state improved. A conversation with the music therapist followed, during which three possibilities were discussed: 1) improved psycho emotional state could be a consequence of the improved speaking and breathing ability – participant commented that performing the exercises and seeing them work gave her a sense of control over her disease, which had been important in normalizing her emotional state; 2) improved bulbar symptoms could have decreased the occurrence of emotional lability, or Pseudobulbar Affect (Smith, Pioro et al., 2017), 3) improved psycho-emotional state due to regular communication with the music therapist could have affected the participant’s bulbar and respiratory symptoms.

At the same session, switching to informal “you” was suggested by the music therapist after the participant had inadvertently used the informal several times. The participant admitted that, as a medical professional, she had been extra careful keeping formal boundaries, even though psychologically it felt to her more beneficial to use the informal “you”.

One of the last sessions was partially video recorded, for research purposes, by a research assistant, with permission of the participant. The participant recognized that the recording process felt different from a regular session, but she insisted that the recording was done because it could benefit other persons with ALS. At the end of the session the participant summarized the symptoms that have been alleviated in the course of the music therapy treatment: shortness of breath at night, choking, emotional instability (PBA) and suicidal thoughts.

The overall disease progression in this participant was rapid and obvious throughout the duration of the study. Her gait was severely compromised by the end of the treatment period and she lost use of her right hand by the end of therapy. Facial asymmetry around lips and cheeks, lesser agility of the right side of the face could be observed.

At the beginning of the last session the participant remarked: “I try not to think that this is our last session”. After that she performed exercises and followed instructions, without much interaction otherwise. A kazoo was given as a small gift to the participant. Relationship closure was difficult for both the participant and the music therapist because of strong rapport and many personal similarities. The music therapist made sure that the family had access to a psychotherapist experienced with ALS.

PARTICIPANT 3

Profile on recruitment

The participant was a 53-year-old female with spinal onset ALS, ALSFRS-R score 42. Her speech was loud and fast, and could be easily understood, but was strained, and a rattling sound occurred on higher pitched sounds. The participant used to sing often and enjoyed singing and listening to the music before the disease onset. The participant reported no breathing issues. Her gait was compromised: she could walk independently, but her walking speed was restricted, especially when walking on uneven grounds. Her hand and arm mobility were not affected, but she reported tingling and spasticity sensations in her arms. The participant was a single mother of a teenage daughter. She continued to work in a leading office manager position. Though the participant gave initial consent to have home-based music therapy, at the beginning of the treatment phase she made a request to have the sessions at her workplace, in a separate office, after working hours. She was not prepared to share the full information about ALS diagnosis and prognosis with her daughter yet, and this session venue allowed her not to force this important moment. Even though the participant enjoyed support from her colleagues, she reported feeling socially isolated because of her disease.

Adherence and self-motivation

The participant attended 11 sessions and completed the independent exercise routine in 33% of all opportunities (self-reported).

Therapy process

This participant was usually just finishing work when the music therapist arrived for the session and was tired after long working hours. She mostly did not have time for the suggested independent exercises routine or was too tired to perform exercises. She reported practicing abdominal breathing while on public transportation.

A trusting relationship soon formed between the participant and the music therapist. The participant felt safe to speak about her ALS-related problems, if she felt like it. Eventually, the participant shared recordings of her favorite music and commented on both the expressiveness of the music and the meaning of the lyrics. During one session the participant's teenage daughter was present in the office when the music therapist arrived. The music therapist, the participant and her daughter had a brief conversation, not touching upon the disease and music therapy. The daughter left before the music therapy session started.

The participant's lung capacity was not compromised and she had no problems performing the melodica exercise: the sound was loud and stable, the music piece was slowed down to 52 bpm from original tempo to extend exhale. Diaphragmatic breathing was taught to the participant as a tool for building up additional respiratory capacity. It took the participant several sessions to understand the mechanics of this new type of breathing. Later in the course of treatment, abdomen, chest and mixed types of breathing were introduced, and the participant showed preference for mixed breathing. Decreasing the inbreath-outbreath cycle speed as prompted by the music therapist, in order to support speech, appeared challenging for the participant. She commented that she was used to leading a fast tempo life, being a single mother, and it was difficult for her to slow down in general. In agreement with this insight was the fact that it was equally challenging for the participant to fully relax during the music-assisted relaxation exercise: she tended to open her eyes before the exercise finished. The participant chose "Air" by Bach for her music-assisted relaxation routine. The participant shared that her visualized "safe place" for music-assisted relaxation was geothermal pools in Italy.

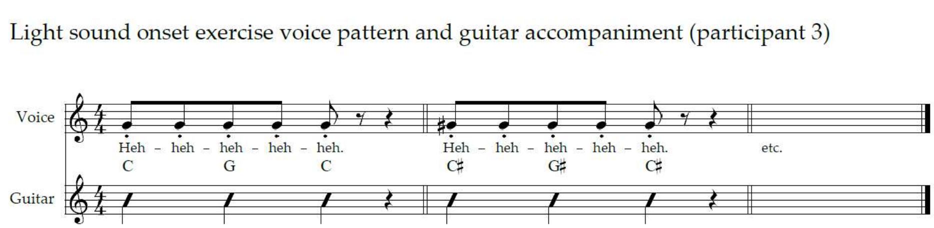
Throughout the treatment the music therapist kept constantly reminding the participant about the necessary precautions using her speaking voice. The participant found it difficult to overcome habitual excessive and loud speaking, in a fast tempo, both in the office and at home.

The perceivable rattling sound and sometimes uneven tone were characteristic of the participant's voice whenever she spoke, otherwise her speech was clear and the speaking rate appeared normal. Dealing with this rattling sound, not characteristic of ALS as described in the literature (Watts and Vanryckeghem, 2001), became a major objective of the treatment and, at the same time, a major obstacle for the music therapy protocol implementation.

Potential causes of the abnormal sound were discussed, including ALS-related vocal cord changes, spasticity, sputum. The participant said she did not feel spasticity around her throat and sputum was not a problem. Among other considerations was the fact that music therapy sessions took place at the end of the long working day; it was likely that after a long day of talking the participant's voice was simply too tired for additional exercises. The participant remembered she used to speak quietly before the birth of her daughter, but then changed her habits and now often experienced tightness in her neck and throat after speaking, especially around the root of her tongue. Finally, the participant recalled that her voice issues started about a year ago, after she returned from a bus road trip where everyone sang out loud, including her. Could the rattling be due to physical damage of vocal cords?

At session 3 the music therapist provided the participant with a phoniatrist's contact information and explained that a vocal cord examination was necessary since her voice problems might very likely be due to vocal chords damage, unrelated (or indirectly related) to ALS, as recommended by previous research for any occasions of speech changes atypical for ALS (Pattee, Plowman et al., 2019). The participant, however, did not schedule an appointment with a phoniatrist to assess the condition of her vocal cords. The music therapy protocol had to be significantly adapted for the rest of the treatment. The work mostly focused on breathing exercises. Vocalization exercises requiring full vocal cords closure were mostly excluded and modified: quiet, relaxed, breathy vocalization was encouraged. Below is an example of an adapted exercise for the light sound onset (Figure 77). This exercise calls for the light, "breathy" initiation of the sound, and the vocal cords come fully together only for a brief amount of time, thus preventing the strain.

Figure 49. Transcription of adapted Light sound onset exercise (participant 3)



The music therapist took special precautions to prevent over-tiring the participant's voice during the sessions. Several adaptive techniques were used. These included the vocal fry technique (producing creaky sound by relaxing vocal cords), the heavy breathing technique (exhalations on /s/ and /h/), increasing breath support to provide a steady airstream for speech support, vocalizing only very quietly (piano to pianissimo), switching from chest voice to head voice whenever possible. Glissando exercises were not tolerated well by the participant and were excluded. Additionally, the music therapist asked the participant to focus on experiencing a warm, smooth feeling in her throat while performing exercises and to stop immediately if she felt tired or in pain. Multiple opportunities were provided for the participant's vocal rest during therapy sessions.

The individualized exercises for independent practice provided to the participant mostly included breathing, stretching and music-assisted relaxation exercises, with minimal vocalization, for safety.

Song choice for therapeutic singing was not easy for the participant ("I don't listen much recently", she commented), but then a Soviet pop song about hope ("Надежда" - "Hope"), with moderate tempo and simple phrasing, was chosen: "I may as well use it as a support now", said the participant. Similarly to the other participants, the singing range of this participant turned out to be much larger than her speaking range. Upon this discovery, she commented several times: "Maybe my voice is worse because I do not sing anymore". However, singing with a raspy, rattling sound and fatigued voice was going against the therapy objectives and safety.

Upon the voice fatigue issue being discussed during the second session, the music therapist suggested that the participant should not sing the song, but the participant said she would still like to try. The experience turned out to disappoint her as her voice sounded unclear and off-pitch ("What I have become!", was her reaction). Since both singing the song and not singing in session were equally frustrating for the participant, the music therapist suggested singing another song from the same era, with abbreviated, staccato phrasing, faster tempo and exaggerated articulation ("Черный кот" - "Black Cat") during future sessions. Later yet, this song was substituted for a traditional Russian pentatonic lullaby ("Котики серые" – "Gray Kitties") sung on /m/ with very light sound onset and breathy voice. The main goal for singing was to achieve tone stability, to practice quieter sound and to avoid fatigue.

At later sessions (10 through 12) the participant spoke at higher pitch, lighter, with less strain and less rattling. She reported following the suggested voice health guidelines whenever she remembered to do so, and said that being aware of how to use her voice and being connected to her body and breathing had been helpful. At the 11th session the participant said she would love to try singing the song initially chosen for the therapeutic singing exercise. She sang almost without rattling in her voice, then smiled and commented that she was happy to be able to sing, because she thought that she would never do so again. At the end of the session the patient reported that she did not experience fatigue, and there was no strain in her voice.

During the last session the participant commented that even despite the challenges, the music therapy sessions had been helpful as they provided her with a better understanding of her voice production and breathing, and that, she felt, gave her more control. She said she was developing the habit of using her voice gently rather than forcefully, preserving energy, using breath support, speaking in the higher ("head") register to avoid strain. A kazoo was given to the participant as a farewell gift. The participant was directed towards music therapy services through ALS Moscow Centre and advised to change her exercise routine if the rattling issue was to be resolved after a consultation with a specialist.

PARTICIPANT 4

Profile on recruitment

The participant was an 81-year-old male with slowly progressing spinal onset type ALS and ALSFRS-R score of 39. His speech was clear and loud, and could be easily understood. He did not report any issues with breathing, but commented on difficulty breathing in through the nose, due to his individual anatomy and frequent sinus problems. Mobility of his arms and hands was not limited, but he needed assistance standing up. He could walk without support, slowly. It was challenging for the participant to hold posture, potentially due to the effects of aging/old age? age, unhealthy posture habits and/or progressing ALS: “It is now more difficult for me to hold my head upright”, in the participant’s own words. Music has always been a significant part of this participant’s life. He used to play the cello growing up, and singing was an important activity in his family. The participant used to work as a geologist, and lived in a small city apartment with his wife. Adult children sometimes visited the couple. A specially trained social worker visited regularly to help with the errands and hygiene. The participant’s wife expressed her wish to be present during the music therapy sessions, to help (e.g. with face massage) and to participate when appropriate.

Adherence and self-motivation

The participant attended 11 sessions and completed the independent exercise routine in 39% of all opportunities.

Therapy process

Music turned out to be an essential part of this participant’s life. “Air” by Bach was chosen by the participant for music-assisted relaxation almost immediately, without even listening to the audio tracks. Song choice was a long and important part of the first session and included listening to many songs by Glinka and Schuman on YouTube and then the participant singing a capella, quietly, before deciding on a classical Russian romance by Glinka (“Жаворонок” – “Lark”).

The sessions took place in the tiny space of a Soviet-designed kitchen – the place where it is necessary to stand up and to move the chair under a small table in order for another person to be able to approach the stove or the fridge. The participant, his wife and the music therapist were situated on the three open sides of the table. This arrangement allowed the participant to sit on a chair, with a pillow behind his back for support, and to rest his arms upon the table during the exercises and to support his weight this way, as needed. The location also coloured the sessions into nostalgic and intimate tones: in Soviet Russia tiny kitchens served as places for meeting friends, having profound conversations and singing songs together.

Caregiver, the participant's wife, played important role during the treatment phase, she was there to open the door and to meet the music therapist, was present during sessions, participated (and benefited) from the music-assisted relaxation exercise and other exercises, helped with face massage, and, at later sessions, took part in therapeutic singing. It felt as a very natural display of support rather than as a disturbance, and was simply an organic extension of this life-long relationship and mutual care. Sometimes their adult daughter joined the session. Her presence, similarly, did not feel artificial or forced (although she had to sit almost in the corridor, for the lack of space).

The science and logic behind the music therapy protocol were of great interest to this participant, a scientist himself. The participant said several times that his habit of processing everything cognitively prevented him from relaxing fully during the music-assisted relaxation exercise and during (and into) diaphragmatic breathing. At the end of the second session the participant commented: "I feel like this session has been a definite advance: I now better understand the mechanics of what I am supposed to do, even though it still requires a lot of intellectual effort". At a later session, the participant commented that the vowel shape exercise had been confusing for him, as muscle effort (articulation) was separated from breath and vocalization. The music therapist explained how this exercise was intended for muscle toning and for increasing vocal apparatus effectiveness, after which the participant could perform the exercise with ease.

When the individualized exercises for independent practice in between music therapy sessions were provided for the participant in a printout and on a CD, he appeared very pleased. Reading the systematic instructions was comforting for him, he said.

Peaceful acceptance of this disease's slow progression over years was striking in this family. Once the participant spoke about the anticipated later stages of ALS, touched on the use of non-invasive ventilation, and commented: "It is good that we do these exercises now, I will need to be able to breathe through the nose".

It was observed that the participant had a tendency to strain his throat and to overwork his vocal cords in attempts to produce strong sound while speaking. The subsequent objective was to work on developing diaphragmatic breathing, resonance and exaggerated articulation which would allow for more effective speech production. The participant learned to look for a "brighter" sound whilst performing the sustained vowels and the gliding vowels exercises.

Due to collapsed posture, the participant initially moved chest, shoulders and head a lot during exercises. The solution was to use the table for support and to using a magnetic photo of the participant's grandson, on the fridge, as a focal point to prevent the participant's head from moving up and down during the exercises. Upper body side turns were added to the stretching exercises set to help with the posture (Lunetta, Lizio et al., 2016).

As the participant's theoretical and practical knowledge of speech production increased, he started to reflect on the ALS-related or age-related changes of his voice: "I started noticing that my speech is quieter and not always resonant", "I realize now how my voice has been worsening, is less flexible and I need more effort to speak". These revelations discouraged the participant for a brief time, but as therapy progressed and he transferred the learned techniques to daily communication, he started noticing positive quality changes of his voice. In the beginning of almost any session he reported "talking a lot", "also humming" or "a lot of talking recently". At a family celebration, his relatives noticed the change and commented that the participant's voice was brighter and louder. At later sessions (eighth and on), the participant spoke about the benefits of increased body awareness, and also mentioned that the idea of finding singing resonance, rather than simply following printed instructions, discussed around the third or the fourth sessions helped him to make progress.

Vocal Health guidelines had to be discussed again and again with the participant. The participant enjoyed using his voice and talked extensively even between the exercises in sessions. When the music therapist noted at the end of one session that it was necessary to refrain from talking during the session to prevent voice fatigue, the participant responded with a smile: "Can you imagine how it would be for me to lose my voice?". The participant used suggested opportunities to stop, rest and even to drink warm tea between the exercises. He came up with an idea of "silent breaks": during the rest time between the exercises the music therapist and the participant's wife were to leave the room temporarily, so that the participant was not "tempted to talk". This arrangement worked and was kept till the end of the treatment.

Reflecting on his experience, the participant said that music therapy provided him with a tool to take care of his breathing and voice, and that the music therapy sessions were enjoyable as a space for communication and singing activities. He also said that he sometimes felt physically tired after the session, but felt more of a resource for speaking as a result of the session. Later he said he felt that the music therapist modeling and conducting all the exercises had been essential to his success and progress in therapy. Anticipating the upcoming therapy closure, the participant commented it could be challenging for him to follow the exercise routine without the regular structure provided by the music therapist's visits.

Therapeutic song singing was a very important part of each session. After the first performance the participant said that he did not sing for a long time, and now his whole body felt physically tired after singing a song – something he did not remember from the past experience. At the second session the participant relaxed into actual singing, very artful and touching, together with his spouse who sang quietly along. The music therapist felt it was safe to fade out and to let the participants experience their own singing. The process of singing carried a lot of emotional meaning for the participant, and the singing itself was very artistic and soulful, if not technically impeccable. However, after singing, the participant always graded his performance, adding some criticism, which often was unnecessarily harsh. Several recordings of the songs were made and shared with the family to be kept as keepsakes. When the participant listened back, he did not particularly like the result, but commented that "for a medical exercise that was all right".

The therapeutic relationship was special and deep on an interpersonal, humanistic level. The participant and his wife were keen to show their hospitality to the music therapist. Tea and food were offered every time. Very soon both the participant and the caregiver felt comfortable speaking about their past careers, their family, current events of their life, ALS-related medical and philosophical issues, including life expectancy, dying and coping. In all of this they were very tactful and attentive to boundaries. Once the participant shared some of his poetry with the music therapist. That was poetry of high aesthetic quality, and the poems touched upon the meaning of life, mortality, love for his wife, his experience with the disease, including a past period of suicidal thoughts upon learning the diagnosis. Conversation about living in the moment, enjoying communication with others and finding peace followed. Formal “You” was used by everyone, characteristic of educated, “academic” communication in Russian.

Music-assisted relaxation was something both the participant and his wife enjoyed. However, visual imagery (“traveling to a safe, comforting place”) presented a challenge for the participant, because, per his comment, the music had much more meaning and harmony in itself. During the exercise they both smiled, eyes open, gaze unfocused, breathed deeply, and seemingly soaked every note in. Apparently, the music and this small kitchen were their safe space.

Relationship closure was special with this participant: the closing session was scheduled for the day other than a regular music therapy session, to provide an opportunity for more informal, relaxed closure. Several takes of the song used in the therapeutic singing exercise were recorded as a keepsake for the family. When the protocol session ended, the participant shared the printed-out poems he wrote in the past and a short film created by his family about his ALS experience. His wife gifted the music therapist with a small amethyst sample the couple collected in a geological expedition. The therapist gave to the participant and his wife two kazoos of different colours. Music sharing followed: the music therapist performed a special song for the family; then the participant’s daughter joined everyone for several music rounds and an African farewell song (taught and sang by the music therapist, with elements of improvisatory call-and-response). Saying goodbye, the participant said that he was going to perform the suggested exercises “now and then”, and his wife assured the music therapist that they would “stick to the routine” as much as possible.

PARTICIPANT 5

Profile on recruitment

The participant was a 43-year-old female with bulbar onset type ALS. Her ALSFRS-R score was 38 points. Her speech was slurred and quiet, with excessive nasality, very difficult to understand. She could not utter more than several syllables without running out of air; the air audibly escaped through the nose, she gasped for breath when speaking. Mobility of her limbs was limited, she could walk with support. The participant did not work outside of the house. She lived in a city apartment with her husband and two young children. Either her mother or her mother-in-law visited every day to help with errands and childcare. The participant considered it important that the children were present and participated in music therapy sessions.

Adherence and self-motivation

The participant attended 11 sessions and completed the independent exercise routine in 33% of all opportunities.

Therapy process

This was the only participant who presented with bulbar onset ALS. The participant's condition progressed rapidly during the 6 weeks of the study: at the time of the early sessions she could walk without support to open the door for the music therapist, whilst later she used a cane, and then a walker. She missed one of the last sessions because she fell and cut and bruised her face. She mostly lost upper limb mobility in these weeks as well. Multiple adaptations of the protocol were needed because of these changes, such as adaptive sitting posture during the sessions (sitting in the chair, supported by a pillow, with arms crossed over the knees for stability) and adaptations of music therapy exercises. When excessive salivation became a problem, all exercises were adjusted to allow for pauses for swallow control.

Music therapy sessions took place in the participant's living room. Two regular chairs for the music therapist and for the participant were situated facing each other, at about 1.5-meter distance. Young (primary school aged) children of the participant were present during most sessions. Despite reading, discussing and signing the informed consent, including the participant information sheet, the participant and her family perceived music therapy treatment as an opportunity for the children to share music activities with their mother. Since no childcare was available, the music therapist adapted to this expectation: the children participated in some activities, such as music assisted relaxation and therapeutic song singing, and played with musical instruments during the others.

The participant appeared very anxious about following the instructions and doing the exercises "just right", she often commented that it was difficult for her to relax, that she felt constant need to be “in charge” and perceived herself as “not enough”. Her body confirmed it: she looked tense, her chin was up, the head moved a lot, facial muscles and the jaw were very tense, sometimes jaw tremor was observed. Despite the anxiety, the participant smiled and made eye contact with the therapist during sessions. Encouragement and talking about successes (e.g. wide vocal range, improved exhale length, resonant tone) were important in the sessions. The participant was encouraged and gradually learned to regard music therapy sessions as self-care time and to allow the music therapist to take care of her. This led eventually to a better rapport. Switch from formal to informal “you” was made after several sessions.

The participant kept asking multiple questions regarding ALS aetiology, possibilities of treatment and physical abilities of other patients at ALS Centre Moscow. Apparently, she regarded the music therapist as a person she could trust to provide relevant information and to safely discuss these matters. Eventually, the participant felt safe to open about the emotional tension in her family between her mother and her mother in law, as well as about her dissatisfaction in marital relationship, and about the way it negatively affected her psychological wellbeing. It was apparent that the participant had a great need for psychological support, which the music therapist was not in the place to provide, due to the limitations of the study protocol. After a discussion, the participant and her family were referred to a psychologist from the ALS Centre Moscow to alleviate these issues.

Physical and psycho-emotional relaxation, learning abdominal breathing for speech support, increasing articulatory precision, decreasing nasal air emission and improving lip seal were the individual therapy objectives for this participant.

The soft palate exercise and changing the consonant in interrupted “hah” sigh exercise from /m/ to /g/ appeared helpful for decreasing nasality. The melodica exercise was especially helpful for improving lip seal and was very motivating as the participant worked on increasing uninterrupted exhalation time. Initially, when attempting to play the melodica the participant was able to produce no more than two brief notes on one exhale, which was discouraging for her. The music therapist suggested trying the same exercise with her nose closed. With the nose closed, the patient was able to produce 8 notes on one exhale during the first attempt, then 13 notes during the second attempt. This demonstrated to the patient that there was enough air in her lungs for this exercise and that the main goal became to control the airflow and to work on proper velopharyngeal closure. The participant attempted the exercise again with her nose open and could play five notes in one exhale this time. This amount increased in subsequent sessions. The participant appeared happy about this success.

The participant noted more precise articulation during the exercises. As with other participants, her comfortable singing range was wide at almost one octave (F - Eb), whilst the speaking range was limited and at a lower range.

A small mirror was used as a focal point to decrease the participant’s head and shoulder movements while singing.

The participant particularly enjoyed the music-assisted relaxation part of the protocol, for which “Spiegel im spiegel” by Arvo Pärt was chosen. She commented that she felt relaxed and that the music therapist's narration felt like a lullaby. Once after the first part of the exercise she smiled, thanked the music therapist and said that she relaxed so much she fell asleep for a moment. Whilst this relaxation routine was important as a self-care opportunity for the participant, her children sometimes were present during the exercise and took part in the “musical journey”. They lay on the floor or sat leaning on their mother’s lap during the exercise, eyes closed. The music therapist adjusted the narration to suit both the mother and the children. Once the child asked the mother about the location where she "traveled", and it turned out that both imagined the beach. Sometimes the children assisted their mother in facial massage, which was pleasing for all.

The song for therapeutic singing was a popular Soviet war song (“Катюша” – “Katusha”). The participant suggested the song, because it was familiar to the children and had a special meaning for her: she learned this song from her mother as a child and they used to sing it together. It took several sessions and a lot of encouragement on the part of the music therapist for the participant to overcome her reservations and to actually sing, rather than to whisper to the song: she appeared to enjoy the process. At the end of the session the participant commented that she felt more air in her lungs.

The children usually took part in song singing. Once the participant's mother was present and she apparently enjoyed hearing her daughter and grandchildren sing. The participant's singing was resonant, with clearly articulated words and organic phrasing. However, she completely dismissed her own efforts and progress upon finishing the song ("I only spoil it"). At a later session another song – a lullaby from a Russian cartoon ("Колыбельная медведицы" – "Lullaby Of A Mother Bear") – was added to the repertoire: the children asked for another song they knew, and singing was obviously enjoyable and not fatiguing for the participant. At session 10 the participant enjoyed singing both songs in full voice. When finished, she smiled and did not make critical comments about her performance.

During the last week of the treatment phase, the participant moved with the family to the summer house, a two hour driving distance from Moscow. The participant felt that she could not affect this change and appeared distressed because of the possibility of missing the two last sessions. The music therapist made the choice to travel to the patient by car for the last session. Session 11 was missed because she had the falling accident (described above). However, she put extra effort into performing independent exercises. At the beginning of the last session the participant reported that she performed independent exercises on four days out of five. This amount was very prominent: previously the participant reported not being able to find time to do the exercises, because, per her comment, she "had to care for the children" and she was "doing everything so slowly now". The research nurse reported that the participant had been having issues with self-care or doing anything at all for herself since the time of the diagnosis.

At the end of the last session the participant started speaking about her experience in music therapy and the supportive role the music therapist played for her in the weeks of treatment. She burst into tears and it was difficult for her to stop. The therapist provided the space for the participant to safely express her feelings, comforted her and thanked her for her work in therapy. Then the gifts (kazoos of different colours) were given to the participant and her children, with the permission of the participant. A rock and roll improvisation was played on the guitar and four kazoos by everyone for the closure. The improvisation helped to gently distract the participant from the raw emotions and to shift the mood, whilst it also provided an opportunity for the family to share an enjoyable activity.

PARTICIPANT 6

Profile on recruitment

The participant was a 62-year-old male with recent spinal onset type ALS and an ALSFRS-R score of 37. His voice sounded slightly nasal, but his speech was loud, with expressive intonations, and could be easily understood. The participant mentioned that salivation when speaking was a problem, his speech recently became slower and it took longer for him to swallow his food. He could walk without support, though slowly and with caution. Mobility of his upper limbs was not affected. The participant was a high-profile lawyer and still worked part-time from his home, but reported that pseudobulbar affect and speech problems interfered with his work. He lived in a city apartment with his wife, who was very involved in caregiving and chose to be present during music therapy sessions. Religious views: Orthodox Christian.

Adherence and self-motivation

The participant attended 12 sessions and completed the independent exercise routine in 64% of all opportunities.

Therapy process

Therapy took place in the participant's spacious living room, where the participant sat in a chair, and the therapist sat facing him in an armchair, with a coffee table between them. The caregiver, the participant's wife, was present in the room to assist with the start of each session, but did not sit down and did not participate.

Excessive salivation and reported emotional lability (pseudobulbar affect) comprised issues for this participant during the study. These issues interfered with his work and frustrated him. The emotional lability was not observed during the music therapy sessions. The participant said that being around other people and speaking with them was helpful: "The more I speak, the easier it is". He also reported having difficulty swallowing.

Pauses for saliva management had to be allowed during the initial session and then, again, during the last sessions, when the participant's condition deteriorated significantly, which included significant mobility decline. During the first two sessions excessive salivation presented a challenge for the participant when he attempted to perform the melodica exercise (the exhale was too short for the suggested phrasing), as well as the consonant range cantillation exercise (exercise VIII): he could not produce more than four units on one exhale. However, the participant insisted on returning to the exercise after performing more exercises with the guitar accompaniment. At the time he could produce 14 unit repetitions on one exhale. The order of the exercises was reversed for future sessions. The participant appeared very proud of his achievement. The consonant range exercise and song singing became his favorite activities. Sometimes he started the exercise before the music therapist provided instructions and opened the song lyrics on iPad in the middle of the session. This vehemence for achievement in therapy was very characteristic of this participant. Special care had to be taken to often remind him not to overwork when exercising in sessions and independently. Overperforming, the participant often pushed air too abruptly on exhale or strained vocal cords, ignoring prompts from the music therapist. The music therapist demonstrated multiple times that quieter speech and singing could be more resonant than pushed voice. Dynamic levels for most exercises were decreased.

It was important for the participant to do as many things independently as he could, and the music therapist supported this intention. The participant appeared to enjoy being in control of the communication and process in therapy, which sometimes visually manifested in episodes where he physically “conducted” the therapist who provided the guitar accompaniment. The music therapist adapted to this need by minimizing the verbal instructions and by inviting the participant to briefly reflect on the therapy process at the end of each session. The participant was very open about his ALS-related challenges and enjoyed sharing memories from the past, when he used to work as a ski instructor in a beautiful mountain region. He shared that the mountains were the comfort place he visualized during the music-assisted relaxation. The participant used the formal and informal “you” intermittently when addressing the music therapist, which may be interpreted as a sign of developing trust in the therapeutic relationship.

The participant’s condition progressed fast: after several sessions his movements were visibly slower and less precise, and it was difficult for him to stand up from a sitting position. He had a fall during the sixth week of treatment, right before the music therapy session. When the music therapist arrived, the participant was not able to lift himself or change position. Upon consideration, the music therapist assisted the caregiver helping the participant up, which took about 40 minutes (see Chapter 11. Discussion for implications). The participant decided to go on with an abbreviated music therapy session after that. It was agreed that the participant would sit in an armchair, which provided more support. The exercise routine appeared to bring the participant comfort. The medical team was notified.

At the start of the next session the participant was seated in the chair, as suggested by the therapy protocol. When the music therapist commented that switching from an armchair to the chair only for a music therapy session was not worth the risk of falling, the participant commented that he “was not going to live in that armchair anyway”. However, the participant sat in an armchair or on the sofa during later sessions.

Main individual therapy objectives for this participant were to increase articulation speed and precision and to find resonance for vocalization. Later, with the increase of nasality, improving velopharyngeal closure became an objective as well. By the fourth session the participant had difficulty pronouncing roller /r/, regular in Russian speech, and perceivably slowed down when pronouncing plosives /b/, /d/, /g/. Syllable /re/, sung staccato, helped with articulating /r/; jaw relaxation through stretches was helpful to improve the plosive consonants.
The participant chose “Spiegel im spiegel” by Arvo Pärt for music-assisted relaxation, but then decided to try “Air” by Bach and continued to enjoy the latter. He chose a Soviet romance about a farewell (“Сиреневый туман” – “Purple Fog”) for therapeutic song singing. He considered several folk songs initially, but rejected them for being “too sad”. He later asked to add another, humorous song ("Говорят мы бяки-буки" – “They Say We Are Baddies”) to this exercise.

Initially the participant rejected the guitar accompaniment and insisted on singing along to a karaoke track. However, by the end of the first verse, it became obvious that the participant had difficulty keeping up with the tempo and the key of the karaoke track. When he stopped, the music therapist offered to accompany him instead. When the participant agreed, the music therapist accompanied him on the guitar in a comfortable key and tempo, and sang the melody lightly in the upper register without the words (in a "trumpet" timbre, closed mouth) to provide the patient with an opportunity to showcase his singing. The participant appeared to enjoy his arrangement, conducted the music therapist and pretend-played an “air guitar”. In later sessions the music therapist had to slow down the accompaniment towards the end of the song to give the opportunity for the participant to increase articulation precision. The participant’s singing was more articulated and resonant than his speaking.

The participant insisted on adding karaoke songs and classical poem recitation to his independent exercise routine. Eventually, the participant noticed that the tonalities on the recorded exercises were “most resonant” for his voice, and was surprised upon learning that those were tonalities chosen specifically for him by the music therapist, based on observation. The music therapist suggested replacing karaoke with pre-recorded guitar accompaniment in suitable keys and tempi for participant exercise.

During the fifth week of the treatment phase the participant moved to his summer house right outside of Moscow. It took more time for the music therapist to get to this destination using public transportation, and presented new difficulties as the environment was noisier. However, the participant experienced fewer physical obstacles there, was able to move around on his mobility scooter, and looked happier overall. He was now assisted by two male support workers who lived on the premises.

When, at session 10, the music therapist reminded the patient that treatment was going to be finished after two more sessions, the patient asked about "the other part of treatment" in October, although no conversations about possible additional treatment have occurred before. The music therapist and the caregiver clarified to the participant that the upcoming closure was final. Starting at the 11th session the participant suddenly switched back to formal “you” and kept the communication friendly, but very business-like. Very likely, this was a sign of an emotional withdrawal as a reaction to the anticipated therapy closure. At the start of the last session the participant reported not feeling well and commented: “My body resists the fact that this is our last session”. The participant appeared to enjoy playing kazoo (the farewell gift) a lot. He commented that, if anything, music therapy had been a joyful experience for him.

PARTICIPANT 7

Profile on recruitment

The participant was a 49-year-old female with spinal onset type ALS. Her ALSFRS-R score was 31 points. Her voice had features of hypernasality and sounded strained. Speech was of regular speed and could be easily understood. Her breath was labored. The participant had lost mobility in her lower limbs. She relied on technology to maintain functional independence and used a wheelchair. The participant reported she was “not a singer” and probably was tone-deaf, however she used to play the piano and enjoyed listening to music. The participant used to work as a store assistant, but was now retired due to the disease. She lived in a city apartment with her adult daughter. Religious views: Orthodox Christian.

Adherence and self-motivation

The participant attended 12 sessions and completed the independent exercise routine in 45% of all opportunities.

Therapy process

During the first session the participant said that she had laryngitis, and that she was not going to sing in therapy, because she entered the study only “to help the science”. Two sessions were focused predominantly on breathing and relaxation techniques, and the protocol was only partially implemented.

The participant chose “Spiegel im Spiegel” by Arvo Pärt for music-assisted relaxation. She had difficulty choosing a song for therapeutic singing, said that she would not sing anyway and commented: "I know music, I even taught my daughter to play the piano, but I cannot sing. I hear that my pitch is off and it irritates me". She said she "didn't care" about music, mentioned she attended concerts, but could not specify a genre or performer that was of interest to her. At the end of the second session the therapist played and sang several songs (traditional, movie, children's), asking for feedback, before discovering the song that caught her attention was found: “Под небом голубым” – “Under The Blue Sky”. She listened attentively and calmly, looking away from the therapist. The patient's attitude visibly changed after the therapist had sung the song. She looked more relaxed, let down her guard, and smiled. Then, surprisingly (and contrary to her previous statements) the participant told the therapist that her voice problems seemed to be linked to her disease: "It is something new".

Establishing a trusting relationship was essential before attempting any voice work. The music therapist assured the participant that the most important thing was that she would feel comfortable and safe during music therapy sessions, without the need to perform perfectly. The switch from formal to informal “you” happened at the third session. The participant appeared more relaxed when she gained a basic understanding of the session structure and expectations. It was important that the music therapist explained the rationale behind each exercise and demonstrated each exercise, inviting the participant to join in only if she felt comfortable doing so. The therapeutic relationship that developed eventually was friendly, but distant.

During the third session the whole protocol was implemented, including singing exercises, with the exception of therapeutic song singing. The participant sang the exercises perfectly in tune, it was obvious she enjoyed her success doing that and producing long phrases without running out of air. The music therapist made several stops to make sure that the participant released tension, relaxed and went back to deep, evenly distributed abdominal breathing.

Eventually, the participant disclosed more about her drive to be "the best" at everything she attempted. For this reason, she never wanted to sing, because she knew “it was not her gift”. Discussion followed about the difference between music performance and music therapy. The therapeutic song singing exercise was adapted: the participant was instructed to synchronize her breathing with the music therapist who was singing, as if she was singing herself.

The participant said she liked the song, but she appeared thoughtful and even sad when breathing to the song. At a later session, the music therapist suggested changing the song to a more upbeat one (“Этот мир придуман не нами" – “This World Has Not Been Invented By Us”), and the participant agreed to do so. She appeared content and even smiled during the song.

Learning body-awareness was difficult for this participant. She appeared rigid physically, and she said she could not feel her abdomen or her larynx moving during exercises, even when asked to focus on these sensations. She commented that she attempted learning diaphragm breathing previously in yoga classes, but could not do it.

Across several sessions the participant reported the sensation of running out of air in the middle of a breath and the urge to gasp for breath even though there still was air in her lungs. The participant connected this sensation with becoming more conscious about how breathing occurred in her body and being slightly confused about the mechanics of it. The music therapist led the participant in making several long exhales to demonstrate that there was a lot of air. This strategy was helpful for the participant. Later, following several discussions and trying various techniques, the music therapist gently drew the participant's attention to the fact that, when breathing normally (not taking abdominal breaths), she had a tendency to gasp for breath and to move her shoulders. The participant agreed that this had been the pattern in the last year, and even demonstrated a video of herself speaking with gasping. Therapy focused subsequently on learning abdominal and mixed breathing with the purpose to adopt it for everyday breathing and speaking. The participant said that she would try to break the habit of gasping for breath, as it was not necessary anymore: deeper breathing provided enough air.

By the eighth session the participant reported that she noticed she was using abdominal breathing throughout the day. To further work on breath control and to prevent habitual gasping, an adapted breathing exercise was developed: three deep abdominal breaths, three deep chest breaths, three mixed breaths at a comfortable pace. At the end of the session, after the regular set of the exercises, the participant commented on being comfortable with her breathing.

Hypernasality was addressed by changing the consonant in interrupted "hah" sigh exercise from /m/ to /g/. The participant was advised to lightly pull her jaw with one or both hands to help with relaxed articulation of consonants /b/, /d/, /g/ during exercises.

As the therapy relationship developed, the participant was very willing to discuss her condition during the session. Talking caused vocal fatigue, which led to less tolerance for the further exercises. However, these instances provided an opportunity for the music therapist to observe the transfer of learned skills to daily communication. After five minutes of active talking the participant's voice became more nasal, and in several more minutes gasping for air was observed, with characteristic upward movement of the shoulders. These changes were discussed with the participant. The participant acknowledged that talking for prolonged periods of time tended to leave her almost unable to speak. The importance of proper voice care, including vocal rest, slowing the speech down, speaking at a comfortable dynamic level, using abdominal breathing and taking breaks as needed, were reinstated in the conversation that followed.

The participant reported not having much time for independent practice and only performed some of the exercises, as described in a printout, during the first four weeks of the study. Later she started using the audio guide and commented that having the music therapist sing patterns on audio recording was helpful.

During the last (12^{th}) session the participant appeared to especially enjoy music-assisted relaxation. She breathed deeply, smiled and took her time at the end of the exercise before opening her eyes. After that she unexpectedly mentioned that she had previously experienced relaxation and imagery sessions when she was in acute psychiatric care. This information was new for the music therapist. No further details were provided. The implications for feasibility of the study protocol are described in Chapter 11. Discussion.

Therapy closure was formal, but warm. A kazoo was given as a farewell gift. The therapist and the participant thanked each other for the experience and said goodbyes.

PARTICIPANT 8

Profile on recruitment

The participant was a 70-year-old female, with spinal onset ALS, and ALSFRS-R score of 39 points. She lived in a city apartment with her family. Sadly, this participant died due to diabetes progression before any further information could be obtained for this study. The music therapist had no chance to meet the participant.

CHAPTER 11

DISCUSSION

This applied research formulates the music therapy protocol to support respiratory and bulbar functions in early and mid-stage ALS, provides the evidence that the suggested set of exercises is tolerated well by the patients and is feasible to implement by a music therapist in home settings, assembles a comprehensive battery of outcome measurements for objective assessment of the effectiveness of the intervention, tests feasibility of data collection using them for the first time and provides the empirical evidence of the benefits the protocol might provide to persons with ALS.

The following chapter presents a discussion of the study process and its main findings and contains the provisional suggestions for clinical practice and the rationale for further research of music therapy applications in ALS palliative neurorehabilitation.

MAIN STUDY FINDINGS

Feasibility of the suggested study protocol

Analysis of the primary data provides the evidence that it is feasible to implement the suggested study protocol for home-based music therapy as an intervention to support respiratory and bulbar functions in early and mid-stage ALS. The recruitment rate was 100%, the retention rate was 87.5% and the mean adherence was 95.4% - values above the target markers for the protocol feasibility.

Safety and tolerability of the music therapy protocol

The safety and tolerability of the music therapy interventions was the main focus of the protocol development. This priority was based on limited evidence in these areas for any form of exercise for people with ALS to help with respiration and bulbar function, music-based or other. A thorough understanding of the mechanisms of the interventions is required before implementing them in research and clinical practice in order to protect people with ALS against fatigue and emotional distress. The protocol and exercises were developed based on the researcher’s clinical observations, scientific inquiry, the evidence from neurorehabilitative music therapy research with other clinical populations (Magee *et al.*, 2017; Bukowska *et al.*, 2016; Gregory, 2002; Kim, 2010; Särkämö *et al.*, 2008; Tamplin *et al.*, 2013) and extensive consultations with ALS care experts from around the world.

Quantitative and qualitative data were collected to measure short-term and long-term safety and tolerability of the treatment protocol. These data show that the music therapy protocol was safe to implement and tolerated well by the participants.

Short-term safety of the music therapy protocol was assessed by measuring the change in ratings on Ease of Respiration Numerical Rating Scale and the change in ratings on Ease of Speech Numerical Rating Scale before and after every music therapy session (self-reported). Unchanged or higher score post-treatment was considered the marker of the treatment protocol's safety. Mean group trends for both numerical rating scales indicate that the treatment was safe. Individual mean post values for both scales were unchanged or positive for all the participants, with the exception of participant 7, for whom individual mean post values lowered post-treatment on both scales. This was the participant who did not comply with the protocol as suggested by the researcher (in particular, she almost entirely omitted singing) and seemingly had issues with mind-body connection (for example, noticing that her abdomen moves during the breathing exercise). She mentioned being admitted to a hospital in the past due to mental health issues. This information provides implications for planning further research (discussed later in this chapter).

Long-term outcomes of the music therapy treatment, including biomedical data, interviews with the participants and the therapist’s observation notes, allow to conclude that the intervention was well tolerated by the group of seven persons with ALS who met this study’s inclusion criteria and participated in the research.

Most bulbar and respiratory functional parameters were sustained or improved at a higher rate during the treatment period, as compared to the run-in (control) period, as evident from the mean trends for the 32 biomedical measurement parameters across respiratory, speech and swallowing domains. Since bulbar and respiratory functions are expected to decline with ALS progression, such change in trends during the treatment phase is a sign that the intervention was safe and, possibly, beneficial for the participants. A subsequent study with a larger cohort needs to be conducted to assess the effectiveness of the intervention.

Qualitative data from the interviews with the participants - persons with ALS and their caregivers - demonstrates that the treatment was tolerated well and perceived as beneficial.

All the participants with ALS reported music therapy to be a pleasurable experience and perceived the suggested independent music therapy exercises as easy to perform. This is consistent with previous findings that musical cueing during physical exercises decreased perceived exertion and perceived fatigue, as compared to treatment not supported by music (Clark *et al.*, 2017; Lim, Miller and Fabian, 2011). Most participants - persons with ALS believed that music therapy was beneficial for their speech and respiration and that it helped them learn new breathing and vocal skills, but did not affect their swallowing. Some participants perceived that music therapy improved their communication (see Personal perspectives of the participants – persons with ALS, in Chapter 7). Most caregivers reported that music therapy improved or sustained bulbar and respiratory functions of the participants with ALS. Some caregivers reported that the music therapy process and, in particular, communication with the music therapist had a positive effect on the psychological state of the participants with ALS (see Personal perspectives of the participants – caregivers of persons with ALS, in Chapter 7).

The qualitative data in the form of therapist's notes recorded during the treatment phase of this study also indicates that the music therapy protocol is safe, if implemented, with necessary individual modifications, by a professional music therapist. Proficiency in music therapy requires the complex combination of knowledge that includes music perception and production mechanisms, music composition, performance and goal-oriented improvisation, basic psychology, psychopathology, social science, anatomy, physiology and neurology, treatment planning, documentation, research and ethics. This diverse expertise allows music therapists to plan music interventions and to provide and adjust musical structures in real time to support health goals in the context of multidisciplinary ALS care. The role of the therapist in clinical implementation of this treatment protocol is further discussed in the section “Implications for clinical practice” of this chapter.

Structure and modifications of the music therapy protocol

An innovative, ALS-specific music therapy protocol was developed by the principal researcher and used as a treatment intervention in this study. The music therapy session following the suggested protocol resembles an adaptive voice lesson, where a music tutor works with a singer to improve posture, breath support, resonance, intonation, articulation and voice projection. However, this protocol, through the use of music, musical structures and musical interactions, focuses on non-musical, rehabilitative goals and objectives. These goals, which are ALS-specific and common for the whole cohort, are to increase breath support and muscle relaxation, to maintain speech rate, prevent or decrease hypernasality, and to maintain swallow coordination. The individual objectives were related to these goals, but depended on the particular symptoms, progress, actual assessment and the observed current state of each participant. Main objectives for participant 1 included reducing voice strain, excessive nasality and shortness of breath; for participant 2 the objectives were to decrease nasal air emission, to improve lip seal, to improve articulation and to develop diaphragmatic breathing; for participant 5 the main objective was to increase body awareness. For participant 6, who was progressing rapidly, these objectives had to be changed several times throughout the treatment. Initially, the objectives were to increase articulation speed and precision and to find resonance for vocalization. Later objectives were improving velopharyngeal closure (due to increased nasality) and jaw relaxation in order to improve plosives. The flexible protocol structure allowed modification of the training load for each participant, and all the exercises within the protocol could be further adjusted to precisely suit the individual needs and capabilities. For example, during the initial sessions, when the participants were actively learning about the mechanics of voice production, going through the protocol required more time, more directions and modeling from the therapist were needed, and the therapeutic work was mainly focused on the body posture and the diaphragmatic breathing. Later, when the participants had familiarized themselves with the protocol and internalized the basics of breath support for vocal production, more time could be devoted to the individual objectives, such as finding resonance or increasing articulation precision. Some exercises were modified to slightly increase the workload intensity (by increasing the tempo or the singing range). Yet later in the course of treatment a few new exercises were introduced, including a mixed breathing exercise and an additional velopharyngeal port exercise - both described in detail in the Implications for clinical practice section of this chapter.

Facilitating musical structures, mostly in the form of the guitar accompaniment composed by the principal researcher, make this music therapy treatment inherently different from the speech therapy or the physical therapy process. Priming, the ability of an external auditory cue to stimulate recruitment of motor neurons at the spinal cord level, and cueing of the movement period by rhythmic synchronization throughout the whole duration and trajectory of the movement (Thaut and Abiru, 2010; Thaut, McIntosh and Rice, 1997) are the essential mechanisms behind the use of music in sensorimotor rehabilitation. Rhythmic stimulation increases endurance and motivation (Alter *et al.*, 2015), and enhances memory and cognition (Nelson *et al.*, 2013). Rhythm can be employed to improve temporal characteristics of speaking, such as fluency, articulatory rate, pause time and intelligibility of speaking (Thaut and Hoemberg, 2016).

Whilst the rhythm is essential, there are many more “dimensions” (i.e. parameter characteristics) to the facilitating musical structures. These include the tempo, pitch, tonality and rhythm changes and can be modified by the music therapist during the session in various ways to best support the work on the rehabilitative objectives for each participant. For example, the range of a singing exercise can be expanded after the participant has learned to better control their laryngeal elevation or the tempo in melodica exercise could be decreased to allow longer phrases, which means longer exhalation (i.e. potentially increased lung capacity). And vice versa, the tempo of singing exercises can be gradually reduced to accommodate the deterioration of function experienced as a result of the disease progression, still allowing the work on articulation.

One example of the unique effect music-supported therapy has is the fact that for all the participants their comfortable singing range was more extensive than their speaking range. It appears to be safe and effective to ask participants to sing slightly higher than their normal (as affected by ALS) speaking range. Whilst the speaking range of the participant with bulbar onset was very limited, her speech was monotonous and its fundamental frequency was perceivably low, her comfortable singing range was wide at almost one octave. The vocal strain also decreased during singing. This discovery was very pleasant and motivating for the participants. As evident from the participants' comments and interviews (see Personal perspectives of the participants – persons with ALS, in Chapter 7), these vocal skills gained in therapy also generalized to their everyday communication.

However, unlike a vocal coach, the therapist has to be similarly attentive to the non-musical elements of the protocol. For example, if a participant presents with severe hypernasality, the music therapist can replace the "hah-mah-mah" sequence with the "hah-gah-gah" sequence in a singing exercise to help the participant strengthen their velopharyngeal closure; or, if excessive jaw muscle tightness is a problem, the participant can be instructed to support the jaw with their fingers on exercises such as XI.3 ("hah-eh-ee-oh-uh") or XI.4 (long syllable). To make these modifications, the therapist has to be a skilled clinician and to have a deep theoretical understanding of the anatomical and neurological mechanisms behind the bulbar and respiratory functional changes in ALS. The diversity of the necessary clinical adaptations of the same basic music therapy protocol is exemplified by the audio recording of the individualized sets of exercises for post-intervention independent practice provided for each participant, which can be found among the Supplementary materials. Suggested adaptations and modifications of the protocol can be found in the Implications for clinical practice section later in this chapter.

Home-based music therapy treatment

The treatment was delivered to the study participants in their homes twice weekly for the duration of six weeks. The length of each music therapy session was approximately one hour. However, additional time was sometimes needed to maintain a meaningful conversation and to attend to psychosocial needs of the participants, which often were immense, due to the lack of regular psychological support in the care system. Sometimes the sessions had to be shortened to prevent fatigue in participants who felt tired or unwell.

It can be argued that more frequent sessions could likely benefit the participants, and, in fact, the guidelines for rhythm speech cueing intervention with patients with spastic, ataxic or mixed dysarthria suggest the frequency of three to four days per week as recommended (Thaut and Hoemberg, 2016). In the recent RCT on active music therapy for persons with ALS 30-minute long individual sessions were conducted three times per week (Raglio *et al.*, 2016). However, the treatment took place in a medical facility during a one-month long hospitalization. This periodicity, however, did not appear viable in the context of home-based care in a megalopolis environment. The results of the current study suggest that three home visits per day is the optimal number of sessions delivered by one music therapy practitioner who travels to the clients' homes to provide services (refer to Table 12. Weekly schedule of the principal researcher during treatment phase).

It is important to be also mindful of the fact that entering private spaces of the clients may cause some disruption to their daily routine and therefore some stress, even if it is positive. The Russian cultural concept of "visiting", when the host (participant and/or caregiver) feels the urge to treat the visitor (therapist) to a cup of coffee or a meal (see the Therapeutic Relationships section in Chapter 7. Feasibility Data Analysis Results) is one example. The therapist needs to focus on finding the culturally appropriate, professional, yet personable therapeutic boundaries with each client: the acceptance and the limits of physical touch, the appropriate humor, the timely, carefully weighted personal disclosure, the use of personal space of the client's home have to be considered. Risk assessment and lone worker policy (discussed in more detail later in this chapter) have to be in place. Advanced (if possible, ALS-specific) ethics training and weekly professional supervision can be recommended to a therapist conducting home-based sessions with this population.

Independent music therapy exercise

Whilst this research is primarily focused on the clinical intervention delivered by a practitioner, it is understood that benefits of the treatment largely depend on the level of individual involvement of each participant. Decreased motivation is common in persons with ALS (Lillo, Mioshi and Hodges, 2012). Little is known about the causes of this, but it can be argued that a sense of agency when deciding if, when and how to perform the independent exercise may be beneficial for persons living with ALS. During the pilot trial of the music therapy protocol used in this study a caregiver commented: “One reason the music therapy exercise program is important for my wife is that this is one of a few things she is able to do independently”. Music therapy treatment with elements of coaching was decided upon. Health coaching, a service in which providers facilitate participants in changing lifestyle-related behaviors for improved health and quality of life, or establishing and attaining health promoting goals, has to be considered as a promising model of home-based clinical care. It empowers patients to gain some autonomy and control over their condition, and encourages active participation, self-discovery and accountability in health management (Wolever *et al.*, 2013).

Individual instructions for independent exercise in audio and in print out formats were provided to each participant at session 3, after the initial assessment that took place during the first two visits. Visual guides and verbal descriptions necessary for understanding anatomy and physiology of voice production were offered to all participants at the time of the initial sessions as well. For some participants this set was adjusted during the treatment phase: exercises were omitted or added, extended or transposed to suit their individual objectives and limitations.

There were no target requirements for the home exercise program: the participants engaged in the independent practice at their own pace and only if they chose to do so. Resulting self-reported adherence to suggested independent exercise routine (53%) was significantly lower than the music therapy sessions attendance (95.4%). All the participants attempted the independent exercise routine at least several times. When asked, none reported that performing the exercise set presented a challenge. Being busy, not feeling well and being tired were the usual reasons for omitting the exercise. Possible ways to increase compliance, such as setting a target, a schedule and/or a system or reminders, are discussed later in this chapter.

Most persons with ALS reported being motivated to continue performing independent music therapy exercises after the treatment ended. Individualized sets of exercises for post-intervention independent practice were provided to each participant at the end of session 11. The ranges and tempos of the exercises were limited to each participant’s “comfort zone”, to avoid the risk of overworking muscles and damaging vocal cords. Any exercises that proved to be challenging to perform without support from the music therapist (as reported by participants) were excluded. For example, Exercise VIII (cantillation of the syllable sequence /mananga/) was excluded for all participants and Exercise X (impulse diaphragmatic breathing) was excluded for participants who were easily fatigued. The participants had an opportunity to discuss the new exercises with the therapist during the last session. All the participants found the new exercises comfortable to perform.

Considering that ALS is, in most cases, a rapidly progressive disease, it was crucial to ensure the continuity of services after the end of the treatment phase. The participants were advised to seek help from the music therapy staff at ALS Moscow Centre to adjust the exercise sets as needed in the future. These music therapists were provided with all the information needed for providing these services.

Discussion of the biomedical data

No statistical analysis was performed, since a much larger cohort would be needed to make reliable calculations. Whilst the mean trends for the majority of biomedical measurement parameters suggest that the music therapy intervention was beneficial for the participants' bulbar and respiratory functions, no consistent patterns could be found for the changes in outcome measurements across the group. There were no participants for whom all the trends were positive. There were no participants for whom all the trends were negative. No patterns for the demographics (sex and age) or types of onset affecting the participants' responses to treatment were found. Similarly, no correlation between adherence to the suggested independent exercise routine and changes in outcome measurements was found.

The biomedical data were collected as secondary data in this study, mostly in order to understand if the chosen outcome measurements and parameters were feasible and sensitive enough to measure the changes in bulbar and respiratory functioning in ALS across the 16 weeks. Collecting these data also provided the first insight into the potential effects of the music therapy protocol on respiration, speech, cough and swallowing of persons with ALS.

Whilst respiratory function assessment tools for ALS are largely standardized, evaluation of bulbar dysfunction in ALS stays the front and central topic of ALS clinical care and research. Broad variability of clinical settings and available resources further complicate the search for a unified, effective approach to bulbar assessment. Only recently, a year after the completion of the intervention period, “Provisional best practices guidelines for the evaluation of bulbar dysfunction in Amyotrophic Lateral Sclerosis” suggesting the first uniform assessment of speech and swallow function in ALS were published (Pattee *et al.*, 2019). However, many evaluation parameters recommended in these guidelines were used in the current study.

For example, videofluoroscopic study (VFSS) has been recommended in the guidelines document as the most accurate tool to assess the risk for silent aspiration and dysphagia in people with ALS. This is a laboratory-based test, which may impose more burden onto the participants than home-based tests. The participants are required to travel to a medical facility, the procedure takes at least 30 minutes, and some participants may find the taste and consistency of the barium unpleasant. However, our study demonstrates that, with adequate support from a community-based ALS care centre, VFSS procedure was tolerated well by ALS patients. Such support included volunteer assistance with transportation and navigating the non-accessible urban environment. All the participants chose to take part in all three VFSS assessments during the first 12 weeks of the study.

Frame-by-frame analysis of video clips recorded during videofluoroscopic study was used to assess long-term changes in swallowing for this study. The analysis was performed during the data-analysis phase of the study by a highly qualified speech-language pathologist who was blinded to the time order of the video clip recordings and used published operational definitions (Steele *et al.*, 2019). Such specialist analysis of VFSS video clips has been reported to be a reliable (Waito *et al.*, 2019) and feasible way to evaluate swallowing dysfunction in ALS.

Additionally, the swallowing subscale of the self-reported Center for Neurologic Study-Bulbar Function Scale (CNS-BFS) was used to assess the participants’ perceived change in swallowing ability. This subscale was chosen over the Eating Assessment Tool-10 (Plowman *et al.*, 2016a) recommended by the 2019 guidelines, firstly, because it takes shorter time (which is essential when multiple measurements are obtained) and, secondly, for consistency, since the Center for Neurologic Study-Bulbar Function Scale (CNS-BFS), speech subscale, was used to assess the self-perceived change in speech.

The “Provisional best practices guidelines” document recommends that the CNS-BFS scale and clinician-based ratings of dysarthria severity based on a spontaneous speech sample and a short paragraph oral reading sample are used to assess speech in ALS. Voice samples were used to assess long-term changes in speech for this study. However, as discussed in Chapter 4. Outcome measures and data collection, acoustic analysis of voice samples in Praat computer program was preferred to clinician-based perceptual analysis for objectivity and logistic convenience (Gadesmann and Miller, 2008; Pierce, Cotton and Perry, 2013; Teixeira, Oliveira and Lopes, 2013). Whilst instrumental evaluations, including acoustic, aerodynamic and kinematic methodologies (Rong *et al.*, 2016; Yunusova *et al.*, 2011) can provide even more precise information regarding bulbar decline in ALS, these require a trained specialist's presence, may be invasive, and require purchase of specialist and expensive equipment and materials.

Voice sampling requires less expensive and less specialized equipment (Shure WH20XLR Dynamic Headset Microphone, Alesis iO Dock audio interface, Apple iPad 2 tablet and GarageBand software were used in this study). The process of recording takes less than 10 minutes of participants' time and does not require the presence of a highly trained speech language specialist at the point of data collection, as it may be performed by a trained research assistant. Acoustic analysis of these voice samples has to be planned and carried out by a qualified phonetician or speech-language specialist who is blinded to the time order of the recordings. Such analysis is a largely automated, objective, fast and inexpensive way to assess speech in ALS when instrumental evaluation is not possible.

One important exception to this is nasalance assessment. Increased nasalance (hypernasality) is a prominent characteristic of speech decline in ALS and directly affects speech intelligibility (Carrow *et al.*, 1974). Acoustic analysis does not offer consistent assessment of hypernasality in speech, unlike other speech parameters. Clinician-based analysis of the recorded samples was conducted for this study to assess nasalance of the voice samples perceptually. Low inter-rater reliability was calculated between the three raters, who were qualified speech pathologists. It may be concluded that perceptual analysis of nasalance in ALS is not reliable as well. Aerodynamic measure of nasal flow has been recently reported to be the most efficient way to evaluate velopharyngeal dysfunction in ALS (Eshghi *et al.*, 2019a) and cam be recommended for evaluation of nasalance in clinical practice and in future research.

To summarize, the standard home-based instrumental respiratory tests, videofluoroscopic study (VFSS) with subsequent frame-by-frame analysis of video clips, acoustic analysis of recorded voice samples, along with self-reported scales such as CNS-BFS used in this study, appear to be feasible and effective way to assess respiratory and bulbar function in ALS. Aerodynamic measure of nasal flow can be recommended for evaluation of nasalance in ALS.

Mean trends suggesting that the bulbar and respiratory functional parameters declined or showed slower rate of improvement during the treatment period were observed for the following outcome measures: Fundamental frequency and Vowel Space Area for speech, Penetration-Aspiration Scale score (PAS) nectar and Penetration-Aspiration Scale score (PAS) pudding for swallowing. However, the changes in these trends were minimal, each representing nearly a flat line on a graph (see Figures 43, 45, 70 and 72). It is important to note that the measurement parameters derived from VFSS clips were available only for five participants, due to the missing data, which resulted from the low quality of the recording in two cases (see Chapter 8. Biomedical data analysis results).

Most mean trends suggesting beneficial changes during the treatment period were reversed during the follow-up period, i.e. in the absence of music therapy treatment facilitated by a therapist. These trends include: Forced Vital Capacity (FVC), Maximal Inspiratory Pressure (

MIP) and Maximal Expiratory Pressure (MEP) for respiration, Center for Neurologic Study-Bulbar Function Scale (CNS-BFS) speech subscore, Maximum Phonation Time (MPT), Jitter (local), Shimmer (local), Maximum Repetition Rate – Alternating (MRR-A), Maximum Repetition Rate – Sequential (MRR-S), Harmonics-to-Noise Ratio (NHR), Speaking rate, Hypernasality level for speech and self-reported Center for Neurologic Study-Bulbar Function Scale (CNS-BFS) swallowing subscore for swallowing. No videofluoroscopic study results are available for the follow-up period, in accord with the study design.

To conclude, the biomedical data collected for this study provided a comprehensive, ALS-specific assessment of changes in respiration, speech, swallowing and cough across the run-in, treatment and follow-up phases of the study. These data provide the first evidence that the music therapy protocol is safe to use in early and mid-stage ALS and suggest that engagement in music therapy treatment was beneficial for the research participants' bulbar and respiratory functions. A subsequent study with a larger cohort is necessary to draw definite conclusions about the rehabilitative effects of the treatment.

STUDY LIMITATIONS

This research has been conducted as partial fulfilment of the requirements of Anglia Ruskin University (Cambridge, UK) for the degree of Doctor of Philosophy. In this, it has been a self-directed, autonomous research project, where the topic, the funding, the design and the implementation were conceived and carried out by the principal researcher, with the critical and effective support of the academic supervisors. Many limitations of the study are the direct consequences of the nature and format of such self-directed doctoral study and the expectations in its regard. The possible ways to overcome these limitations are discussed in "Implications for further research" section of this chapter.

Resources limitations

As noted above, working in the format of a PhD study, rather than as a part of a larger, institution-driven scientific project, the principal researcher had to conduct the treatment and the data analysis almost single-handedly, with the exception of the VFSS video analysis, and within the limitations of the available resources. This affected the design of the study, including the number of participants recruited and the outcome measures chosen.

The availability of local resources was another major limiting factor. For example, nasalance is an important speech parameter in ALS. However, there are no reliable tools to assess nasalance acoustically. Aerodynamic measure of nasal flow would be the preferred way of assessment. However, the equipment to conduct such assessment or the funds to acquire this equipment were not available. Perceptual analysis of the voice samples was conducted instead, and the results were inconclusive due to the low (53%) inter-rater reliability.

There are certain limitations to this research resulting from the disparity of treatment and evaluation between ALS clinical facilities around the world (Pattee *et al.*, 2019). Videofluoroscopic study (VFSS) is not usually performed for the patients at ALS Centre Moscow. Planning the test is beyond the professional expertise of a music therapist. The principal researcher had to rely on practice and advice of the local speech-language professionals (logopedists). Even though it was possible to arrange the test and to ensure the logistics of it, the procedure was not clearly enough defined and could not be carried out in accordance with the internationally acceptable quality standards. This resulted in the data missing due to a mistake in video capturing: some clips were only recorded by an external video camera, but not by the built-in Medical DVD recorded by the BV Pulsera Mobile C-arm fluoroscope. For the participants with the missing high-quality video recordings, no VFSS data were analyzed; VFSS data on samples with liquid consistency were not analyzed (see Missing VFSS data section, in Chapter 8. Biomedical data analysis results).

With the exception of VFSS data, the data analysis for this study was ultimately performed by the principal researcher, who also developed the experimental protocol and provided the treatment. Combining these roles could lead to biased interpretation of the data. For example, the acoustic analysis of the voice samples needs to be planned and performed by a specialist who has relevant training and professional experience conducting such analysis. There was no such person on the team. With the help of consultants, the principal researcher, who has Master's degree and a professional background in linguistics, was able to plan the data collection and to perform the analysis. However, such an arrangement could contribute to bias in data analysis. Similarly, even though the interviews with the participants were carried out by a research assistant, the principal researcher still could not be blinded to the time sequence and to the authorship of the recorded texts, and, consequently, could interpret and present the semantics of their discourse with a degree of bias.

Lastly, certain limitations result from the use of novel assessment tools in this research. New clinical and assessment guidelines and tools emerge frequently in ALS care. Whereas the Russian translation of the Edinburgh Cognitive and Behavioural ALS Screen and the ALS functional rating scale (revised), used in recruitment, has been validated, it was not the case with the Center for Neurologic Study Bulbar Function Scale (CNS-BFS). The subscores of the scale were used in this study for brief and convenient self-reported assessment of speech and swallowing dysfunction. The scale was only validated in English in April 2018 and the Russian translation made by the principal researcher and used in this study has not been validated.

Site bias

There may has been some site bias. The staff at ALS Centre Moscow was introduced to music therapy treatment several years before the study and the service was well accepted and desirable in the ALS community of the Centre. This may have affected the recruitment and the overall feasibility of the study.

Language and cultural bias

Language and cultural bias may has presented a limitation to this cross-cultural study and need to be carefully considered. In addition to the linguistic equivalence, the functional, cultural and metric equivalence, are the factors that need to be considered when research methods are translated to other (Peña, 2007).

The interviews were conducted in Russian, the language native to the participants and the research assistants, and translated into English by the principal researcher, who speaks both Russian and English. Even though language and cultural bias (Sanchez and Vargas, 2016) is, hopefully, minimized when the translator is fluent in both languages and cultures, it still has to be considered.

Ethics

The local research culture peculiarities predicated further limitations. This research protocol was conducted in compliance with international ethics guidelines on research with human participants, the Declaration of Helsinki and with General Data Protection Regulation. Ethical approvals for this study were obtained, as required by the Doctoral school, from the Faculty Research Degrees Sub Committee at Anglia Ruskin University (Cambridge, UK) and from the local ethics committee in Moscow, Russia. However, the latter presented a difficulty. Only biomedical research with human participants currently requires ethical approval in Russia. The music therapy profession is not officially recognized in Russia, the music therapy research with rehabilitative goals is not considered biomedical research and, thus, does not require an ethical approval. Ethics clearance was obtained from Moscow Municipal Independent Ethics Committee, but the procedure lacked the scrutiny usual for this kind of research. For example, no detailed risk assessment was required, and no lone worker policy was in place for the treatment phase of the study. Without written policies, the principal researcher had to rely solely on the professional guidelines and the code of ethics defined by the Certification Board for Music Therapists (USA) - the certification body the principal researcher is affiliated with. These guidelines are very broad and do not provide answers for the ambiguous situations a music therapist may encounter during home visits in a culture which is very different from the American culture. When such ambiguities arose, the principal researcher had to come up with the most ethical and culturally appropriate, yet subjective, solutions. The examples include helping a patient up after a fall, adapting the treatment protocol to focus predominantly on safety in a situation when no comprehensive examination of vocal cords could be arranged for a participant, and continuing sessions with a participant experiencing obvious distress due to psychological tension in the family.

Unequal phase durations

Finally, the duration of the follow-up phase was planned to be shorter (at four weeks) than the run-in and the treatment phases (six weeks each), due, again, to the cultural context. In the summer most people in Russia who are unemployed move temporarily to their country houses. Extending the follow-up period to six weeks could prevent full follow-up data collection. This context had to be considered when planning a study in the spring going into the summer. The calculations were adapted for the biomedical data trends to factor in the shorter follow-up period.

The research limitations described above have to be taken into careful consideration when planning a follow-up study. These limitations can be largely prevented with advanced budgeting and resources allocation, proper risk assessment, defining the lone worker guidelines for the therapist(s) providing the home-based treatment, including a speech-language specialist and a psychologist on the research team and separating the roles of therapist and the data analyst among different researchers.

IMPLICATIONS FOR FURTHER RESEARCH

Need for further research

The palliative rehabilitation model intended to preserve function and independence of persons living with ALS through enablement and self-management has been recently advocated in ALS care (Harding, Hall and Lloyd, 2019). The most recent cohort studies suggest that individualized, monitored physical exercise is safe to perform for persons with ALS (Clawson *et al.*, 2018) and that the strictly monitored exercise programs may reduce motor deterioration in ALS, as compared to the "usual care" (Lunetta *et al.*, 2016; van Groenestijn *et al.*, 2019). In line with these findings is the emerging evidence that respiratory training is well-tolerated and may lead to improvements in respiratory and bulbar function in ALS (Plowman *et al.*, 2019).

Music therapy aimed at physical rehabilitation of persons with neurological diseases is now clinically practiced in many countries and is actively researched (Thaut and Hoemberg, 2016) However, it is still a novel type of treatment that needs further introduction to healthcare systems and the increased levels of evidence. Limited literature exists to support the positive effect of music therapy treatment on psychological state and quality of life for persons living with ALS and their families (Kondo, 2017b; Raglio *et al.*, 2016; Schmid, 2016), however no research on use of music therapy in physical rehabilitation of persons with ALS was found.

This feasibility study is the first evidence for music therapy as a supportive treatment option in bulbar and respiratory rehabilitation in ALS. It introduced the idea of rehabilitative music therapy services for ALS, formulates the music therapy treatment protocol to support bulbar and respiratory functions in early and mid-stage ALS, assembles a comprehensive battery of outcome measurements for objective assessment of the effectiveness of the intervention, tests feasibility of data collection using them for the first time and provides the empirical evidence of the benefits the suggested treatment might provide to persons with ALS. The study protocol is feasible and provides a solid basis for a subsequent large-cohort research to assess the effectiveness of the suggested music therapy intervention.

Future study aims and design

Whilst randomized control trial (RCT) is considered the gold standard for evidence-based practice, there are limitations to this design specific to music therapy treatment for ALS. For example, blinding of the participants is not possible in a music therapy trial (Bradt, 2012) and there are ethical implications for randomization of the palliative patients into the control group, since no other comprehensive treatment for bulbar and respiratory decline in ALS was found in the literature. ALS presentation and progression are very heterogeneous and existing measures of assessment of ALS progression have limited sensitivity, which results in the need for long trials with large sample sizes. Better understanding of the disease would improve the overall clinical study design and allow for small sample sizes, for example, through stratification based on predictive baseline values (Ong, Tan and Holbrook, 2017).

Every person with ALS follows their own pattern of disease progression, and it is the individual rate of decline to date that may, to some extent, predict their future decline. It can be argued therefore that the design of the subsequent study should employ the same ABA design as the current study, where the participants serve as their own controls. The duration of the study should be 18 weeks: six weeks run-in phase (no treatment), six weeks therapy phase (home treatment two times per week) and six weeks wash out phase (no treatment, but the participants are encouraged to continue the independent exercise routine). Depending on the recruitment strategy, all the participants may start the trial simultaneously (like in the current study) or at various time points.

This being said, with all the limitations carefully considered, RCT design can still be utilized, as it was done in the recent studies on active music therapy for ALS (Raglio *et al.*, 2016), expiratory strength training in ALS (Plowman *et al.*, 2019) and aerobic exercise therapy for ALS (van Groenestijn *et al.*, 2019) with 30, 48 and 57 participants, respectively. The recruited participants will have to be randomized into two arms, one receiving the music therapy treatment for six weeks and the other receiving standard of care (no therapy) or an alternative treatment, e.g. respiratory training (Plowman *et al.*, 2019), meditation (Pagnini *et al.*, 2017) or yoga (Jugdutt, 2018). An additional feasibility study will have to be conducted prior to a larger RCT to evaluate the process of randomization and to establish the protocols for the control group treatment.

Recruitment strategy

Consecutive sampling strategy appears to be a fitting approach to recruitment for a follow-up study. Such a strategy allows to recruit all newly diagnosed patients at the facility if they meet the inclusion and exclusion criteria, thus preventing bias on recruitment in regards to the disease onset type, presentation, location, etc. The discussion about benefits and drawbacks of restricting the inclusion criteria to a specific type of onset when planning clinical trials for ALS continues among the researchers in the field. During the 29th International Symposium on ALS/MND in Glasgow (2018) the live debate event, entitled Innovation Landscape in ALS/MND: Designing Tomorrow's Clinical Trials Today, Inclusion and Exclusion Criteria, only highlighted the ambiguity behind the use of broad versus narrow inclusion and exclusion criteria used in ALS clinical trials. Recruiting new patients with Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) bulbar subscore ≥ 9, but ≤ 11, and the forced vital capacity (FVC) greater than 60%, regardless of the disease onset, allowed to gain the perspective on the most organic integration of the music therapy protocol under research into real life clinical ALS care. As a result, responses to the treatment protocol were observed, recorded and analyzed from patients of various demographics, rate of progression and onset types. This information is crucial for implementing the tested treatment protocol in clinical practice.

It is recommended that any future research is conducted in collaboration with ALS care centres that comply with current internationally accepted guidelines for ALS care (NICE, 2016). The information about the study may be distributed to the patients with early and mid-stage ALS when they are first referred to the centre, and search can be performed in the centre database to find and contact the participants who have been recently diagnosed and meet the inclusion criteria.

The relatively low prevalence of ALS and the relatively narrow recruitment criteria could make recruiting a large cohort challenging. A longer study may be planned with ongoing recruitment, where the participants enter the trial at different times, depending on the availability of the staff to conduct the treatment and the assessments, until the desired number of the participants is reached. Consecutive sampling strategy could still be employed in this scenario.

Another option to recruit a large sample size would be to organize a multi-site study. Regional organizations such as European Network to Cure ALS, Motor Neurone Disease Association in UK, the ALS Association in USA, Asociacion ELA Argentina may be approached. However, another feasibility study will be needed in this case to ensure the continuity of the treatment and of the research process.

Psychological screening on recruitment

The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) score was used among the inclusion criteria for the current study to assess cognitive health of the potential participants. Based on the feasibility data from the current study, it is strongly advised that a mental health assessment is added to the list of the inclusion criteria for the follow-up study.

Psychological distress, social isolation, tensed interpersonal relationships within the immediate family were observed for the participants of the current study. Often in sessions, the music therapist felt the ethical obligation to provide the basic psychological support, need for which was acute for some participants.

In the absence of effective treatment, psycho-emotional needs of persons living with ALS are many and their quality of life is predominantly dependent upon psychological, supportive and spiritual factors (Chiò *et al.*, 2004). Anxiety and depression are prevalent and undertreated in ALS (Pagnini *et al.*, 2012; Kurt *et al.*, 2007; Thakore and Pioro, 2016) and may complicate music therapy treatment implementation. The emotional state of a person affects voice production (Welham and Maclagan, 2003), which means that mental health issues in participants may confound the study results. One of the participants, a medical doctor herself, was very articulate describing her psychological needs in relation to her physical condition. She reported feeling depressed and having anxiety and reported that "emotions got in the way", adding to the strain in the body, and that she "could not speak with anyone without crying". The participant commented about feeling less anxious and more relaxed at the end of some sessions.

Screening for depression, anxiety, hopelessness, availability of social support and psychiatric illness at recruitment needs to be considered (Chiò *et al.*, 2004). This would serve two vital purposes. Firstly, with such screening in place, it is less likely that the overall physical state of the research participants, including their bulbar and respiratory functioning, will be affected by fluctuations in their mental health. Secondly, such screening may allow referrals to specialist care for those candidates who have actual mental health needs, which the music therapist, who strictly implements the study protocol, has no opportunity to fully address.

Study planning and implementation

Similar to ALS clinical care, planning and implementing an ALS supportive care study requires a cross-disciplinary expertise and effort. A music therapist who has theoretical knowledge and significant clinical experience in both neurologic and person-centered music therapy, a speech-language specialist experienced in evaluation and treatment of respiratory and bulbar dysfunction in ALS have to comprise the core of the research team. A psychologist experienced with the ALS population, a statistician, a budgeting specialist, research assistants, research nurses, coordinators and social workers or trained volunteers to assist during the laboratory visit have to be employed. It is essential that the music therapist who implements the protocol can make, as needed, references to specialist care, including, but not limited to a psychologist, a palliative care specialist, a neurologist, a nutritionist, a physical therapist.

Diligent protocols have to be written out for the music therapy treatment, for the respiratory assessment, for recording voice samples and for analyzing speech outcomes, for videofluoroscopic study and the analysis of the resulting video clips. All research team members have to be trained in the protocols pertinent to their field of expertise before the start of the trial and familiar with the basics of ALS clinical care.

Thorough risk assessment for providing home-based services has to be conducted prior to the start of the data collection and the treatment and the lone worker policies need to be in place for the therapist and all the research assistants and volunteers who make home visits to the research participants.

It is essential that the therapist, the data collector and the data analyst roles are separated in order to avoid bias in interpreting the results. The data analyst has to be blinded to the sequential order of data samples.

The aspects unique to each instance of home-based treatment have to be taken into account and, preferably, protocolized. Examples include the presence or absence of family members and other caregivers during the therapist's visit and the actual treatment and the use of the residential space.

Lastly, the treatment and the assessment have to be planned and implemented in a culturally-appropriated, non-biased way. The research team members have to be well aware of the local culture and be able to connect to participants in an authentic, yet professional manner. The assessment tools have to be translated and adapted as needed. The music pieces used in therapy intervention have to be considered within the cultural context as well.

Data collection and analysis

Whilst the wide array of outcome measurement parameters used in this study may appear excessive, it is essential to use the comprehensive, integrative approach when assessing the therapy-induced changes when researching music therapy applications for ALS rehabilitation. ALS is a rapidly progressive neurodegenerative disease. Exercise in ALS, including respiratory training (Plowman *et al.*, 2019), has been considered controversial until recently (see The role of exercise in ALS care, in Chapter 1). Currently, when studying the effect of exercise for ALS, the researcher has to be careful not only to provide the evidence for the benefits of the treatment, but also to ensure that the suggested intervention has no adverse effect on patients. Music therapy protocol used in this study is structured in such a way that it affects multiple bulbar and respiratory parameters. Hypothetically, it could conversely affect speech, swallowing and breathing domains. Hence, the multiple, comprehensive assessment parameters are necessary.

Collecting these extensive data should not, however, present a significant burden for the research participants. The respiratory and cough tests conducted by a research nurse at the participant's home, take about 10 minutes, combined. Similarly, the process of collecting the necessary voice samples for acoustic speech analysis is also home-based and takes about 10 minutes. The Center for Neurologic Studies – Bulbar Function Scale (CNS-BFS) speech and swallowing subscales assessments take about two minutes each.

Videofluoroscopic study (VFSS) assessment is the most effort- and time-consuming as it requires a visit to the laboratory, the procedure itself takes about 30 minutes, involves (if minimal and safe) radiation exposure and some participants may find the taste and consistency of the barium unpleasant. However, the current study demonstrates that the test was tolerated well by the research participants. As discussed above, a well-defined protocol for the videofluoroscopic study and the subsequent analysis needs to be in place, written out by a qualified speech-language specialist who is experienced with the framework suggested by (Steele *et al.*, 2019). Local laboratory practices and restrictions have to be evaluated prior to the start of the study to make sure the protocol can be thoroughly implemented.

Aerodynamic assessment of nasal air emission should be added to the list of the outcome measures and used to evaluate velopharyngeal dysfunction in ALS (Eshghi *et al.*, 2019b).

As discussed in Chapter 8. Biomedical data analysis results, voice sampling procedure was modified. For ethical considerations, a decision was made to not record spontaneous speech as it caused emotional distress in some participants. The oral reading passage was shortened to prevent voice fatigue. It can be recommended that no spontaneous speech samples are collected for the subsequent study and that the oral reading task is limited to a one-minute sample. The Bamboo passage can be recommended to be used as the oral reading task for native English speakers (Yunusova *et al.*, 2016). Analogous passages will have to be identified to evaluate the change in speech parameters in other languages.

Following is the suggested list of outcome measures and parameters to assess the effect of the music therapy treatment protocol on the bulbar and respiratory functions of the participants for the subsequent study. For all the outcome measures the data has to be collected at four points: Week 1 (baseline), Week 6 (beginning of treatment), Week 12 (end of treatment) and Week 18 (end of wash-out).

Outcome measures to assess the long-term changes in respiration:

Change of Forced Vital Capacity (FVC);

Change of Maximal Inspiratory Pressure (MIP);

Change of Maximal Expiratory Pressure (MEP).

Outcome measures to assess the long-term changes in cough:

Change of Peak Expiratory Flow (PEF).

Outcome measures to assess the long-term changes in speech:

Change of Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Speech subscore;

Change in acoustic assessment parameters of recorded voice (Maximum Phonation Time (MPT), Maximum Repetition Rate – Alternating (AMR), Maximum Repetition Rate – Sequential (SMR), Jitter, local, Shimmer, local, Harmonics-to-Noise Ratio (HNR), Vowel Space Area (VSA), Fundamental frequency (F0), Speaking rate, oral reading, Speech-pause ratio, oral reading, Pause frequency, oral reading);

Change of aerodynamic measure of nasal flow.

Outcome measures to assess the long-term changes in swallowing:

Change of Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Swallowing subscore;

Change in videofluoroscopic swallowing study (VFSS) results (Time-to-Laryngeal Vestibule Closure, liquid 10 mL, nectar 10 mL and pudding 10 mL; Maximum Pharyngeal Constriction Area, liquid 10 mL, nectar 10 mL and pudding 10 mL; Maximum Pharyngeal Constriction Area, liquid 10 mL, nectar 10 mL and pudding 10 mL, Peak position of the Hyoid Bone, liquid 10 mL, nectar 10 mL and pudding

10 mL; Penetration-Aspiration Scale Score (worst), liquid 10 mL, nectar 10 mL and pudding 10 mL; Total Pharyngeal Residue C24area, liquid 10 mL, nectar 10 mL and pudding 10 mL; Laryngeal vestibule closure, liquid 10 mL, nectar 10 mL and pudding 10 mL.

As discussed above, the analysis of these data has to be conducted by a qualified specialist (or specialists) other than the therapist delivering the music therapy treatment. The data analyst needs to be blinded to the sequential order of data samples.

It is essential that the "Provisional best practices guidelines for the evaluation of bulbar dysfunction in Amyotrophic Lateral Sclerosis" (Pattee *et al.*, 2019) or similar subsequent documents are taken into account, the local assessment practices and restrictions are considered and the scrupulously detailed protocols for data collection and analysis are in place when planning respiratory and bulbar assessment in ALS for clinical care and research.

Increasing adherence to independent exercise

As discussed previously, the self-reported adherence to the suggested independent exercise routine (53%) was significantly lower than the music therapy sessions attendance (95.4%). In the current study the independent exercise was presented to the participants as "suggested" rather than "required". This allowed to assess the organic motivation and response of the participants to the exercise, providing important data on tolerance.

For the subsequent study, additional strategies to increase adherence to the exercise may be considered. Firstly, the independent exercise may be presented to the research participants as obligatory, or required, rather than optional. Secondly, various ways to increase adherence to exercise could be used. These may include a daily reminder, in a form of a text message or a call to the participant (Jangi *et al.*, 2018) or asking the participants to keep a diary of exercise (McBride *et al.*, 1999; Friedman *et al.*, 2010). However, these strategies have to be carefully weighed against their potential to increase the burden of persons with ALS and their caregivers, who participate in research.

IMPLICATIONS FOR CLINICAL CARE

This study adds the much-needed evidence for music therapy applications in ALS care. The home-based music therapy treatment protocol to support bulbar and respiratory functions was tolerated well by persons with early and mid-stage ALS and perceived by them as motivating, pleasurable and beneficial. Though further, large-cohort research is needed to assess the clinical effectiveness of the protocol through the statistical analysis and to understand how it may affect survival, the treatment protocol may be recommended for experimental clinical use by professional, certified music therapists with persons who have early and mid-stage ALS (as defined by the inclusion criteria of this study).

The therapist has to be mindful of the logistical, cultural and psychological implications of conducting home-based treatment, as discussed in section Home-based music therapy treatment of this chapter. The therapist has to comply with the care guidelines and the ethical requirements of the local ALS clinical care facility. Risk assessment and lone worker policy have to be in place before the treatment starts.

Protocol implementation

Because of the complexity, heterogeneity and the relatively fast progression of the disease, it is advisable that music therapists working with ALS patients collaborate closely with the multidisciplinary care team (see Figure 4. ALS multidisciplinary care model). Music therapy interventions informed through consultations with other team specialists (for example, a speech language therapist, a social worker, a neurologist, a nutritionist, a physical therapist) will be best tailored to the needs, capabilities and limitations of every patient, and, vice versa, the observations from music therapy sessions can inform the work of the team, for the benefit of the patients.

The music therapist does not simply provide the structure, the instructions and the live music accompaniment during the session. The ongoing in-session assessment and adjustments of the protocol are key to music therapy effectiveness. The therapist needs to be sensitive to the smallest changes in the quality of the client's voice and breath, body posture, affect, behavior and language and to respond to these changes verbally, non-verbally and musically in order to meet the therapy goals.

This study demonstrates the importance of responsive, empathetic therapeutic relationships between the therapist and the patient. Establishing, maintaining and developing these relationships with the participants and, in some cases, their family members turned out to be an important part of the treatment, otherwise protocolized and very formal, as it allowed to gain trust of the participants, to make the therapy process feel safe to them, to encourage and to motivate them. The music therapist has to pay careful attention to her tone of voice, speech pace, vocabulary, use of humor, personal distance, body language and other aspects of interpersonal communication in sessions to create the environment that is most conducive to each participant's progress in therapy.

Active modeling of all exercises, careful attention to the patient's body posture, to the movements of their abdomen, to the quality and resonance of their voice were key to treatment at its initial stages, when the participants learned about the mechanics of respiration, relaxation and sound production. It is important that the music therapist performs all the exercises together with participants, with the goal to provide guidance and support and to make the exercises feel safe and manageable for the participants. Gradually the modeling can be faded and the agency passed on to the participant.

Listed below are the protocol exercises with brief commentary regarding their use in clinical practice. For detailed description of the protocol exercises refer to Appendix N - Experimental music therapy protocol for ALS. Each client's current level of functioning, disease progression and individual response to the exercise must be carefully considered and factored in when implementing the protocol.

I. Session opening and assessment. Pre- and post-session assessment for ease of respiration and ease of speech may help the therapist to understand how the client reacts to the protocol.

II. Body alignment exercise. Sitting posture may be adapted as needed and props may be used (e.g. a pillow under lower back, a table in front of the client, etc).

III. Diaphragmatic breathing exercises. Proceed by the protocol for several sessions, until the client learns how to use diaphragmatic breathing and is able to do it with minimal effort. Later (approximately by the tenth session) mixed breathing technique can be introduced. The procedure is as follows: after completing the set of the diaphragmatic breathing exercises the client is instructed to switch to the chest breathing, i.e. breathing without employing the abdomen muscles, in the way that the chest movements are visible. Three repetitions are recommended. The therapist asks the client to briefly reflect on the difference in the body sensations during the diaphragmatic breathing and the chest breathing. After that the mixed breathing technique is introduced. The therapist asks the client to combine the chest breathing and the abdominal breathing and to "breathe fully, as comfortable". Three repetitions are recommended. This exercise extension should be practiced during subsequent sessions. The purpose of this exercise is to increase the client's awareness of the possible breathing techniques, thus providing them with more respiration options to use in a real-life setting.

IV. Controlled breathing and lip seal exercise. Proceed by the protocol.

V. Music assisted relaxation for voice production. Proceed by the protocol.

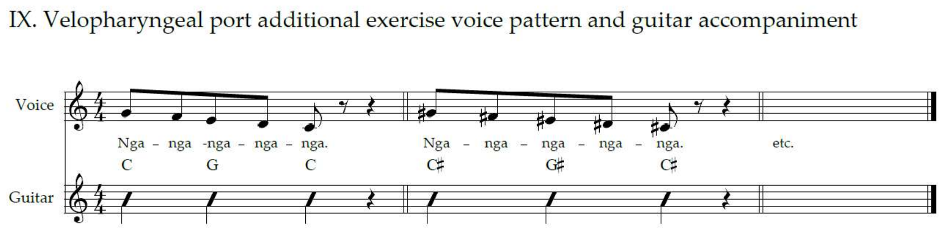
VI. "Ping pong" soft palate exercise. Proceed by the protocol.

VII. Phonation exercises. Therapist needs to make sure that the client does not strain their voice; the sound must be light and breathy. For clients with prominent hypernasality, /g/ sound can be substituted for /m/ in Exercise VII.2.

VIII. Consonant range cantillation exercise. This exercise is fun and motivating, and some clients tend to overdo it, which can potentially lead to unnecessary fatigue. Therapist has to be mindful of this and limit the number of repetitions as needed.

IX. Velopharyngeal port exercise. If the original exercise is tolerated well by the client, an additional version (extension) of the exercise can be introduced later in the course of treatment. This extension exercise follows the same musical pattern, but is sung on "nga" syllable and allows for greater voice resonance. This version should immediately follow the velopharyngeal port exercise described in the original protocol. The tempo and range should match the capabilities of each client. See the notation in Figure 78. Transcription of exercise IX. Velopharyngeal port additional exercise.

Figure 50. Transcription of exercise IX. Velopharyngeal port additional exercise



X. Impulse diaphragmatic breathing exercise. This exercise requires significant physical effort (abdomen movement). It may be excluded for the clients who are easily fatigued.

XI. Sustained vowels production exercises. Clients who experience muscle tightness around their jaw, which prevents them from precisely articulating the vowels, may be encouraged to hold their jaw with fingers during these exercises to relax the jaw into the proper position.

XII. Laryngeal elevation through vocalization (gliding vowels) exercise. Proceed by the protocol.

XIII. Vocal cords relaxation exercises. Proceed by the protocol. These exercises (separately or in complex) can be used at any time during the session if the client experiences voice fatigue.

XIV. Preferred song performance. The song may be changed if it presents physical difficulty for the client after adjustments in the tempo and the key have been made or if the client has a strong emotional reaction to this song.

XIV. Session closure and assessment. Proceed by the protocol.

The ranges and tempos of the exercises have to be adjusted to match the actual abilities of each client at the current session. Initially these ranges and tempos should be limited to each client's "comfort zone" and then gradually expanded to moderately challenge the client.

Clients who experience improved speech as a result of therapy may start overusing their voice. The therapist needs to make every effort to prevent the client from overusing their voice by excessive talking both in music therapy sessions and in everyday situations. A handout similar to the one presented in Appendix H - Voice care guidelines for research participants - people with ALS, should be provided for each client. The therapist needs to keep regularly reminding the client not to overuse their voice.

Independent exercise routine and duration of treatment

It has been argued earlier in this section that more frequent music therapy sessions following the protocol could potentially benefit persons with ALS. The feasibility data on tolerance of the protocol, short-term, and recommendations for other clinical populations (Thaut and Hoemberg, 2016) allow us to conclude that it would be safe to increase the frequency of the home-based treatment up to four sessions per week, if it is practical for each particular clinical situation.

Independent exercise routine should be introduced during the second week of treatment. Exercises, with the necessary individual adjustments based on clinical observations, should be presented in both the audio format and as printed out instructions. The audio guide should provide the spoken instructions for each exercise and the supporting musical structures consisting of the accompaniment (including the metronome sound) and the singing and breathing patterns performed in their entirety by the music therapist. Participants of the study reported that the patterns performed by the therapist were helpful (as opposed to providing the accompaniment only). The independent exercises sets have to be adjusted on a regular basis to best suit the client's current needs and abilities.

Recording the audio guide tracks for the independent exercise sets and adjusting them regularly in response to each client's progress and disease-related changes requires considerable effort and time from a music therapist. Alternatively, the accompaniment for the exercises could be recorded as midi piano or midi guitar using any professional audio recording software (e.g. Logic, ProTools, Cubase) where the therapist can make individual adjustments, such as transposition (pitch changes) and tempo changes. However, the study participants commented that the music therapist's singing was an important component of the audio guide, modeling and leading their exercises. Unfortunately, quality voice tracks automation may not be as easily achieved as instrumental accompaniment automation.

The duration of the treatment was six weeks during the study, for the research purposes. It can be argued that ongoing music therapy services may be appropriate for persons with ALS as a supportive treatment, because of the ongoing deterioration of bulbar and respiratory functions, as well as of the overall physical condition that is characteristic of this disease. The exercises may be gradually adapted and then excluded as appropriate according to the actual level of client's functioning. The articulation exercises will have to be excluded first, and vocalization and breathing exercises have to be modified and gradually faded out over the course of several months (or years, depending on the disease progression). The goals of the treatment can be gradually shifted from physical rehabilitation to psychological support and quality of life. The music assisted relaxation can become the bridging intervention to the end-of-life music therapy treatment.

Equipment

Equipment needed to implement this music therapy protocol is not numerous, relatively inexpensive and portable. It includes an acoustic guitar in a case, a melodica in a case, a smartphone with a music player app and a metronome app, a pocket-size speaker for sound amplification and a binder containing visual aids, treatment protocol, assessment scales and data entry forms. However, an individual replaceable tube mouthpiece for the melodica has to be provided to each patient and the expenses have to be planned accordingly.

Addressing the psychological needs of persons with ALS

There is evidence that psychological well-being is related to improved prognosis and slower disease progression in people with chronic conditions (Hernandez *et al.*, 2017). Clinical observations from the music therapy sessions with people with ALS preceding the current study and feedback from the study participants suggest that communication with the music therapist affects the participants' immediate emotional state positively and may lead to perceived short-term improvements in speech production.

Balancing physical rehabilitation goals of the treatment protocol and psycho-emotional needs of study participants may at times present an ethical dilemma for the music therapist. The time for each session is limited and the protocol is structured to reach very particular objectives from bulbar and respiratory domains. The music therapist may consider using a psychological screening test on intake to rule out pathological mental health conditions, consulting with a psychologist from the multidisciplinary team who follows the patient prior to start of treatment and/or making a referral as needed if the client presents with psychological distress during the course of treatment.

Music therapy for ALS: possibilities beyond the current protocol

Albeit currently underused, music therapy could be one of the modalities of supportive rehabilitation in ALS, providing multiple benefits for persons with ALS and their families. The treatment protocol designed for this study illustrates only some of the possible clinical music therapy applications for ALS. Music therapy is multifaceted and can affect the whole person (Magee, 2020). Music therapy interventions tailored to individual clinical needs, preferences and capabilities of persons with ALS can be designed to provide opportunities for psycho-emotional support and counseling, relaxation and sleep facilitation, verbal and nonverbal self-expression and communication, mood enhancement, energy boost and motivation, pain management, improving family relationship dynamics, socialization, behavioural and cognitive symptoms management, and, with proper precautions, for physical rehabilitation. Music therapy can also address caregiver's stress, which is one of the main factors contributing to the caregiver burden in ALS (Lillo, Mioshi and Hodges, 2012; Aoun *et al.*, 2013; Galvin *et al.*, 2016). During the current study family members who participated in sessions fed back that music therapy had a beneficial psychological effect for them, bringing them opportunities for communication and positive emotions. Interventions for children and young caregivers of persons with ALS are much needed and awaited in the field (Kavanaugh *et al.*, 2020). Such interventions have to be planned by a professional music therapist, with consideration to the best practice, patients' physical and psychological safety, the published evidence from music therapy and ALS-related research and, preferably, in collaboration with other specialists – members of the ALS multidisciplinary care team.

Telehealth options for providing the music therapy treatment may be explored. The Discussion chapter of this thesis is being written during the worldwide lockdowns due to coronavirus (SARS-CoV-2) pandemic. Persons with ALS are at higher risk for developing more serious complications from the COVID-19 illness. Music therapy video sessions conducted through online platforms (such as HIPAA compliant platform called Doxy.me) may become an alternative to the in-person treatment, reducing the risk of infection. At the same time this may allow to increase the music therapy service capacity by eliminating the time needed for travel. Online music therapy services are a largely uncharted territory for now, with the logistics, technology, ethics, advantages and limitations still being discovered. Whilst no literature on music therapy telehealth could be found, reportedly, many music therapists around the world are currently offering online services for a wide range of clinical populations. New evidence and new professional guidelines are likely to emerge in the following years to support this kind of work.

CONCLUSION

ALS is a devastating fatal disease leading to over 100,000 deaths worldwide each year, and its prevalence is increasing. The disease affects not only the physical functioning of individuals, but also the psychological well-being of its sufferers and their caretakers, in a major way. No curative treatment currently exists.

In recent years the idea of rehabilitative support with the purpose to improve the quality of life and the functional independence of persons with ALS has received attention. New evidence on the exercise to support physical functioning of persons with ALS emerges. Contrary to the previous understanding, moderate, individualized, specialist-supervised exercise is now considered safe and beneficial for persons with ALS.

Music therapy is the evidence-based professional clinical application of music and its elements. Advances in neuroimaging and growing scientific evidence have made it possible to use music more effectively to treat cognitive, sensory, and motor dysfunctions that come from human neurologic diseases.

This study presents the first music therapy protocol to support bulbar and respiratory functions of persons with early and mid-stage ALS. The data from the 16-weeks ABA design feasibility trial suggest that the music therapy protocol has no adverse effect on bulbar and respiratory functions of persons with ALS, short-term or long-term, and that the home-based treatment was perceived as pleasant, motivating and beneficial by the seven research participants.

Based on this information, the treatment protocol, with necessary individual adjustments outlined in this thesis, may be recommended for use in clinical practice by professional music therapists who work with persons affected by ALS. However, higher level of evidence for protocol effectiveness is still needed.

A comprehensive battery of outcome measurements and parameters to reliably evaluate the therapy-induced change in bulbar and respiratory functions was defined. Using these measurements, the biomedical data were collected as secondary data in this during the trial. Positive trends for bulbar and respiratory parameters were observed as a result of the music therapy treatment.

The study protocol was feasible, with minor modifications that were described. A follow-up large-cohort study with the aim to assess the effectiveness of the treatment protocol is warranted.

Finally, music therapy, in various forms and applications, may deliver a unique combination of psychological, physical, social and communicative benefits for persons with ALS, their families and caregivers. This research is one of the steps in the line of work to provide solid scientific evidence for the successful integration of music therapy services into a clinic-based multidisciplinary ALS care.

REFERENCES

Abrahams, S., Newton, J., Niven, E., Foley, J. and Bak, T. H. (2014) 'Screening for cognition and behaviour changes in ALS', *Amyotroph Lateral Scler Frontotemporal Degener,* 15(1-2), pp. 9-14.

Achi, E. Y. and Rudnicki, S. A. (2012) 'ALS and Frontotemporal Dysfunction: A Review', *Neurol Res Int,* 2012, pp. 806306.

Adams, J., Lee, M. and Peng, W. (2018) 'Critical Review of Complementary and Alternative Medicine Use in Amyotrophic Lateral Sclerosis: Prevalence and Users' Profile, Decision-Making, Information Seeking, and Disclosure in the Face of a Lack of Efficacy', *Neurodegener Dis,* 18(4), pp. 225-232.

Almeida, J., Silvestre, R., Pinto, A. and Carvalho, M. (2012) 'Exercise and amyotrophic lateral sclerosis', *Official Journal of the Italian Neurological Society,* 33(1), pp. 9-15.

Alter, D., O'Sullivan, M., Oh, P., Redelmeier, D., Marzolini, S., Liu, R., Forhan, M., Silver, M., Goodman, J. and Bartel, L. (2015) 'Synchronized personalized music audio-playlists to improve adherence to physical activity among patients participating in a structured exercise program: a proof-of-principle feasibility study', *Sports Medicine - Open,* 1(23).

AMTA (2019) *American Music Therapy Association Code of Ethics*.

Andersen, P. M., Abrahams, S., Borasio, G. D., de Carvalho, M., Chio, A., Van Damme, P., Hardiman, O., Kollewe, K., Morrison, K. E., Petri, S., Pradat, P. F., Silani, V., Tomik, B., Wasner, M., Weber, M. and Sclerosis:, E. T. F. o. D. a. M. o. A. L. (2012) 'EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force', *Eur J Neurol,* 19(3), pp. 360-75.

Anonymous (2020) *Unproven treatments*: Motor Neurone Disease Association. Available at: https://www.mndassociation.org/research/about-mnd-research/clinical-trials/unproven-treatments/ (Accessed: March 15 2020.

Aoun, S. M., Bentley, B., Funk, L., Toye, C., Grande, G. and Stajduhar, K. J. (2013) 'A 10-year literature review of family caregiving for motor neurone disease: moving from caregiver burden studies to palliative care interventions', *Palliat Med,* 27(5), pp. 437-46.

Arthur, K. C., Calvo, A., Price, T. R., Geiger, J. T., Chiò, A. and Traynor, B. J. (2016) 'Projected increase in amyotrophic lateral sclerosis from 2015 to 2040', *Nat Commun,* 7, pp. 12408.

Ashworth, N. L. (2012) 'Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease', *The Cochrane Database Of Systematic Reviews,* (2), pp. CD004156.

Atassi, N., Yerramilli-Rao, P., Szymonifka, J., Yu, H., Kearney, M., Grasso, D., Deng, J., Levine-Weinberg, M., Shapiro, J., Lee, A., Joseph, L., Macklin, E. A. and Cudkowicz, M. E. (2013) 'Analysis of start-up, retention, and adherence in ALS clinical trials', *Neurology,* 81(15), pp. 1350-5.

Baird, A. and Samson, S. (2015) 'Music and dementia', *Prog Brain Res,* 217, pp. 207-35.

Baker, F., Wigram, T. and Gold, C. (2005) 'The effects of a song-singing programme on the affective speaking intonation of people with traumatic brain injury', *Brain Inj,* 19(7), pp. 519-28.

Bakker, L. A., Schröder, C. D., van Es, M. A., Westers, P., Visser-Meily, J. M. A. and van den Berg, L. H. (2017) 'Assessment of the factorial validity and reliability of the ALSFRS-R: a revision of its measurement model', *J Neurol,* 264(7), pp. 1413-1420.

Bandini, A., Green, J., Wang, J., Campbell, T., Zinman, L. and Yunusova, Y. (2018) 'Kinematic Features of Jaw and Lips Distinguish Symptomatic From Presymptomatic Stages of Bulbar Decline in Amyotrophic Lateral Sclerosis', *Journal of Speech, Language and Hearing Research (Online),* 61(5), pp. 1118-1129.

Bedlack, R. and Hardiman, O. (2009) 'ALSUntangled (ALSU): a scientific approach to off-label treatment options for people with ALS using tweets and twitters', *Amyotroph Lateral Scler,* 10(3), pp. 129-30.
Bedlack, R. S., Joyce, N., Carter, G. T., Paganoni, S. and Karam, C. (2015) 'Complementary and Alternative Therapies in Amyotrophic Lateral Sclerosis', *Neurol Clin,* 33(4), pp. 909-36.
Bello-Haas, V. D. (2007) 'A randomized controlled trial of resistance exercise in individuals with ALS', *Neurology,* 68(23), pp. 2003.
Bernardi, L., Porta, C. and Sleight, P. (2006) 'Cardiovascular, cerebrovascular, and respiratory changes induced by different types of music in musicians and non-musicians: the importance of silence', *Heart,* 92(4), pp. 445-52.
Beukelman, D., Fager, S. and Nordness, A. (2011) 'Communication Support for People with ALS', *Neurology Research International,* 2011.
Boersma, P. and van Heuven, V. (2001) 'Speak and unSpeak with PRAAT', *Glot international,* 5(9/10).
Bonafede, R. and Mariotti, R. (2017) 'ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles.(Report)(Brief article)', *Frontiers in Cellular Neuroscience,* 11.
Borrell-Carrió, F., Suchman, A. L. and Epstein, R. M. (2004) 'The biopsychosocial model 25 years later: principles, practice, and scientific inquiry', *Ann Fam Med,* 2(6), pp. 576-82.
Bourke, S. C., Tomlinson, M., Williams, T. L., Bullock, R. E., Shaw, P. J. and Gibson, G. J. (2006) 'Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial', *Lancet Neurol,* 5(2), pp. 140-7.
Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., Bakken, S., Kaplan, C. P., Squiers, L., Fabrizio, C. and Fernandez, M. (2009) 'How we design feasibility studies', *Am J Prev Med,* 36(5), pp. 452-7.
Bowen, L. K. (2013) 'Effects of Parkinson's Disease on Fundamental Frequency Variability in Running Speech', *Journal Of Medical Speech-Language Pathology,* 21(3), pp. 235.
Bradt, J. (2012) 'Randomized Controlled Trials in Music Therapy: Guidelines for Design and Implementation', *J Music Ther,* 49(2), pp. 120-49.
Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative Research in Psychology,* 3, pp. 77-101.
Brinkmann, J. R., Andres, P., Mendoza, M. and Sanjak, M. (1997) 'Guidelines for the use and performance of quantitative outcome measures in ALS clinical trials', *J Neurol Sci,* 147(1), pp. 97-111.
Brooks, B. R., Miller, R. G., Swash, M., Munsat, T. L. and Diseases, W. F. o. N. R. G. o. M. N. (2000) 'El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis', *Amyotroph Lateral Scler Other Motor Neuron Disord,* 1(5), pp. 293-9.
Brédart, A., Marrel, A., Abetz-Webb, L., Lasch, K. and Acquadro, C. (2014) 'Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience', *Health and Quality of Life Outcomes,* 12, pp. 15.
Bukowska, A., Ekrężałek, P., Ebujas, P., Emirek, E. and Emarchewka, A. (2016) 'Neurologic music therapy training for mobility and stability rehabilitation with Parkinson's disease - A pilot study', *Frontiers in Human Neuroscience,* 9(2016).
Burns, J., Labbé, E., Williams, K. and McCall, J. (1999) 'Perceived and Physiological Indicators of Relaxation: As Different as Mozart and Alice in Chains', *Applied Psychophysiology and Biofeedback,* 24(3), pp. 197-202.
Byock, I. (1999) *Dying well: peace and possibilities at the end of life.* New York: Riverhead Books
Canga, B., Azoulay, R., Raskin, J. and Loewy, J. (2015) 'AIR: Advances in Respiration - Music therapy in the treatment of chronic pulmonary disease', *Respir Med,* 109(12), pp. 1532-9.

Carrow, E., Rivera, V., Mauldin, M. and Shamblin, L. (1974) 'Deviant speech characteristics in motor neuron disease', *Arch Otolaryngol,* 100(3), pp. 212-8.
Chen, A. (2008) 'The role of exercise in amyotrophic lateral sclerosis', *Physical Medicine And Rehabilitation Clinics Of North America,* 19(3), pp. 545.
Cheng, H. W. B., Chan, K. Y., Chung, Y. K. J., Choi, C. W., Chan, C. H., Cheng, S. C., Chan, W. H., Fung, K. S., Wong, K. Y., Chan, O. M. I. and Man, C. W. (2018) 'Supportive & palliative interventions in motor neurone disease: what we know from current literature?', *Ann Palliat Med,* 7(3), pp. 320-331.
Chernenkaya, V. Y., Gorbachev, K. V., Gorbachev, D. V., Ataulina, A. I., Fominykh, V. V., Brylev, L. V. and Guekht, A. B. (2018) '[The Edinburgh Cognitive and Behavioral ALS Screen (ECAS): a Russian version.]', *Zh Nevrol Psikhiatr Im S S Korsakova,* 118(12), pp. 36-39.
Chiao, G. Z., Larson, C. R. and Yajima, Y. e. a. (1994) 'Neuronal activity in nucleus ambiguus during deglutition and vocalization in conscious monkeys', *Experimental Brain Research,* 100(1), pp. 29–38.
Chiò, A. (2009) 'Prognostic factors in ALS: A critical review', *Amyotrophic Lateral Sclerosis: Official Publication Of The World Federation Of Neurology Research Group On Motor Neuron Diseases,* 10(5-6), pp. 310.
Chiò, A., Gauthier, A., Montuschi, A., Calvo, A., Di Vito, N., Ghiglione, P. and Mutani, R. (2004) 'A cross sectional study on determinants of quality of life in ALS', *J Neurol Neurosurg Psychiatry,* 75(11), pp. 1597-601.
Clark, I. N., Baker, F. A., Peiris, C. L., Shoebridge, G. and Taylor, N. F. (2017) 'Participant-selected music and physical activity in older adults following cardiac rehabilitation: a randomized controlled trial', *Clin Rehabil,* 31(3), pp. 329-339.
Clawson, L. L., Cudkowicz, M., Krivickas, L., Brooks, B. R., Sanjak, M., Allred, P., Atassi, N., Swartz, A., Steinhorn, G., Uchil, A., Riley, K. M., Yu, H., Schoenfeld, D. A., Maragakis, N. J. and consortium, n. (2018) 'A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis', *Amyotroph Lateral Scler Frontotemporal Degener,* 19(3-4), pp. 250-258.
Clemens-Cortez, A. (2013) 'Burnout in Music Therapists: Work, Individual, and Social Factors', *Music Therapy Perspectives,* 31(2).
Cohen, N. S. (1992) 'The effect of singing instruction on the speech production of neurologically impaired persons', *Journal of Music Therapy,* 29, pp. 87-103.
Corcia, P., Pradat, P. F., Salachas, F., Bruneteau, G., le Forestier, N., Seilhean, D., Hauw, J. J. and Meininger, V. (2008) 'Causes of death in a post-mortem series of ALS patients', *Amyotrophic lateral sclerosis,* 9(1).
Czaplinski, A., Yen, A. A. and Appel, S. H. (2006a) 'Amyotrophic lateral sclerosis: early predictors of prolonged survival', *J Neurol,* 253(11), pp. 1428-36.
Czaplinski, A., Yen, A. A. and Appel, S. H. (2006b) 'Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population', *Journal of Neurology, Neurosurgery & Psychiatry,* 77(3), pp. 390.
Dal Bello-Haas, V. and Florence, J. 2013. Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev.
Davies, R., Baker, F. A., Tamplin, J., Bajo, E., Bolger, K., Sheers, N. and Berlowitz, D. (2016) 'Music-assisted relaxation during transition to non-invasive ventilation in people with motor neuron disease: A qualitative case series', *British Journal of Music Therapy,* 30(2), pp. 74-82.
Davis, W. B., Gfeller, K. E., Thaut, M. and American Music Therapy Association. (2008) *An introduction to music therapy : theory and practice.* 3rd edn. Silver Spring, Md.: American Music Therapy Association.

del Aguila, M. A., Longstreth, W. T., McGuire, V., Koepsell, T. D. and van Belle, G. (2003) 'Prognosis in amyotrophic lateral sclerosis: a population-based study', *Neurology,* 60(5), pp. 813-9.
Desport, J. C., Preux, P. M., Truong, T. C., Vallat, J. M., Sautereau, D. and Couratier, P. (1999) 'Nutritional status is a prognostic factor for survival in ALS patients', *Neurology,* 53(5), pp. 1059-63.
Donovan, N. J., Kendall, D. L., Young, M. E. and Rosenbek, J. C. (2008) 'The Communicative Effectiveness Survey: Preliminary Evidence of Construct Validity', *American Journal of Speech-Language Pathology,* 17(4), pp. 335-Language Pathology, 2008, Vol.17(4), p.335-347.
Drory, V. E. (2001) 'The value of muscle exercise in patients with amyotrophic lateral sclerosis', *Journal Of The Neurological Sciences,* 191(1-2), pp. 133.
Eley, R. and Gorman, D. (2010) 'Didgeridoo playing and singing to support asthma management in Aboriginal Australians', *J Rural Health,* 26(1), pp. 100-4.
Engel, G. L. (1977) 'The need for a new medical model: a challenge for biomedicine', *Science,* 196(4286), pp. 129-36.
Eshghi, M., Richburg, B., Yunusova, Y. and Green, J. R. 'I nstrumental Evaluation of Velopharyngeal Dysfunction in Amyotrophic Lateral Sclerosis', *International Congress of Phonetic Sciences ICPHS*, pp. 2996–3000.
Eshghi, M., Richburg, B., Yunusova, Y. and Green, J. R. 'Instrumental Evaluation of Velopharyngeal Dysfunction in Amyotrophic Lateral Sclerosis', *International Congress of Phonetic Sciences ICPHS*, pp. 2996–3000.
Eshghi, M., Stipancic, K. L., Mefferd, A., Rong, P., Berry, J. D., Yunusova, Y. and Green, J. R. (2019c) 'Assessing Oromotor Capacity in ALS: The Effect of a Fixed-Target Task on Lip Biomechanics', *Front Neurol,* 10, pp. 1288.
Fang, T., Al Khleifat, A., Meurgey, J.-H., Jones, A., Leigh, P. N., Bensimon, G. and Al-Chalabi, A. (2018) 'Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study', *The Lancet Neurology,* 17(5), pp. 416-422.
Fernandez-Lazaro, C. I., García-González, J. M., Adams, D. P., Fernandez-Lazaro, D., Mielgo-Ayuso, J., Caballero-Garcia, A., Moreno Racionero, F., Córdova, A. and Miron-Canelo, J. A. (2019) 'Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study', *BMC Fam Pract,* 20(1), pp. 132.
Fishbach, A. and Choi, J. (2012) 'When thinking about goals undermines goal pursuit', *Organizational Behavior and Human Decision Processes,* 118.
Forrest, L. 'Using Music Therapy in the Symptom Management of Patients
with Motor Neurone Disease'. *10th World congress on music therapy*, Oxford, UK.
Friedman, S. H., Kaplan, R. S., Rosenthal, M. B. and Console, P. (2010) 'Music Therapy in Perinatal Psychiatry: Use of Lullabies for Pregnant and Postpartum Women with Mental Illness', *Music and Medicine,* 2, pp. 219-225.
Gadesmann, M. and Miller, N. (2008) 'Reliability of speech diadochokinetic test measurement', *Int J Lang Commun Disord,* 43(1), pp. 41-54.
Galvin, M., Corr, B., Madden, C., Mays, I., McQuillan, R., Timonen, V., Staines, A. and Hardiman, O. (2016) 'Caregiving in ALS - a mixed methods approach to the study of Burden', *BMC Palliat Care,* 15(1), pp. 81.
Green, J. R., Beukelman, D. R. and Ball, L. J. (2004) 'Algorithmic Estimation of Pauses in Extended Speech Samples of Dysarthric and Typical Speech', *J Med Speech Lang Pathol,* 12(4), pp. 149-154.
Green, J. R., Yunusova, Y., Kuruvilla, M. S., Wang, J., Pattee, G. L., Synhorst, L., Zinman, L. and Berry, J. D. (2013) 'Bulbar and speech motor assessment in ALS: Challenges and future

directions', *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration,* 14(7-8), pp. 494-500.
Gregory, D. (2002) 'Music Listening for Maintaining Attention of Older Adults with Cognitive Impairments', *Journal of Music Therapy,* 39(4), pp. 244-264.
Gwathmey, K. G. and Berggren, K. N. (2019) 'Reflections on the implementation of the provisional best practices guidelines for the evaluation of bulbar dysfunction in ALS', *Muscle Nerve,* 59(5), pp. 523-524.
Haas, F., Distenfeld, S. and Axen, K. (1986) 'Effects of perceived musical rhythm on respiratory pattern', *J Appl Physiol (1985),* 61(3), pp. 1185-91.
Haneishi, E. (2001) 'Effects of a music therapy voice protocol on speech intelligibility, vocal acoustic measures, and mood of individuals with Parkinson's disease', *Journal Of Music Therapy,* 38(4), pp. 273.
Hanser, S. B. (2018) *The new music therapist's handbook.* 3rd edn.: Berklee Press Publications.
Hanson, K., Yorkston, K. and Britton, D. (2011) 'Dysarthria in amyotrophic lateral sclerosis: a systematic review of characteristics, speech treatment, and augmentative and alternative communication options.(Report)', *Journal of Medical Speech - Language Pathology,* 19(3), pp. 12.
Hardiman, O. (2012) 'The expansions of ALS', *Neurology,* 79(9), pp. 842.
Harding, Z., Hall, C. and Lloyd, A. (2019) 'Rehabilitation in palliative care: a qualitative study of team professionals', *BMJ Support Palliat Care*.
Hecht, M. (2002) 'Subjective experience and coping in ALS', *Amyotrophic Lateral Sclerosis And Other Motor Neuron Disorders: Official Publication Of The World Federation Of Neurology, Research Group On Motor Neuron Diseases,* 3(4), pp. 225.
Hernandez, R., Bassett, S. M., Boughton, S. W., Schuette, S. A., Shiu, E. W. and Moskowitz, J. T. (2017) 'Psychological Well-Being and Physical Health: Associations, Mechanisms, and Future Directions', *Emotion Review,* 10(1), pp. 18-29.
Holden, S. K., Sheffler, J., Stewart, R., Thompson, S., Persson, J., Finseth, T., Sillau, S. and Kluger, B. M. (2019) 'Feasibility of Home-Based Neurologic Music Therapy for Behavioral and Psychological Symptoms of Dementia: A Pilot Study', *J Music Ther,* 56(3), pp. 265-286.
Horne-Thompson, A. and Grocke, D. (2008) 'The effect of music therapy on anxiety in patients who are terminally ill', *Journal of palliative medicine,* 11(4), pp. 582.
Illán-Gala, I., Alcolea, D., Montal, V., Dols-Icardo, O., Muñoz, L., de Luna, N., Turón-Sans, J., Cortés-Vicente, E., Sánchez-Saudinós, M. B., Subirana, A., Sala, I., Blesa, R., Clarimón, J., Fortea, J., Rojas-García, R. and Lleó, A. (2018) 'CSF sAPPβ, YKL-40, and NfL along the ALS-FTD spectrum', *Neurology,* 91(17), pp. e1619-e1628.
Jangi, M., Ferandez-de-Las-Penas, C., Tara, M., Moghbeli, F., Ghaderi, F. and Javanshir, K. (2018) 'A systematic review on reminder systems in physical therapy', *Caspian J Intern Med,* 9(1), pp. 7-15.
Jensen, L., Djurtoft, J. B., Bech, R. D., Nielsen, J. L., Jørgensen, L. H., Schrøder, H. D., Frandsen, U., Aagaard, P. and Hvid, L. G. (2017) 'Influence of Resistance Training on Neuromuscular Function and Physical Capacity in ALS Patients', *Journal of Neurodegenerative Diseases,* 2017.
Ji, A. L., Zhang, X., Chen, W. W. and Huang, W. J. (2017) 'Genetics insight into the amyotrophic lateral sclerosis/frontotemporal dementia spectrum', *J Med Genet,* 54(3), pp. 145-154.
Jugdutt, B. I. (2018) 'Can Yoga and Physiotherapy Benefit Patients in Weight Loss Programs and with ALS?', *Journal of Yoga and Physiotherapy*.
Jungblut, M., Huber, W., Pustelniak, M. and Schnitker, R. (2012) 'The impact of rhythm complexity on brain activation during simple singing: an event-related fMRI study', *Restor Neurol Neurosci,* 30(1), pp. 39-53.

Kamat, S. S. a. (2015) *Practical applications of mechanical ventilation.* Second edition. edn.
Kaplan, M. (2010) 'A frame of reference for motor skill acquisition', in Kramer, P. and Hinojosa, J. (eds.) *Frames of reference for pediatric occupational therapy.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins.
Kaub-Wittemer, D., Steinbüchel, N. V., Wasner, M., Laier-Groeneveld, G. and Borasio, G. D. (2003) 'Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers', *Journal of Pain and Symptom Management,* 26(4), pp. 890-896.
Kavanaugh, M. S., Cho, C. C., Howard, M., Fee, D. and Barkhaus, P. E. (2020) 'US data on children and youth caregivers in amyotrophic lateral sclerosis', *Neurology,* 94(14), pp. e1452-e1459.
Kearney, E., Giles, R., Haworth, B., Faloutsos, P., Baljko, M. and Yana, Y. (2017) 'Sentence-Level Movements in Parkinson's Disease: Loud, Clear, and Slow Speech', *Journal of Speech, Language, and Hearing Research,* 60(12), pp. 3426-3440.
Khairoalsindi, O. A. and Abuzinadah, A. R. (2018) 'Maximizing the Survival of Amyotrophic Lateral Sclerosis Patients: Current Perspectives', *Neurol Res Int,* 2018, pp. 6534150.
Khalfa, S., Bella, S. D., Roy, M., Peretz, I. and Lupien, S. J. (2003) 'Effects of Relaxing Music on Salivary Cortisol Level after Psychological Stress', *Annals of the New York Academy of Sciences,* 999(1), pp. 374-376.
Kim, H. M., Choi, K. H. and Kim, T. W. (2013) 'Patients' radiation dose during videofluoroscopic swallowing studies according to underlying characteristics', *Dysphagia,* 28(2), pp. 153-8.
Kim, S. J. (2010) 'Music Therapy Protocol Development to Enhance Swallowing Training for Stroke Patients with Dysphagia', *Journal of Music Therapy,* 47(2), pp. 102-119.
Kitano, K., Asakawa, T., Kamide, N., Yorimoto, K., Yoneda, M., Kikuchi, Y., Sawada, M. and Komori, T. (2018) 'Effectiveness of Home-Based Exercises Without Supervision by Physical Therapists for Patients With Early-Stage Amyotrophic Lateral Sclerosis: A Pilot Study', *Arch Phys Med Rehabil,* 99(10), pp. 2114-2117.
Knibb, J. A., Keren, N., Kulka, A., Leigh, P. N., Martin, S., Shaw, C. E., Tsuda, M. and Al-Chalabi, A. (2016) 'A clinical tool for predicting survival in ALS', *Journal of Neurology, Neurosurgery & Psychiatry*.
Koelsch, S. (2014) 'Brain correlates of music- evoked emotions', *Nature Reviews Neuroscience,* 15(3), pp. 170.
Kondo, K. (2017a) 'Music therapy for patients with amyotrophic lateral sclerosis receiving home mechanical ventilation', *Journal of the Neurological Sciences,* 381(561 – 756).
Kondo, K. (2017b) 'Music therapy for patients with amyotrophic lateral sclerosis receiving home mechanical ventilation', *Journal of the Neurological Sciences,* 381(561 – 756).
Kurt, A., Nijboer, F., Matuz, T. and Kübler, A. (2007) 'Depression and anxiety in individuals with amyotrophic lateral sclerosis: epidemiology and management', *CNS Drugs,* 21(4), pp. 279-91.
Langhammer, B., Sagbakken, M., Kvaal, K., Ulstein, I., Nåden, D. and Rognstad, M. K. (2019) 'Music Therapy and Physical Activity to Ease Anxiety, Restlessness, Irritability, and Aggression in Individuals With Dementia With Signs of Frontotemporal Lobe Degeneration', *J Psychosoc Nurs Ment Health Serv,* 57(5), pp. 29-37.
Last, J. M. (2007) *A dictionary of public health.* New York ; Oxford: Oxford University Press.
Lee, J. (2017) 'Acoustic and tongue kinematic vowel space in speakers with and without dysarthria', *International Journal of Speech-Language Pathology,* 19(2), pp. 195-205.
Lillo, P., Garcin, B., Hornberger, M., Bak, T. H. and Hodges, J. R. (2010) 'Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis', *Arch Neurol,* 67(7), pp. 826-30.

Lillo, P., Mioshi, E. and Hodges, J. R. (2012) 'Caregiver burden in amyotrophic lateral sclerosis is more dependent on patients' behavioral changes than physical disability: a comparative study', *BMC Neurology,* 12, pp. 156-156.
Lim, H. A., Miller, K. and Fabian, C. (2011) 'The effects of therapeutic instrumental music performance on endurance level, self-perceived fatigue level, and self-perceived exertion of inpatients in physical rehabilitation', *J Music Ther,* 48(2), pp. 124-48.
Lings, J. 'From 'can't' to 'can' : an exploration of the experience of
improvisation with a client with Motor Neurone Disease ', *Counterpoints: Music Therapy Practice*
in the 21st Century, First BAMT conference, Birmingham, UK.
Lisle, S. and Tennison, M. (2015) 'Amyotrophic Lateral Sclerosis: the Role of Exercise', *Current Sports Medicine Reports,* 14(1), pp. 45-46.
Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., Samus, Q., Schneider, L. S., Selbæk, G., Teri, L. and Mukadam, N. (2017) 'Dementia prevention, intervention, and care', *Lancet,* 390(10113), pp. 2673-2734.
Longinetti, E. and Fang, F. (2019) 'Epidemiology of amyotrophic lateral sclerosis: an update of recent literature', *Curr Opin Neurol,* 32(5), pp. 771-776.
Lunetta, C., Lizio, A., Sansone, V., Cellotto, N., Maestri, E., Bettinelli, M., Gatti, V., Melazzini, M., Meola, G. and Corbo, M. (2016) 'Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial', *Official Journal of the European Neurological Society,* 263(1), pp. 52-60.
Lyle, H. (2014) *Vocal Yoga: The Joy of Breathing, Singing and Sounding.* Bluecat Music & Publishing.
MacNeill, E. (2015) *Complementary Therapies Fact Sheet*.
MacNeill, E. (2016) *Alternative Treatments Fact Sheet*.
Magee, W. 1998. Singing my life, playing my self: investigating the use of familiar pre-composed music and unfamiliar improvised music in clinical music therapy with individuals with chronic neurological illness. ProQuest Dissertations Publishing.
Magee, W. (2020) 'Why include music therapy in a neuro-rehabilitation team?', *Advances in clinical neuroscience and rehabilitation*.
Magee, W. L., Clark, I., Tamplin, J. and Bradt, J. (2017) 'Music interventions for acquired brain injury', *Cochrane Database Syst Rev,* 1, pp. CD006787.
Majmudar, S., Wu, J. and Paganoni, S. 2014. Rehabilitation in amyotrophic lateral sclerosis: Why it matters.
Martin-Harris, B. and Jones, B. (2008) 'The videofluorographic swallowing study', *Phys Med Rehabil Clin N Am,* 19(4), pp. 769-85, viii.
Maslan, J., Leng, X., Rees, C., Blalock, D. and Butler, S. G. (2011) 'Maximum Phonation Time in Healthy Older Adults', *Journal of Voice,* 25(6), pp. 709-713.
Matsuo, K. (2008) 'Anatomy and physiology of feeding and swallowing: normal and abnormal', *Physical Medicine & Rehabilitation Clinics of North America,* 19(4), pp. 691-708.
Matsuo, K. and Palmer, J. B. (2009) 'Coordination of mastication, swallowing and breathing', *Japanese Dental Science Review,* 45(1), pp. 31-40.
McBride, S., Graydon, J., Sidani, S. and Hall, L. (1999) 'The therapeutic use of music for dyspnea and anxiety in patients with COPD who live at home', *J Holist Nurs,* 17(3), pp. 229-50.
McClosky, D. B. (2011) *Your Voice at Its Best.* Waveland Press, Inc.

McCullough, G. H., Kamarunas, E., Mann, G. C., Schmidley, J. W., Robbins, J. A. and Crary, M. A. (2012) 'Effects of Mendelsohn Maneuver on Measures of Swallowing Duration Post Stroke', *Topics in Stroke Rehabilitation,* 19(3), pp. 234-243.
Mefferd, A. S., Green, J. R. and Pattee, G. (2012) 'A Novel Fixed-Target Task to Determine Articulatory Speed Constraints in Persons with Amyotrophic Lateral Sclerosis', *Journal of Communication Disorders,* 45(1), pp. 35-45.
Mendelsohn, M. S. (1987) 'Function in the pharyngoesophageal segment', *The Laryngoscope,* 97(4), pp. 483.
Miller, G. R., Jackson, E. C., Kasarskis, J. E., England, D. J., Forshew, S. D., Johnston, J. W., Kalra, C. S., Katz, C. J., Mitsumoto, C. H., Rosenfeld, C. J., Shoesmith, C. C., Strong, C. M. and Woolley, C. S. (2009) 'Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology', *Neurology,* 73(15), pp. 1227-1233.
Nater, U. M., Abbruzzese, E., Krebs, M. and Ehlert, U. (2006) 'Sex differences in emotional and psychophysiological responses to musical stimuli', *International Journal of Psychophysiology,* 62(2), pp. 300-308.
Nelson, L. A., Macdonald, M., Stall, C. and Pazdan, R. (2013) 'Effects of interactive metronome therapy on cognitive functioning after blast-related brain injury: a randomized controlled pilot trial', *Neuropsychology,* 27(6), pp. 666-79.
NFOSD 2018. Swallowing Exercises Clinician Template. National Foundation of Swallowing Disorders.
Ng, A. S., Rademakers, R. and Miller, B. L. (2015) 'Frontotemporal dementia: a bridge between dementia and neuromuscular disease', *Ann N Y Acad Sci,* 1338, pp. 71-93.
Author (2016) *NG42: Motor Neurone Disease: Assessment and Management*: National Institute for Health and Clinical Excellence. Available at: https://www.nice.org.uk/guidance/ng42.
Nishio, M. and Niimi, S. (2000) 'Changes over Time in Dysarthric Patients with Amyotrophic Lateral Sclerosis (ALS): A Study of Changes in Speaking Rate and Maximum Repetition Rate (MRR)', *Clinical Linguistics & Phonetics,* 14(7), pp. 485-497.
Oh, S. I., Park, A., Kim, H. J., Oh, K. W., Choi, H., Kwon, M. J., Ki, C. S., Kim, H. T. and Kim, S. H. (2014) 'Spectrum of cognitive impairment in Korean ALS patients without known genetic mutations', *PLoS One,* 9(2), pp. e87163.
Ong, M. L., Tan, P. F. and Holbrook, J. D. (2017) 'Predicting functional decline and survival in amyotrophic lateral sclerosis', *PLoS One,* 12(4), pp. e0174925.
Paganoni, S., Karam, C., Joyce, N., Bedlack, R. and Carter, G. 2015. Comprehensive rehabilitative care across the spectrum of amyotrophic lateral sclerosis. *Neurorehabilitation.*
Pagnini, F., Marconi, A., Tagliaferri, A., Manzoni, G. M., Gatto, R., Fabiani, V., Gragnano, G., Rossi, G., Volpato, E., Banfi, P., Palmieri, A., Graziano, F., Castelnuovo, G., Corbo, M., Molinari, E., Riva, N., Sansone, V. and Lunetta, C. (2017) 'Meditation training for people with amyotrophic lateral sclerosis: a randomized clinical trial', *Eur J Neurol,* 24(4), pp. 578-586.
Pagnini, F., Simmons, Z., Corbo, M. and Molinari, E. (2012) 'Amyotrophic lateral sclerosis: time for research on psychological intervention?', *Amyotroph Lateral Scler,* 13(5), pp. 416-7.
Palovcak, M., Mancinelli, J., Elman, L. and McCluskey, L. 2007. Diagnostic and therapeutic methods in the management of dysphagia in the ALS population: Issues in efficacy for the out-patient setting. *In:* Palovcak, M. (ed.).

Paris, G., Martinaud, O., Petit, A., Cuvelier, A., Hannequin, D., Roppeneck, P. and Verin, E. (2013) 'Oropharyngeal dysphagia in amyotrophic lateral sclerosis alters quality of life', *Journal of Oral Rehabilitation,* 40(3), pp. 199-204.
Patel, B. P. and Hamadeh, M. J. (2009) 'Nutritional and exercise-based interventions in the treatment of amyotrophic lateral sclerosis', *Clinical Nutrition,* 28(6), pp. 604-617.
Pattee, G. L., Plowman, E. K., Focht Garand, K. L., Costello, J., Brooks, B. R., Berry, J. D., Smith, R. A., Atassi, N., Chapin, J. L., Yunusova, Y., McIlduff, C. E., Young, E., Macklin, E. A., Locatelli, E. R., Silani, V., Heitzman, D., Wymer, J., Goutman, S. A., Gelinas, D. F., Perry, B., Nalipinski, P., Stipancic, K., O'Brien, M., Sullivan, S. L., Pioro, E. P., Gargiulo, G., Green, J. R. and Subcommittee, C. M. o. t. N. B. (2019) 'Provisional best practices guidelines for the evaluation of bulbar dysfunction in amyotrophic lateral sclerosis', *Muscle Nerve,* 59(5), pp. 531-536.
Peckham, A. (2010) *The Contemporary Singer: Elements of Vocal Technique.*
Pedersen, I. N. and Wigram , L. O. B. T. (2002) *A Comprehensive Guide to Music Therapy: Theory, Clinical Practice, Research and Training.* Jessica Kingsley Publishers.
Pelletier, C. L. (2004) 'The effect of music on decreasing arousal due to stress: a meta-analysis', *J Music Ther,* 41(3), pp. 192-214.
Peretz, I. and Zatorre, R. J. (2005) 'Brain Organization for Music Processing', 56(1), pp. 89-114.
Petering, H. and McLean, J. 'An interdisciplinary approach of music therapy and nursing in the care of people with motor neurone disease'. *6th Australian Palliative Care Conference 2001:"Palliative Care - Learning to Live"*.
Peña, E. D. (2007) 'Lost in translation: methodological considerations in cross-cultural research', *Child Dev,* 78(4), pp. 1255-64.
Phukan, J., Elamin, M., Bede, P., Jordan, N., Gallagher, L., Byrne, S., Lynch, C., Pender, N. and Hardiman, O. (2012) 'The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population- based study', *Journal of Neurology, Neurosurgery & Psychiatry,* 83(1), pp. 102.
Pierce, J. E., Cotton, S. and Perry, A. (2013) 'Alternating and sequential motion rates in older adults', *International Journal of Language & Communication Disorders,* 48(3), pp. 257-264.
Pietkiewicz, I. and Smith, J. A. (2014) 'A practical guide to using Interpretative Phenomenological Analysis in qualitative research psychology', *Czasopismo Psychologiczne – Psychological Journal,* 20(1), pp. 7 - 14.
Pinto, A. C., Alves, M., Nogueira, A., Evangelista, T., Carvalho, J., Coelho, A., de Carvalho, M. and Sales-Luís, M. L. (1999) 'Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise?', *Journal of the Neurological Sciences,* 169(1), pp. 69-75.
Pinto, S. (2012) 'Respiratory exercise in amyotrophic lateral sclerosis', *Amyotrophic Lateral Sclerosis: Official Publication Of The World Federation Of Neurology Research Group On Motor Neuron Diseases,* 13(1), pp. 33.
Pinto, S. (2017) 'Correlation between Forced Vital Capacity and Slow Vital Capacity for the assessment of respiratory involvement in Amyotrophic Lateral Sclerosis: a prospective study', *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration,* 18(1-2), pp. 86.
Pinto, S. and de Carvalho, M. (2015) 'The R of ALSFRS-R: does it really mirror functional respiratory involvement in amyotrophic lateral sclerosis?', *Amyotroph Lateral Scler Frontotemporal Degener,* 16(1-2), pp. 120-3.
Plowman, E. K. (2015) 'Is there a role for exercise in the management of bulbar dysfunction in amyotrophic lateral sclerosis?', *Journal of Speech, Language, and Hearing Research,* 58(4), pp. 1151.
Plowman, E. K., Tabor, L. C., Robison, R., Gaziano, J., Dion, C., Watts, S. A., Vu, T. and Gooch, C. (2016a) 'Discriminant ability of the Eating Assessment Tool-10 to detect

aspiration in individuals with amyotrophic lateral sclerosis', *Neurogastroenterology & Motility,* 28(1), pp. 85-90.

Plowman, E. K., Tabor, L. C., Wymer, J. and Pattee, G. (2017) 'The evaluation of bulbar dysfunction in amyotrophic lateral sclerosis: survey of clinical practice patterns in the United States', *Amyotroph Lateral Scler Frontotemporal Degener,* 18(5-6), pp. 351-357.

Plowman, E. K., Tabor-Gray, L., Rosado, K. M., Vasilopoulos, T., Robison, R., Chapin, J. L., Gaziano, J., Vu, T. and Gooch, C. (2019) 'Impact of expiratory strength training in amyotrophic lateral sclerosis: Results of a randomized, sham-controlled trial', *Muscle Nerve,* 59(1), pp. 40-46.

Plowman, E. K., Watts, S. A., Tabor, L., Robison, R., Gaziano, J., Domer, A. S., Richter, J., Vu, T. and Gooch, C. (2016b) 'Impact of expiratory strength training in amyotrophic lateral sclerosis', *Muscle & Nerve,* 54(1), pp. 48-53.

Quanjer, P. H., Lebowitz, M. D., Gregg, I., Miller, M. R. and Pedersen, O. F. (1997) 'Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society', *Eur Respir J Suppl,* 24, pp. 2S-8S.

Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R. and Yernault, J. C. (1993) 'Lung volumes and forced ventilatory flows', *Eur Respir J,* 6 Suppl 16, pp. 5-40.

Qureshi, M. M. (2006) 'Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS)', *Amyotrophic Lateral Sclerosis: Official Publication Of The World Federation Of Neurology Research Group On Motor Neuron Diseases,* 7(3), pp. 173.

Qutub, K., Lacomis, D., Albert, S. M. and Feingold, E. (2014) 'Life factors affecting depression and burden in amyotrophic lateral sclerosis caregivers', *Amyotroph Lateral Scler Frontotemporal Degener,* 15(3-4), pp. 292-7.

Raglio, A., Bellandi, D., Baiardi, P., Gianotti, M., Ubezio, M. C. and Granieri, E. (2012) 'Music therapy in frontal temporal dementia: a case report', *J Am Geriatr Soc,* 60(8), pp. 1578-9.

Raglio, A., Bellelli, G., Traficante, D., Gianotti, M., Ubezio, M. C. and Villani, D. (2008) 'Efficacy of Music Therapy in the Treatment of
Behavioral and Psychiatric Symptoms of Dementia', *Alzheimer Disease
& Associated Disorders,* 22, pp. 158–162.

Raglio, A., Giovanazzi, E., Pain, D., Baiardi, P., Imbriani, C., Imbriani, M. and Mora, G. (2016) 'Active music therapy approach in amyotrophic lateral sclerosis: a randomized-controlled trial', *Int J Rehabil Res,* 39(4), pp. 365-367.

Ramig, L. A. (1988) 'Acoustic analysis of voices of patients with neurologic disease: rationale and preliminary data', *The Annals Of Otology, Rhinology, And Laryngology,* 97(2 Pt 1), pp. 164.

Riessman, C. K. (2008) *Narrative methods for the human sciences.* London: SAGE.

Roman, A. (2014) *Suggestions and Information about Speech Changes & Augmentative Alternative Communication (AAC)*. Available at: http://www.alsa.org/als-care/resources/publications-videos/factsheets/slurred-speech.html (Accessed: 13 October 2019 2019).

Rong, P., Yunusova, Y., Wang, J., Zinman, L., Pattee, G., Berry, J., Perry, B. and Green, J. (2016) 'Predicting Speech Intelligibility Decline in Amyotrophic Lateral Sclerosis Based on the Deterioration of Individual Speech Subsystems', *PLoS One,* 11(5).

Rooney, J. (2017) 'What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis', *Journal of Neurology, Neurosurgery & Psychiatry,* 88(5), pp. 381-386.

Rooney, J., Byrne, S., Heverin, M., Tobin, K., Dick, A., Donaghy, C. and Hardiman, O. (2015) 'A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland', *J Neurol Neurosurg Psychiatry,* 86(5), pp. 496-501.

Ryan, M., Heverin, M., McLaughlin, R. L. and Hardiman, O. (2019) 'Lifetime Risk and Heritability of Amyotrophic Lateral Sclerosis', *JAMA Neurol*.
Sanchez, G. R. and Vargas, E. D. (2016) 'Language bias and self-rated health status among the Latino population: evidence of the influence of translation in a wording experiment', *Qual Life Res,* 25(5), pp. 1131-6.
Sandoval, S., Berisha, V., Utianski, R. L., Liss, J. M. and Spanias, A. (2013) 'Automatic assessment of vowel space area', *J Acoust Soc Am,* 134(5), pp. EL477-83.
Schmid, W. (2016) 'MusicALS: home-based music therapy for individuals with amyotrophic lateral sclerosis (ALS) and their caring families', *Nord. J. Music Ther.,* 25(sup1), pp. 66-66.
Schmid, W. and Ostermann, T. (2010) 'Home-based music therapy--a systematic overview of settings and conditions for an innovative service in healthcare', *BMC Health Serv Res,* 10, pp. 291.
Schoser, B., Fong, E., Geberhiwot, T., Hughes, D., Kissel, J. T., Madathil, S. C., Orlikowski, D., Polkey, M. I., Roberts, M., Tiddens, H. A. and Young, P. (2017) 'Maximum inspiratory pressure as a clinically meaningful trial endpoint for neuromuscular diseases: a comprehensive review of the literature', *Orphanet J Rare Dis,* 12(1), pp. 52.
Shaffer, J. (2016) 'Neuroplasticity and Clinical Practice: Building Brain Power for Health', *Frontiers in psychology,* 1118.
Shiovitz, T. M., Bain, E. E., McCann, D. J., Skolnick, P., Laughren, T., Hanina, A. and Burch, D. (2016) 'Mitigating the Effects of Nonadherence in Clinical Trials', *J Clin Pharmacol,* 56(9), pp. 1151-64.
Sihvonen, A. J., Särkämö, T., Leo, V., Tervaniemi, M., Altenmüller, E. and Soinila, S. (2017) 'Music-based interventions in neurological rehabilitation', *Lancet Neurol,* 16(8), pp. 648-660.
Sinaki, M. and Mulder, D. W. (1986) 'Amyotrophic lateral sclerosis: relationship between serum creatine kinase level and patient survival', *Archives of physical medicine and rehabilitation,* 67(3), pp. 169.
Smirnova, N. S. and Khitrov, M. V. (2013) 'Phoneticheski predstavitelny tekst dlya fundamentalnykh i prikladnykh issledovanii russkoi rechi', *Izvestiya vysshikh uchebnykh zavedenii. Priborostroenie,* 56(2), pp. 5-10.
Smith, R., Pioro, E., Myers, K., Sirdofsky, M., Goslin, K., Meekins, G., Yu, H., Wymer, J., Cudkowicz, M., Macklin, E., Schoenfeld, D. and Pattee, G. (2017) 'Enhanced Bulbar Function in Amyotrophic Lateral Sclerosis: The Nuedexta Treatment Trial', *The Journal of the American Society for Experimental NeuroTherapeutics,* 14(3), pp. 762-772.
Smith, R. A., Macklin, E. A., Myers, K. J., Pattee, G. L., Goslin, K. L., Meekins, G. D., Green, J. R., Shefner, J. M. and Pioro, E. P. (2018) 'Assessment of bulbar function in amyotrophic lateral sclerosis: validation of a self-report scale (Center for Neurologic Study Bulbar Function Scale', *European Journal of Neurology,* 25(7), pp. 907-e66.
Solazzo, A., Monaco, L., Vecchio, L. D., Reginelli, A., Iacobellis, F., Capasso, R., Tamburrini, S., Berritto, D., Barillari, M. R., Monsurrò, M. R., Di Martino, N. and Grassi, R. (2014) 'Earliest videofluoromanometric pharyngeal signs of dysphagia in ALS patients', *Dysphagia,* 29(5), pp. 539-44.
Steele, C. M., Peladeau-Pigeon, M., Barbon, C. A. E., Guida, B. T., Namasivayam-MacDonald, A. M., Nascimento, W. V., Smaoui, S., Tapson, M. S., Valenzano, T. J., Waito, A. A. and Wolkin, T. S. (2019) 'Reference Values for Healthy Swallowing Across the Range From Thin to Extremely Thick Liquids', *J Speech Lang Hear Res,* 62(5), pp. 1338-1363.
Strand, E. A., Buder, E. H., Yorkston, K. M. and Ramig, L. O. (1994) 'Differential phonatory characteristics of four women with amyotrophic lateral sclerosis', *Journal of Voice,* 8(4), pp. 327–339.

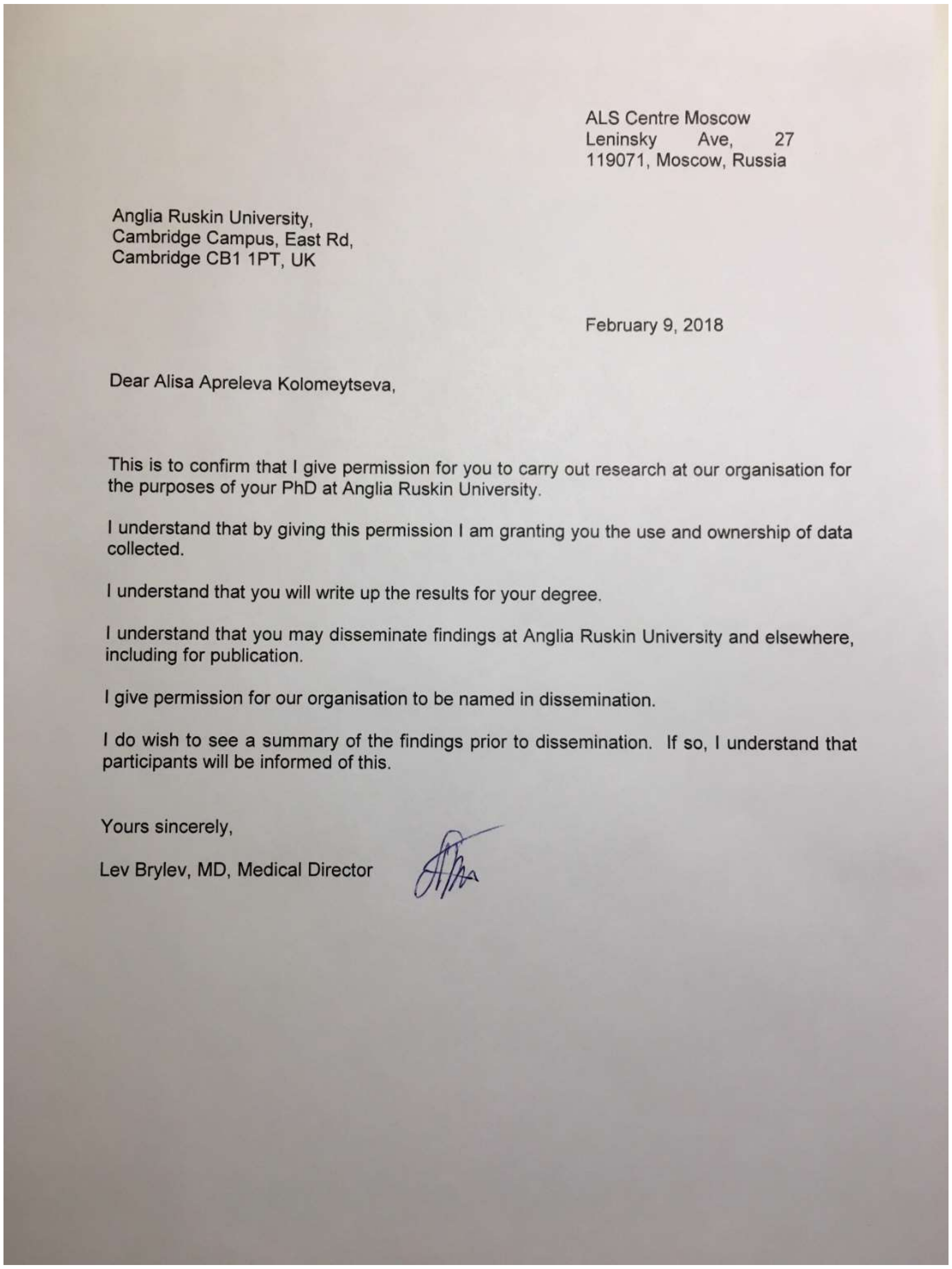
Street, A. J., Magee, W. L., Bateman, A., Parker, M., Odell-Miller, H. and Fachner, J. (2018) 'Home-based neurologic music therapy for arm hemiparesis following stroke: results from a pilot, feasibility randomized controlled trial', *Clin Rehabil,* 32(1), pp. 18-28.
Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., Autti, T., Silvennoinen, H. M., Erkkilä, J., Laine, M., Peretz, I. and Hietanen, M. (2008) 'Music listening enhances cognitive recovery and mood after middle cerebral artery stroke', *Brain,* 131(3), pp. 866-876.
Tabor, L. C., Rosado, K. M., Robison, R., Hegland, K., Humbert, I. A. and Plowman, E. K. (2016) 'Respiratory training in an individual with amyotrophic lateral sclerosis', *Annals of Clinical and Translational Neurology,* 3(10), pp. 819-823.
Tamplin (2011) 'Singing for respiratory muscle training', in Baker, F. and Uhlig, S. (eds.) *Voicework in music therapy*. London: Jessica Kingsley Publishers, pp. 147-170.
Tamplin, J. (2008) 'A pilot study into the effect of vocal exercises and singing on dysarthric speech', *NeuroRehabilitation,* 23(3), pp. 207.
Tamplin, J., Baker, F. A., Grocke, D., Brazzale, D. J., Pretto, J. J., Ruehland, W. R., Buttifant, M., Brown, D. J. and Berlowitz, D. J. (2013) 'Effect of singing on respiratory function, voice, and mood after quadriplegia: a randomized controlled trial', *Arch Phys Med Rehabil,* 94(3), pp. 426-34.
Tamplin, J. and Grocke, D. (2008) 'A Music Therapy Treatment Protocol for Acquired Dysarthria Rehabilitation', *Music Therapy Perspectives,* 26(1), pp. 23-29.
Teixeira, J., Oliveira, C. and Lopes, C. (2013) 'Vocal Acoustic Analysis – Jitter, Shimmer and HNR Parameters', *Procedia Technology,* 9.
Thakore, N. J. and Pioro, E. P. (2016) 'Depression in ALS in a large self-reporting cohort', *Neurology,* 86(11), pp. 1031-8.
Thaut, M. and Hoemberg, V. (2016) *Handbook of neurologic music therapy.* Oxford : Oxford University Press.
Thaut, M., McIntosh, G. and Hoemberg, V. 2015. Neurobiological foundations of neurologic music therapy: rhythmic entrainment and the motor system. *Front. Psychol.*
Thaut, M. H. and Abiru, M. (2010) 'Rhythmic Auditory Stimulation in Rehabilitation of Movement Disorders: A Review Of Current Research', *Music Perception: An Interdisciplinary Journal,* 27, pp. pp. 263-269.
Thaut, M. H., McIntosh, G. C. and Rice, R. R. (1997) 'Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation', *J Neurol Sci,* 151(2), pp. 207-12.
Thoma, M. V., La Marca, R., Brönnimann, R., Finkel, L., Ehlert, U. and Nater, U. M. (2013) 'The effect of music on the human stress response'.
Touré-Tillery, M. and Fishbach, A. (2014) 'How to Measure Motivation: A Guide for the Experimental Social Psychologist', *Social and Personality Psychology Compass,* 8(7), pp. 328-341.
Tsitkanou, S., Della Gatta, P., Foletta, V. and Russell, A. (2019) 'The Role of Exercise as a Non-pharmacological Therapeutic Approach for Amyotrophic Lateral Sclerosis: Beneficial or Detrimental?', *Front Neurol,* 10, pp. 783.
Van den Berg, J. P. (2005) 'Multidisciplinary ALS care improves quality of life in patients with ALS', *Neurology,* 65(8), pp. 1264-1268.
van der Steen, J. T., Smaling, H. J., van der Wouden, J. C., Bruinsma, M. S., Scholten, R. J. and Vink, A. C. (2018) 'Music-based therapeutic interventions for people with dementia', *Cochrane Database Syst Rev,* 7, pp. CD003477.
van Groenestijn, A. C., Schröder, C. D., van Eijk, R. P. A., Veldink, J. H., Kruitwagen-van Reenen, E. T., Groothuis, J. T., Grupstra, H. F., Tepper, M., van Vliet, R. O., Visser-Meily, J. M. A. and van den Berg, L. H. (2019) 'Aerobic Exercise Therapy in Ambulatory Patients With ALS: A Randomized Controlled Trial', *Neurorehabil Neural Repair,* 33(2), pp. 153-164.

Vaughan, S. K., Kemp, Z., Hatzipetros, T., Vieira, F. and Valdez, G. (2015) 'Degeneration of proprioceptive sensory nerve endings in mice harboring amyotrophic lateral sclerosis–causing mutations', *The Journal of Comparative Neurology,* 523(17).
Vignola, A., Guzzo, A., Calvo, A., Moglia, C., Pessia, A., Cavallo, E., Cammarosano, S., Giacone, S., Ghiglione, P. and Chiò, A. (2008) 'Anxiety undermines quality of life in ALS patients and caregivers', *Eur J Neurol,* 15(11), pp. 1231-6.
Vose, A. K., Kesneck, S., Sunday, K., Plowman, E. and Humbert, I. (2018) 'A Survey of Clinician Decision Making When Identifying Swallowing Impairments and Determining Treatment', *J Speech Lang Hear Res,* 61(11), pp. 2735-2756.
Voss, P., Thomas, M. E., Cisneros-Franco, J. M. and de Villers-Sidani, É. (2017) 'Dynamic Brains and the Changing Rules of Neuroplasticity: Implications for Learning and Recovery', *Front Psychol,* 8, pp. 1657.
Waito, A., Plowman, E., Barbon, C., P eladeau-Pigeon, M., Tabor-Gray, L., Magennis, K., Robison, R. and Steele, C. (2019) 'Swallowing Physiology and Impairment in Individuals with Amyotrophic Lateral Sclerosis (ALS)', *Journal of Speech, Language, and Hearing Research*.
Walters, S. J., Bonacho Dos Anjos Henriques-Cadby, I., Bortolami, O., Flight, L., Hind, D., Jacques, R. M., Knox, C., Nadin, B., Rothwell, J., Surtees, M. and Julious, S. A. (2017) 'Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme', *BMJ Open,* 7(3), pp. e015276.
Wan, C. Y., Rüber, T., Hohmann, A. and Schlaug, G. (2010) 'The Therapeutic Effects of Singing in Neurological Disorders', *Music Percept,* 27(4), pp. 287-295.
Watts, C. R. and Vanryckeghem, M. (2001) 'Laryngeal dysfunction in Amyotrophic Lateral Sclerosis: a review and case report', *BMC Ear Nose Throat Disord,* 1(1), pp. 1.
Weismer, G., Jeng, J.-Y., Laures, J. S., Kent, R. D. and Kent, J. F. (2001) 'Acoustic and intelligibility characteristics of sentence production in neurogenic speech disorders', *Folia Phoniatrica et Logopaedica,* 53(1).
Welham, N. V. and Maclagan, M. A. (2003) 'Vocal Fatigue: Current Knowledge and Future Directions', *Journal of Voice,* 17(1), pp. 21-30.
Wheeler, B. L. (2015) *Music therapy handbook. Creative arts and play therapy* New York ; London: The Guilford Press.
Wheeler, B. L. e. and Murphy, K. M. e. (2016) *Music therapy research.* Third edition / edited by Barbara L. Wheeler, Kathleen M. Murphy. edn.
White, C. (2011) 'Brain circuitry model for mental illness will transform management, NIH mental health director says', *BMJ,* 343, pp. d5581.
Wiens, M., Reimer, M. and Guyn, H. (1999) 'Music therapy as a treatment method for improving respiratory muscle strength in patients with advanced multiple sclerosis: a pilot study', *Rehabilitation Nursing,* 24(2), pp. 74-80.
Wilcock, A., Crosby, V., Clarke, D. and Tattersfield, A. (1999) 'Repeatability of breathlessness measurements in cancer patients', *Thorax,* 54(4), pp. 375.
Williams, M. T., Donnelly, J. P., Holmlund, T. and Battaglia, M. (2008) 'ALS: Family caregiver needs and quality of life', *Amyotroph Lateral Scler,* 9(5), pp. 279-86.
Wolever, R. Q., Simmons, L. A., Sforzo, G. A., Dill, D., Kaye, M., Bechard, E. M., Southard, M. E., Kennedy, M., Vosloo, J. and Yang, N. (2013) 'A Systematic Review of the Literature on Health and Wellness Coaching: Defining a Key Behavioral intervention in Healthcare', *Glob Adv Health Med,* 2(4), pp. 38-57.
Wolf, J., Safer, A., Wohrle, J. C., Palm, F., Nix, W. A., Maschke, M. and Grau, A. J. (2017) 'Causes of death in amyotrophic lateral sclerosis; Results from the Rhineland-Palatinate ALS registry/Todesursachen bei amyotropher Lateralsklerose; Ergebnisse aus dem ALS-Register Rheinland-Pfalz.(Report)', *Der Nervenarzt,* 88(8), pp. 911.

Woo, A. S. (2012) 'Velopharyngeal dysfunction', *Seminars in plastic surgery,* 26(4), pp. 170.
Yang, R. (2011) 'Causes and places of death of patients with amyotrophic lateral sclerosis in south-west China', *Amyotrophic Lateral Sclerosis: Official Publication Of The World Federation Of Neurology Research Group On Motor Neuron Diseases,* 12(3), pp. 206.
Yang, Y. H. (2016) 'Parents and Young Children with Disabilities: The Effects of a Home-Based Music Therapy Program on Parent-Child Interactions', *J Music Ther,* 53(1), pp. 27-54.
Yunusova, Y., Graham, N. L., Shellikeri, S., Phuong, K., Kulkarni, M., Rochon, E., Tang-Wai, D. F., Chow, T. W., Black, S. E., Zinman, L. H. and Green, J. R. (2016) 'Profiling Speech and Pausing in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) (Profiling Speech and Pausing in ALS and FTD)', 11(1), pp. e0147573.
Yunusova, Y., Green, J. R., Wang, J., Pattee, G. and Zinman, L. (2011) 'A Protocol for Comprehensive Assessment of Bulbar Dysfunction in Amyotrophic Lateral Sclerosis (ALS)', *Journal of Visualized Experiments : JoVE,* (48).
Zatorre, R. J., Joyce, L. C. and Virginia, B. P. (2007) 'When the brain plays music: auditory–motor interactions in music perception and production', *Nature Reviews Neuroscience,* 8(7), pp. 547.

APPENDICES

Appendix A. Study host organization letter of permission



ALS Centre Moscow
Leninsky Ave, 27
119071, Moscow, Russia

Anglia Ruskin University,
Cambridge Campus, East Rd,
Cambridge CB1 1PT, UK

February 9, 2018

Dear Alisa Apreleva Kolomeytseva,

This is to confirm that I give permission for you to carry out research at our organisation for the purposes of your PhD at Anglia Ruskin University.

I understand that by giving this permission I am granting you the use and ownership of data collected.

I understand that you will write up the results for your degree.

I understand that you may disseminate findings at Anglia Ruskin University and elsewhere, including for publication.

I give permission for our organisation to be named in dissemination.

I do wish to see a summary of the findings prior to dissemination. If so, I understand that participants will be informed of this.

Yours sincerely,

Lev Brylev, MD, Medical Director

Appendix B. Approval form and decision from Moscow Ethics Committee (Russian original and English translation)

РЕШЕНИЕ № 17/16_14.03.2018
МОСКОВСКОГО ГОРОДСКОГО НЕЗАВИСИМОГО
ЭТИЧЕСКОГО КОМИТЕТА

г. Москва «14» марта 2018 г.

Московский городской независимый этический комитет, рассмотрев в ходе заседания №16 от 14.03.2018 г. заявление Брылева Льва Вадимовича от 12.03.2018 г. на проведение этической экспертизы неинтервенционного исследования протоколу «Измерение эффекта протокола музыкальной терапии на дыхательные и бульбарные функции пациентов с ранней и средней стадией бокового амиотрофического склероза: смешанный метод анализа серии ситуационных исследований» в исследовательском центре Автономная некоммерческая организация «Центральная клиническая больница святителя Алексия, митрополита Московского, Московской Патриархии Русской Православной Церкви», с учетом того, что

□ ДА □ НЕТ не прим.	разрешение на проведение клинического исследования лекарственного препарата с участием человека в качестве субъекта, не выдано уполномоченным органом,
□ ДА □ НЕТ не прим.	разрешение на проведение клинического исследования лекарственного препарата с участием человека в качестве субъекта, выдано уполномоченным органом,
□ ДА □ НЕТ не прим.	проведение клинического исследования лекарственного препарата с участием человека в качестве субъекта имеет положительное решение совета по этике Министерства здравоохранения Российской Федерации
□ ДА □ НЕТ не прим.	проведение клинического исследования лекарственного препарата с участием человека в качестве субъекта не имеет решения совета по этике Министерства здравоохранения Российской Федерации

ПРИНЯЛ РЕШЕНИЕ

☑ Одобрить клиническое исследование.

□ Одобрить клиническое исследование. Решение вступает в силу после получения разрешения на проведение клинического исследования Министерства здравоохранения Российской Федерации.

□ Условно одобрить клиническое исследование (с рекомендацией внести изменения в представленные документы с последующей подачей документов в МГЭК в срок до 10 рабочих дней для последующей выдачи заключения об одобрении проведения исследования).

□ Отказать в одобрении клинического исследования (с указанием причин отказа).

□ Отменить или приостановить ранее выданного заключение об одобрении проведения клинического исследования.

Заместитель председателя МГЭК ________ /Хачанова Н.В./

Ответственный секретарь МГЭК ________ /Коваль О.М./

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ИБЧ-14032018-18-18/11

DECISION № 17/16_14.03.2018
MOSCOW MUNICIPAL INDEPENDENT
ETHICS COMMITTEE

Moscow, Russia March 14 2018

Moscow Municipal Independent Ethics Committee, having considered at the meeting on March 14 2018 the application by Lev Vadimovich Brylev, submitted on March 12 2018, for the ethics expertise of non-interventional research protocol "Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series" at the research centre Autonomous Non-Commercial Organization «St. Alexis Central Clinical Hospital», taking into account that:

☐ YES ☐ NO *N/A*	the authorization to conduct a clinical study of a medicinal product with the participation of a person as a subject, not issued by the authorized body
☐ YES ☐ NO *N/A*	permission to conduct a clinical study of a medicinal product with the participation of a person as a subject, issued by the authorized body
☐ YES ☐ NO *N/A*	the authorization to conduct a clinical trial of a drug with human participation as a subject has a positive decision from the Ethics Board of the Ministry of Health of the Russian Federation
☐ YES ☐ NO *N/A*	the authorization to conduct a clinical trial of a medicinal product with human participation as a subject does not have a decision from the Ethics Board of the Ministry of Health of the Russian Federation

DECIDED

☑ To approve the clinical research

☐ To approve the clinical research. The decision comes into force after obtaining permission to conduct a clinical study from the Ministry of Health of the Russian Federation.

☐ To conditionally approve the clinical trial (with a recommendation to amend the submitted documents with the subsequent submission of documents to the Moscow Municipal Independent Ethics Commitee in a time period of no more than 10 business days for the subsequent issuance of an opinion on the approval of the clinical trial)

☐ Deny approval of a clinical trial (indicate the reasons for the denial)

☐ To cancel or suspend a previously issued opinion on the approval of the clinical trial

Vice Chairman of MMIEC	Khachanova N.V.
Executive Secretary of MMIEC	Koval O.M.

Appendix C. Letter of Ethical Approval from Anglia Ruskin University

Anglia Ruskin University

Cambridge | Chelmsford
London | Peterborough

Chelmsford Campus
Bishop Hall Lane
Chelmsford
CM1 1SQ

T: +44 (0)1245 493131

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@angliaruskin
facebook.com/angliaruskin

10 January 2018

MS ALISA APRELEVA KOLOMEYTSEVA
131 Walker Rd, Swampscott, MA
01907
USA

Dept: Arts, Law and Social Sciences
FRA tel: 01223 698708
FRA email: alsspgr@anglia.ac.uk

Doctoral School
Tel No: 01245 684411 (Direct dial)
E-mail: **alssfrdsc@anglia.ac.uk**;

Dear Alisa,

Approval of Research Proposal

I am pleased to inform you that at its meeting on 15 December 2017 the Arts, Laws and Social Sciences Faculty Research Degrees Sub Committee (FRDSC), endorsed the recommendation from the reviewing academics to approve your research proposal application (resubmission stage) for the degree of PhD with progression from MPhil (subject to approval of upgrade of registration).

Your attention is drawn to the following points:-

Conditions of Approval
This approval is subject to attendance at Stage 1 of the compulsory training programme. If you have not already attended or booked this training, please book via ProgressPlatform (https://progressplatform.anglia.ac.uk/). If you experience problems with booking via ProgressPlatform, please contact Allen Mugasha by emailing research.training@anglia.ac.uk or telephone 01245 684209. Please note that you will not be able to submit your final thesis without completing all generic compulsory training.

Title of Research
MEASURING THE EFFECTS OF A MUSIC THERAPY PROTOCOL ON BULBAR FUNCTIONS IN PATIENTS WITH EARLY AND MID-STAGE AMYOTROPHIC LATERAL SCLEROSIS: MIXED METHODS SINGLE CASE STUDY SERIES

Supervisory Team:

1st Supervisor	2nd Supervisor
Dr Alex Street	Prof Jorg Fachner

Continued overleaf ……………………

Upgrade of Registration (from MPhil to PhD)
All research students registered for the degree of PhD with progression from MPhil are required to apply for upgrade of registration if they wish to proceed towards a doctoral qualification. Please see section 3 of the Research Degrees Regulations (September 2017) for further information. The Research Degrees Regulations can be found at http://web.anglia.ac.uk/anet/academic/public/research_degree_regs.pdf.
Your application for upgrade of registration should be submitted within the timescales noted in the Research Degrees Regulations as follows:

For students starting their programme from September 2015 onwards
Full time students: 9 - 18 months after the official programme start date
Part time students: 15 – 24 months after the official programme start date
For students starting their programme prior to September 2015
Full time students: 2 years after the official programme start date
Part time students: 4 years after the official programme start date

Confirmation / Upgrade of Registration is an assessment milestone noted on your "progression" page of the ProgressPlatform research student online system (https://progressplatform.anglia.ac.uk/).

Information for Candidates
I attach some important information which you are asked to note, including a list of publications available for research degree candidates.

Your supervisory team, Director of Research Students and Faculty Research Administrator will be informed of the formal outcome of your research proposal application at FRDSC.

Yours sincerely

pp. [signature]

Dr Sergio Fava
Chair, Arts, Law and Social Sciences Faculty Research Degrees Sub Committee

Appendix D. Participant information sheet, consent and withdrawal form (for participants – persons with ALS, in Russian)

Anglia Ruskin University ЖИВИ СЕЙЧАС The Stephen Hawking Foundation remedywave

ИНФОРМАЦИОННЫЙ ЛИСТОК УЧАСТНИКА ИССЛЕДОВАНИЯ (для людей с БАС)
Версия 1.1, 10 Февраля 2018

Раздел А: Исследовательский Проект

Название исследования

Измерение эффекта протокола музыкальной терапии на дыхательные и бульбарные функции пациентов с ранней и средней стадией бокового амиотрофического склероза: смешанный метод анализа серии ситуационных исследований

(Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series)

Приглашение к участию в исследовании

Мы приглашаем Вас принять участие в клиническом исследовании, изучающем воздействие музыкальной терапии на дыхание, откашливание, глотание и речь людей, страдающих боковым амиотрофическим склерозом. Важно, чтобы Вы понимали, в чём заключается исследование и какова может быть Ваша в нём роль.

Внимательно прочитайте этот информационный листок. Прежде чем принять решение, убедитесь в том, что его содержание полностью Вам понятно. Если Вам что-то неясно или нужна дополнительная информация, пожалуйста, задавайте вопросы. Эту информацию можно обсуждать с другими людьми. Не торопитесь и взвесьте все «за» и «против», прежде чем дать согласие на участие в исследовании.

Цель исследования

Боковой амиотрофический склероз (БАС), также известный как болезнь двигательного нейрона, – это редкое заболевание, влияющее на нервные клетки головного и спинного мозга. При поражении двигательных нейронов мозгового ствола нарушается работа мышц, ответственных за дыхание, откашливание, глотание и речь. Это может приводить к нарушению кашля («дистуссия») и затруднениям при дыхании («диспноэ»), глотании («дисфагия») и речи («дизартрия»). Вы можете подробнее обсудить этим симптомы с Вашим лечащим врачом.

Мы хотим выяснить, могут ли музыкотерапевтические упражения, такие как релаксация, легкая растяжка, дыхание и пение, помочь людям с БАС дольше сохранить нормальное дыхание, глотание, откашливание и речь. Мы также ищем оптимальный метод измерения эффектов музыкальной терапии на эти функции и хотим понять, насколько люди с БАС мотивированы участвовать в исследованиях музыкальной терапии.

Данные, собранные в ходе этого исследования, впоследствии позволят разработать более масштабное исследование эффектов музыкальной терапии на дыхание, глотание, откашливание и речь людей с БАС. Конечная цель этого исследования – создать проверенную систему упражнений, которые могут быть использованы музыкальными терапевтами, работающими с пациентами БАС по всему миру.

Это исследование проводится в рамках программы докторских исследований Университета Англия Раскин (Кембридж, Великобритания) при сотрудничестве с Выездной паллиативной службой помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

Ведущий исследователь – **Алиса Апрелева-Коломейцева**, магистр, сертифицированный музыкальный терапевт (США), сертифицированный неврологический музыкальный терапевт, аспирант Университета Англия Раскин, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. Электронный адрес: alisa.apreleva@pgr.anglia.ac.uk

Научные руководители исследования: **доктор Александр Стрит (Alexander Street)** и **доктор Йорг Фахнер (Jörg Fachner)**, исследователи Кэмбриджского Института Исследований Музыкальной Терапии, Университет Англия Раскин, Young Street, Cambridge, CB1 2LZ, UK (Кэмбридж, Великобритания) (Кэмбридж, Великобритания), и **Лев Вадимович Брылёв**, медицинский руководитель Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

Почему меня приглашают участвовать? Кто ещё получил такое приглашение?

Мы приглашаем недавно диагностированных пациентов Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия, с разрешения медицинского директора Службы. Для исследования нужно не более восьми участников.

Ухаживающим за людьми с БАС, принимающих участие в исследовании, также предложено поучаствовать в небольших интервью. Если ухаживающего у Вас нет, либо он(а) отказался (отказалась) участвовать, либо Вы сами не желаете, чтобы он(а) отвечал(а) на вопросы о Вас, Вы всё равно можете участвовать в исследовании.

Могу ли я отказаться от участия?

Мы понимаем, что участие в исследовании потребует дополнительных сил и времени. Вы имеете полное право отказаться от участия без объяснения причины.

Ваше решение никак не повлияет на услуги, которые Вы получаете в Службе помощи людям с БАС.

Какой пользы я могу ожидать от участия в исследовании?

Каждый человек с БАС, участвующий в исследовании, получит двенадцать бесплатных индивидуальных сеансов музыкальной терапии с сертифицированным музыкальным терапевтом на дому; инструкцию по выполнению несложных ежедневных упражнений с музыкальным сопровождением в виде аудиофайлов; и листовку по поддержанию здоровья речевого аппарата.

Несколько раз в течение исследования будут произведены замеры Вашего дыхания, глотания, откашливания и речи. Если Вы пожелаете, Вы можете получить индивидуальные результаты этих измерений.

Самое главное, Ваше участие позволит собрать ценную и уникальную информацию о влиянии музыкальной терапии при БАС, и откроет путь к дальнейшим исследованиям в области реабилитации людей с БАС.

Получено ли одобрение этического комитета?

Данное исследование получило одобрение Комитета по этике Университета Англия Раскин (Кэмбридж, Великобритания) и Московского городского независимого этического комитета (МГЭК) (Москва, Россия).

Каковы источники финансирования?

Данное исследование частично финансируется Фондом Стивена Хокинга (Великобритания).

Как будут использованы результаты исследования?

Результаты этого исследования будут представлены в докторской диссертации Алисы Апрелевой-Коломейцевой, и получат распространение в виде научных публикаций, презентаций и в средствах массовой информации.

Вы получите основные выводы исследования по электронной почте, как только они станут доступны.

Раздел Б: Ваше участие в исследовании

Что мне нужно будет делать?

Исследование займёт 16 последовательных недель. В течение этого срока

- Вы будете участвовать в тестах, замерах и опросах для измерения и оценки вашего дыхания, глотания, откашливания и речи: большая часть этих мероприятий будет происходить у Вас на дому, но три раза за весь срок Вам придётся приехать в лабораторию;
- Вы примете участие в двенадцати сеансах музыкальной терапии на дому;
- По желанию, Вы можете также выполнять несложные упражнения по 30 минут в день между сеансами музыкальной терапии.

Подробная информация представлена ниже.

УЧАСТИЕ В ЗАМЕРАХ

Замеры Вашего дыхания, глотания, откашливания и речи будут проводиться научным ассистентом – сотрудником Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия у Вас на дому в течение 1-й, 6-й, 12-й и 16-й недель; а также квалифицированным медицинским сотрудником в московской лаборатории (недели 1-я, 6-я, 12-я). Каждый замер занимает не более одного часа. Большая часть этих замеров уже производится в ходе обычного ухода при БАС. Также с Вами будут проведены два коротких опроса (недели 5-я и 13-я). Каждый опрос займёт не более получаса. Далее следует полный список замеров с описаниями.

Замеры дыхания

- **Максимальное давление на вдохе (MIP)** и **Максимальное давление на выдохе (MEP)** – это стандартные тесты, используемые для оценки максимальной силы дыхательных мышц. В ходе этих измерений Вас попросят вдыхать и выдыхать через трубку портативного спирометра.

- **Форсированная жизненная емкость легких (FVC)** – это мера объёма воздуха, который Вы можете выдохнуть после самого глубокого вдоха. В ходе этого измерения Вас попросят с силой выдохнуть через трубку спирометра.

Замеры откашливания

- **Максимальная скорость выдоха при кашле (PCF)** – это показатель эффективности откашливания. Вам нужно будет с силой откашляться в специальное устройство, называемое «измеритель пикового потока».

Замеры глотания

- **Шкала бульбарных функций Центра неврологических исследований (CNS-BFS), показатель глотания** – это опросник из 7 вопросов, призванный измерить затруднения при глотании. Вам нужно будет ответить на каждый вопрос по шкале от "1" (никогда не происходит) до "5" (происходит всё время).

- **Видео-рентгеноскопическое исследование глотания (VFSS, видеорентгеноскопия)** и **волоконно–оптическая эндоскопическая оценка глотания (FEES, эндоскопия)** – это тесты для проверки способности глотать эффективно и безопасно. Это единственные тесты, которые потребуют от Вас визита в лабораторию в Москве. Они будут проведены три раза (недели 1-я, 6-я и 12-я). Вам нужно будет пройти только один из этих тестов – видеорентгеноскопию либо эндоскопию, в зависимости от доступности ресурсов лаборатории.

  Видеорентгеноскопия проводится в отделении рентгенологии. Вам будут предложены еда и напитки, смешанные с барием. Барий делает еду и жидкость видимыми на рентгеновских снимках. Барий безвреден и не задерживается в организме. Вам может быть предложена твёрдая или протёртая пища и более или менее густые жидкости. Во время глотания будут сделаны рентгеновские снимки. Этот тест противопоказан беременным женщинам: Вы не должны участвовать в нём, если Вы думаете, что можете быть беременны.

Эндоскопия даёт сходный результат, но производится по-другому. В этом тесте используется гибкая, очень тонкая трубка с крошечной камерой и источником света на конце – эндоскоп. Медицинский сотрудник опустит эндоскоп через Ваш нос в верхнюю часть глотки. Перед началом теста ваш нос и гортань будут обрызганы специальной жидкостью, чтобы Вы не чувствовали присутствия эндоскопа. Через эндоскоп часть вашей гортани и горла будет видна на экране. Так же, как и при видеорентгеноскопии, Вам предложат глотать различную еду и напитки.

Замеры речи

- **Шкала бульбарных функций Центра неврологических исследований (CNS-BFS), показатель речи** – это опросник из семи вопросов для оценки речи. Вам нужно будет ответить на каждый вопрос по шкале от “1” (никогда не происходит) до “5” (происходит всё время).
- **Акустический замер аудиозаписей голоса** позволяет объективно оценить такие параметры речи как скорость, артикуляция, произношение гласных, смыкание губ, громкость и т.п. Научный ассистент посетит Вас на дому и попросит Вас прочитать вслух короткий текст, произнести несколько слов и определённых слогов (например, «па-та-ка») и поддержать короткий разговор. Вы наденете нательный микрофон Shure WH20XLR, чтобы Ваша речь могла быть записана для последующего анализа. Чтобы измерить носовой характер звука (“назальность”, количество воздуха, исходящего при речи через нос), ассистент попросит вас надеть специальную носовую маску и несколько раз произнести слог «па». Эти звуки также будут записаны для последующего анализа.

- Непосредственно до и после каждого музыкотерапевтического сеанса музыкальный терапевт задаст вам **два вопроса о вашем дыхании и речи.**

Опросы

- Вам будет предложено пройти короткий опрос перед началом музыкотерапевтических сеансов (5-я неделя) и после их завершения (13-я неделя). Опрос будет состоять из нескольких простых вопросов, например: «Каких изменений вы ожидаете от музыкотерапевтических сеансов?». Научный сотрудник запишет ваши ответы и затем прочитает их вслух, чтобы удостовериться, что всё было записано верно. Аудио- и видеозапись вестись не будет.

- Если есть человек, который помогает Вам в быту (ухаживающий), мы также предложим ему (ей) пройти небольшой **опрос** в тот же период (недели 5-я и 13-я). Этот опрос будет включать в себя несколько вопросов о музыкальной терапии и ее влиянии на Вас, например: «Какое влияние, по-вашему, музыкальная терапия может оказать на дыхание и глотание (больного БАС)?»

УЧАСТИЕ В МУЗЫКОТЕРАПЕВТИЧЕСКИХ СЕАНСАХ

В течение шести недель (недели с 7-й по 12-ю) Вы примете участие в двенадцати сеансах музыкальной терапии на дому. Профессиональный сертифицированный музыкальный терапевт будет навещать вас два раза в неделю и проводить сеансы длительностью в один час. Каждый раз Вы будете выполнять упражнения для лёгкой разминки, релаксации, дыхания, глотания и голоса. Сеансы будут напоминать уроки вокала: Вы научитесь правильной осанке, релаксации мышц, эффективному дыханию и правильной подаче голоса. Музыкальный терапевт опишет и продемонстрирует каждое упражнение и сопроводит некоторые упражнения специально написанным аккомпанементом на гитаре. Скорость и громкость сопровождения будут подобраны так, чтобы соответствовать Вашему голосовому диапазону и дыханию.

В течение сеанса у Вас будет достаточно возможностей отдохнуть и восстановиться, чтобы Вы не уставали. Вам не придётся выполнять упражнения, которые покажутся вам утомительными, слишком трудными, или просто не подходящими по какой-то причине. В конце каждого сеанса у Вас будет возможность спеть одну из Ваших любимых песен под гитару, чтобы закрепить полученные в течение сеанса навыки.

Ниже, для примера, описаны несколько упражнений. Музыкальный терапевт продемонстрирует, как выполнять каждое из этих упражнений.

- Вдохните через нос, слегка приоткрыв рот, затем выдохните через рот, без звука. Воздух входит и выходит из лёгких без усилия: не прилагайте усилий, рёбра должны оставаться неподвижны. Тренируясь дышать диафрагмой, положите одну руку на живот, а другую на грудь. Передняя и боковые стороны брюшной стенки слегка расширяются, когда диафрагма на вдохе движется вниз, но грудь и плечи при этом не двигаются.

- Потрите руки друг о друга или согрейте их другим способом и поместите ладони поверх закрытых глаз на несколько секунд. Массируйте лицо мягкими круговыми движениями пальцев обеих рук, двигаясь от волос вниз к щекам, губам и подбородку, останавливаясь подольше на тех участках, которые сильнее напряжены. Когда массируете щеки, позвольте вашей челюсти расслабленно повиснуть. Во время этого упражнения на лице должно отсутствовать какое-либо выражение.

- С помощью терапевта выберите удобный тон из середины Вашего голосового регистра. Начните петь слог «ма» на этом тоне, потом сделайте глиссандо на большую терцию вверх и подержите этот тон до конца такта (Вам не придется изучать теорию музыки, чтобы выполнять эти упражнения: просто повторяйте за терапевтом). Повторите ещё три раза, гармония живого гитарного аккомпанемента в это время меняется. После этого сделайте четыре повтора на слоге «ми» и четыре повтора на слоге «му».

ВЫПОЛНЕНИЕ ЕЖЕДНЕВНЫХ УПРАЖНЕНИЙ

Музыкальный терапевт предложит Вам несколько простых упражнений для ежедневных занятий. Для них Вам будет предоставлен записанный аккомпанемент. Вам потребуется около 30 минут для того, чтобы выполнить эти упражнения. Вы сами можете решать, хотите ли Вы выполнять эти упражнения и как часто Вы будете это делать. У вас будет возможность регулярно обсуждать выполнение этих упражнений с музыкальным терапевтом.

Будет ли моё участие конфиденциальным?

Да, мы сделаем все возможное для обеспечения конфиденциальности.

В ходе этого исследования Вы будете взаимодействовать с представителями нашей исследовательской группы, которые будут собирать данные о вашем дыхании, глотании, откашливании и речи, а также проводить опросы. Мы получим ограниченную информацию из Ваших медицинских записей - например, Ваш диагноз и результаты тестов – для того, чтобы убедиться, что вы отвечаете критериям отбора участников для этого исследования. Мы также запишем Вашу демографическую информация (пол, возраст).

Если Вы согласитесь принять участие в исследовании, Вам будет присвоен уникальный номер, который заменит Ваше имя, например: «Участник 1». Все полученные данные, включая цитаты из опросов и записи голоса, станут информацией об «Участнике 1», так что, когда результаты исследования будут опубликованы, никто не сможет Вас идентифицировать. Если мы проведём опрос с Вашим ухаживающим и приведём из него цитаты, Ваше имя будет также заменено номером.

Участники исследовательской группы, работающие в Службе помощи, по-прежнему будут иметь доступ к Вашим медицинским записям в Выездной паллиативной службе помощи людям с БАС при АНО ЦКБ Святителя Алексия, но те члены исследовательской группы, которые не работают в Службе – руководители, специалист по статистике и другие сотрудники университета Англия Раскин – будет видеть только информацию об «Участнике 1». Все члены нашей исследовательской группы следуют профессиональным стандартам обмена конфиденциальной информацией, а это означает, что они не будут обсуждать или делиться ею с кем-либо за пределами команды.

Несмотря на то, что мы делаем всё возможное, чтобы сохранить Ваше участие в этом исследовании в тайне, мы обязаны сообщить Вам, что возможность того, что Вы будете идентифицированы, всё же остаётся. БАС - редкая группа заболеваний. В Москве и Московской области проживает всего около 950 человек с диагнозом БАС, и только 110 пациентов наблюдается в Выездной паллиативной службе помощи людям с БАС при АНО ЦКБ Святителя Алексия. Служба помощи людям с БАС в Москве будет упомянута в публикациях и презентациях о результатах исследования. Могут быть приведены цитаты из Ваших интервью и продемонстрированы образцы Вашего голоса.

Пожалуйста, внимательно оцените эти риски, принимая решение о том, хотите ли Вы участвовать в нашем исследовании.

Что произойдет с той информацией, которая будет получена от меня?

Ваша личная идентифицируемая информация (форма информированного согласия, номер участника) будет отделена от конфиденциальных данных (медицинская информация, результаты теста, интервью) при первой же возможности.

Вся собранная информация будет защищена паролем и надежно сохранена в компьютерной системе Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия и на сервере университета Англия Раскин. Форма информированного согласия и Ваш номер участника будут храниться отдельно от данных исследования в закрытом сейфе Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия.

Анализ ваших индивидуальных данных (например, изменения результатов теста между 1-й, 6-й, 12-й и 16-й неделями) и данных других участников будут представлены в докторской диссертации Алисы Апрелевой-Коломейцевой, в научных публикациях и презентациях. После завершения исследования, данные не будут использоваться для иных целей, кроме распространения результатов.

Вы сможете получать индивидуальные данные Ваших тестов и измерений. Однако за объяснением результатов этих тестов Вам нужно будет обратиться к своему лечащему врачу, так как участники исследовательской группа не обладают квалификацией, позволяющей интерпретировать эту информацию.

Будут ли возмещены мои транспортные расходы?

Ваши транспортные расходы на три посещения лаборатории будут возмещены или для Вас будет организован бесплатный транспорт.

Каковы возможные недостатки или риски участия в исследовании?

Это исследование потребует с Вашей стороны временных затрат: общая продолжительность всех тестов и опросов составит примерно 8 часов, сеансы музыкальной терапии составят 12 часов, рекомендуемые ежедневные упражнения также потребуют времени. Если Вы считаете, что это может представлять трудность для Вас, то это исследование Вам не подходит.

Музыкальные упражнения, разработанные для этого исследования, безопасны и легки в исполнении. Тем не менее, Вы можете испытывать легкий физический дискомфорт или усталость, связанные с работой мышц при освоении новых методов дыхания и звукоизвлечения. В начале каждого занятия музыкальный терапевт будет напоминать Вам о необходимости сделать передышку, если Вы почувствуете усталость или дискомфорт. Вы сможете отдохнуть по мере необходимости на протяжении всех сеансов. Вам не придется делать какие-либо упражнения, которые вызывают у Вас дискомфорт.

Обсуждение Вашего дыхания, глотания, откашливания и речевых функций во время сеанса музыкальной терапии и тестирования может вызвать у Вас расстройство или тревогу. Терапевт и ассистенты профессионально подготовлены и готовы поддержать Вас, если такая ситуация возникнет. Вам не обязательно участвовать в дискуссиях или отвечать на вопросы, которые могут Вас огорчить.

Наконец, Вы можете испытывать незначительный физический дискомфорт во время тестов: например, при тестировании глотания в лаборатории. Вы можете попросить медицинского специалиста прекратить тест, если процедура доставляет Вам ощутимый дискомфорт.

Могу ли я отказаться от участия в исследовании и как?

Да, Вы можете отказаться от участия в этом исследовании в любой момент, и Вам не нужно объяснять причины. Если Вы хотите отказаться, пожалуйста, обратитесь к исследователю (Алисе Апрелевой-Коломейцевой) или напишите ей по электронному адресу alisa.apreleva@pgr.anglia.ac.uk.

Если Вы решите прекратить участвовать, Вы можете дать согласие на то, чтобы Ваши данные, уже собранные в процессе исследования, все еще использовались в работе, или Вы можете удалить все свои данные из исследования. Вы можете принять решение удалить свои данные в любой момент до 17-й недели с даты начала исследования.

Что ещё мне нужно знать об этом исследовании?

Обратите внимание, что, пока Вы участвуете в этом исследовании, Вы не можете пользоваться другими экспериментальными методами по работе с дыханием, глотанием, откашливанием или речью. Вы по-прежнему будете получать стандартную квалифицированную помощь Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия.

Пожалуйста, сообщите исследовательской группе, если Вы беременны или можете быть беременны, чтобы мы обеспечили для Вас безопасную альтернативу видео-рентгеноскопическому исследованию глотания (VFSS).

Жалобы

Если у вас появятся жалобы, касающиеся этого исследования, пожалуйста, сначала свяжитесь с нами:

- **Алиса Апрелева-Коломейцева**, ведущий исследователь, электронный адрес: alisa.apreleva@pgr.anglia.ac.uk
- **Лев Вадимович Брылев**, медицинский руководитель исследования в Москве; электронный адрес: lev.brylev@gmail.com
- **Дежурный координатор** Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия, электронный адрес: post.alsmoscow@gmail.com и info@alsfund.ru; телефоны: 8 (903) 625-54-52, 8 (901) 593-60-00

Если проблема не будет разрешена, Вы можете обратиться в Секретариат Университета Англия Раскин. Электронные адреса: paul.bogle@anglia.ac.uk и complaints@anglia.ac.uk. Почтовый адрес: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ. Если вы пишете на русском языке, начните свое сообщение фразой: «This is a complaint about a postgraduate research study at Anglia Ruskin University, ALSS department. The following message is in Russian». Пошлите копию сообщения доктору Александру Стрит, научному руководителю в Кембридже, Великобритания, по электронному адресу: alex.street@anglia.ac.uk. Ваша жалоба будет рассмотрена в течение 5 рабочих дней, ответ будет предоставлен в кратчайшие возможные сроки после этого.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ УЧАСТНИКА ИССЛЕДОВАНИЯ (для людей с БАС)

Ф.И.О УЧАСТНИКА: ____

НАЗВАНИЕ ПРОЕКТА: Измерение эффекта протокола музыкальной терапии на дыхательные и бульбарные функции пациентов с ранней и средней стадией бокового амиотрофического склероза: смешанный метод анализа серии ситуационных исследований.

ВЕДУЩИЙ ИССЛЕДОВАТЕЛЬ: Алиса Апрелева-Коломейцева, магистр, сертифицированный музыкальный терапевт (США), сертифицированный неврологический музыкальный терапевт, аспирант Университета Англия Раскин, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. Электронный адрес: alisa.apreleva@pgr.anglia.ac.uk

НАУЧНОЕ РУКОВОДСТВО: доктор Александр Стрит (Alexander Street) и доктор Йорг Фахнер (Jörg Fachner), исследователи исследователи Кэмбриджского Института Исследований Музыкальной Терапии, Университет Англия Раскин, Young Street, Cambridge, CB1 2LZ, UK (Кэмбридж, Великобритания) (Кэмбридж, Великобритания), Лев Вадимович Брылёв, медицинский руководитель Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

- ☐ Я согласен (согласна) принять участие в вышеупомянутом исследовании. Я прочитал(а) Информационный лист участника (версия 1.1, 10 февраля 2018 года) этого исследования. Я понимаю, в чем заключается мое участие в исследовании, и получил(а) удовлетворительные ответы на все мои вопросы.

- ☐ Я понимаю, что я могу отказаться от участия в исследовании в любое время, без объяснения причин.

- ☐ Я могу задать любой вопрос в любое время до и во время исследования.

- ☐ Я понимаю, что произойдет с моими данными, собранными для исследования.

- Я даю разрешение на то, чтобы мои личные документы просматривались членами исследовательской группы, работающей в Выездной паллиативной службе помощи людям с БАС при АНО ЦКБ Святителя Алексия, в том объеме, в котором это необходимо для моего участия в этом исследовании.

- Мне была предоставлена копия этой формы Информированного согласия и Информационный листок участника.

- Я понимаю, что цитаты из моих опросов будут использованы при распространении исследования.

- Я понимаю, что мои записи моего голоса могут использоваться для распространения исследований.

- Я даю разрешение исследовательской группе провести собеседование с ухаживающим за мной человеком.

- Я хочу получать индивидуальные результаты своих тестов.

Защита данных: я согласен (согласна) с тем, чтобы университет Англия Раскин и Выездная паллиативная служба помощи людям с БАС при АНО ЦКБ Святителя Алексия обрабатывали предоставленные мною персональные данные. Я согласен (согласна) на обработку этих данных для любых целей, связанных с исследовательским проектом, как это было мне разъяснено.

Ф.И.О. участника ________________________________ Подпись _________ Дата _________

Ф.И.О. свидетеля ________________________________Подпись _________ Дата _________

Дата 10.02.2018
Версия 1.1.

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Я ХОЧУ ОТКАЗАТЬСЯ ОТ УЧАСТИЯ В ЭТОМ ИССЛЕДОВАНИИ

Если Вы хотите отказаться от участия в этом исследовании, пожалуйста, обратитесь к исследователю (Алисе Апрелевой-Коломейцевой) или напишите ей по электронному адресу alisa.apreleva@pgr.anglia.ac.uk. Вам не нужно указывать причину, по которой вы хотите отказаться. Пожалуйста, сообщите исследователю, разрешаете ли Вы использовать те данные о Вас, которые уже собраны, в описании и распространении результатов исследования.

Appendix E. Participant information sheet, consent and withdrawal form (for caregivers of persons with ALS, in Russian)

ИНФОРМАЦИОННЫЙ ЛИСТОК УЧАСТНИКА ИССЛЕДОВАНИЯ (для ухаживающих)

Версия 1.1, 10 Февраля 2018

<u>Раздел А: Исследовательский Проект</u>

Название исследования

Измерение эффекта протокола музыкальной терапии на дыхательные и бульбарные функции пациентов с ранней и средней стадией бокового амиотрофического склероза: смешанный метод анализа серии ситуационных исследований

(Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series)

Приглашение к участию в исследовании

Мы приглашаем Вас принять участие в клиническом исследовании, изучающем воздействие музыкальной терапии на дыхание, откашливание, глотание и речь людей, страдающих боковым амиотрофическим склерозом. Важно, чтобы Вы понимали, в чём заключается исследование и какова может быть Ваша в нём роль.

Внимательно прочитайте этот информационный листок. Прежде чем принять решение, убедитесь в том, что его содержание полностью Вам понятно. Если Вам что-то неясно или нужна дополнительная информация, пожалуйста, задавайте вопросы. Эту информацию можно обсуждать с другими людьми. Не торопитесь и взвесьте все «за» и «против», прежде чем дать согласие на участие в исследовании.

Цель исследования

Боковой амиотрофический склероз (БАС), также известный как болезнь двигательного нейрона, – это редкое заболевание, влияющее на нервные клетки головного и спинного мозга. При поражении двигательных нейронов мозгового ствола нарушается работа мышц, ответственных за дыхание, откашливание, глотание и речь. Это может приводить к нарушению кашля («дистуссия») и затруднениям при дыхании («диспноэ»), глотании («дисфагия») и речи («дизартрия»).

Мы хотим выяснить, могут ли музыкотерапевтические упражения, такие как релаксация, легкая растяжка, дыхание и пение, помочь людям с БАС дольше сохранить нормальное дыхание, глотание, откашливание и речь. Мы также ищем оптимальный метод измерения эффектов музыкальной терапии на эти функции и хотим понять, насколько люди с БАС мотивированы участвовать в исследованиях музыкальной терапии.

Данные, собранные в ходе этого исследования, впоследствии позволят разработать более масштабное исследование эффектов музыкальной терапии на дыхание, глотание, откашливание и речь людей с БАС. Конечная цель этого исследования – создать проверенную систему упражнений, которые могут быть использованы музыкальными терапевтами, работающими с пациентами БАС по всему миру.

Это исследование проводится в рамках программы докторских исследований Университета Англия Раскин (Кембридж, Великобритания) при сотрудничестве с Выездной паллиативной службой помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

Ведущий исследователь – **Алиса Апрелева-Коломейцева**, магистр, сертифицированный музыкальный терапевт (США), сертифицированный неврологический музыкальный терапевт, аспирант Университета Англия Раскин, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. Электронный адрес: alisa.apreleva@pgr.anglia.ac.uk

Научные руководители исследования: **доктор Александр Стрит (Alexander Street)** и **доктор Йорг Фахнер (Jörg Fachner)**, исследователи Кэмбриджского Института Исследований Музыкальной Терапии, Университет Англия Раскин, Young Street, Cambridge, CB1 2LZ, UK (Кэмбридж, Великобритания), и **Лев Вадимович Брылёв**, медицинский руководитель Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

Зачем меня приглашают участвовать? Кто ещё получил такое приглашение?

Мы приглашаем недавно диагностированных пациентов Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия, с разрешения медицинского директора Службы. Для исследования нужно не более восьми участников.

Ухаживающим за людьми с БАС, принимающими участие в исследовании, также предложено поучаствовать в небольших интервью. Человек с БАС, участвующий в этом исследовании, сказал, что Вы являетесь его ухаживающим и разрешил нам связаться с Вами. Мы приглашаем Вас участвовать в опросах, так как думаем, что Вы можете предоставить ценные сведения для этого исследования.

Другие ухаживающие за людьми с БАС – участниками этого исследования – также будут приглашены.

Могу ли я отказаться от участия?

Мы понимаем, что участие в исследовании потребует дополнительных сил и времени. Вы имеете полное право отказаться от участия без объяснения причины.

Какой пользы я могу ожидать от участия в исследовании?

Каждый человек с БАС, участвующий в исследовании, получит двенадцать бесплатных индивидуальных сеансов музыкальной терапии с сертифицированным музыкальным терапевтом на дому; инструкцию по выполнению несложных ежедневных упражнений с музыкальным сопровождением в виде аудиофайлов; и листовку по поддержанию здоровья речевого аппарата. Несколько раз в течение срока исследования будут произведены замеры их дыхания, глотания, откашливания и речи. По желанию, участники исследования смогут получить индивидуальные результаты этих измерений.

Самое главное, Ваше участие позволит собрать ценную и уникальную информацию о влиянии музыкальной терапии при БАС, и откроет путь к дальнейшим исследованиям в области реабилитации людей с БАС.

Получено ли одобрение этического комитета?

Данное исследование получило одобрение Комитета по этике Университета Англия Раскин (Кэмбридж, Великобритания) и Московского городского независимого этического комитета (МГЭК) (Москва, Россия).

Каковы источники финансирования?

Данное исследование частично финансируется Фондом Стивена Хокинга (Великобритания).

Как будут использованы результаты исследования?

Результаты этого исследования будут представлены в докторской диссертации Алисы Апрелевой-Коломейцевой, и получат распространение в виде научных публикаций, презентаций и в средствах массовой информации.

Вы получите основные выводы исследования по электронной почте, как только они станут доступны.

Раздел Б: Ваше участие в исследовании

Что мне нужно будет делать?

Вам будет предложено пройти короткий опрос перед тем, как человек с БАС, за которым Вы ухаживаете, начнет занятия музыкальной терапией (неделя № 5) и после их завершения (неделя № 13). Опрос будет состоять из нескольких вопросов о сеансах музыкальной терапии и их эффекте, например: «Какое влияние, по-вашему, музыкальная терапия может оказать на дыхание и глотание (человека с БАС)?». Научный ассистент запишет ваши ответы и затем прочитает их вслух, чтобы удостовериться, что всё было записано верно. Аудио- и видеозапись вестись не будет. Интервью будет проводиться у Вас на дому или в другом месте, где Вам будет удобно разговаривать с интервьюером.

Будет ли моё участие конфиденциальным?

Да, мы сделаем все возможное для обеспечения конфиденциальности.

Каждому человеку с БАС, участвующему в исследовании, будет присвоен уникальный номер, заменяющий имя, например: «Участник 1». Все полученные данные, включая цитаты из Ваших опросов, станут информацией об «Участнике 1», так что, когда результаты исследования будут опубликованы, никто не сможет идентифицировать участников.

Когда мы проведём опрос с Вами как с ухаживающим и запишем результаты, имя человека с БАС также будет заменено номером. Ваше имя или другие личные данные, кроме тех, которыми Вы решите поделиться в интервью, будут вписаны только в форму информированного согласия, которую Вы подпишете.

Несмотря на то, что мы делаем всё возможное, чтобы сохранить Ваше участие в этом исследовании в тайне, мы обязаны сообщить Вам, что возможность того, что Вы будете идентифицированы, всё же остаётся. БАС - редкая группа заболеваний. В Москве и Московской области проживает всего около 950 человек с диагнозом БАС, и только 110 пациентов наблюдается в Выездной паллиативной службе помощи людям с БАС при АНО ЦКБ Святителя Алексия. Служба помощи людям с БАС в Москве будет упомянута в публикациях и презентациях о результатах исследования. В исследовании могут быть приведены цитаты из Ваших ответов и упомянут Ваш статус ухаживающего.

Пожалуйста, внимательно оцените эти риски, принимая решение о том, хотите ли Вы участвовать в нашем исследовании.

Что произойдет с той информацией, которая будет получена от меня?

Ваша личная идентифицируемая информация (форма информированного согласия) будет отделена от конфиденциальных данных (результат опроса) при первой же возможности.

Вся собранная информация будет защищена паролем и надежно сохранена в компьютерной системе Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия и на сервере университета Англия Раскин. Форма информированного согласия будет храниться отдельно от данных исследования в закрытом сейфе Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия.

Цитаты из Ваших опросов будут представлены в докторской диссертации Алисы Апрелевой-Коломейцевой, в научных публикациях и презентациях. После завершения исследования, данные не будут использоваться для иных целей, кроме распространения результатов.

Каковы возможные недостатки или риски от участия в исследовании?

Это исследование потребует с Вашей стороны временных затрат: два интервью суммарно займут около одного часа Вашего времени.

Обсуждение Вашей роли ухаживающего за человеком с БАС может вызвать у Вас расстройство или тревогу. Терапевт и ассистенты профессионально подготовлены и готовы поддержать Вас, если такая ситуация возникнет. Вам не обязательно участвовать в дискуссиях или отвечать на вопросы, которые могут Вас огорчить.

Могу ли я отказаться от участия в исследовании и как?

Да, Вы можете отказаться от участия в этом исследовании в любой момент, и Вам не нужно объяснять причины. Если Вы хотите отказаться, пожалуйста, обратитесь к исследователю (Алисе Апрелевой-Коломейцевой) или напишите ей по электронному адресу alisa.apreleva@pgr.anglia.ac.uk.

Если Вы решите прекратить участвовать, Вы можете дать согласие на то, чтобы Ваши данные, уже собранные в процессе исследования, все еще использовались в работе, или Вы можете удалить все свои данные из исследования. Вы можете принять решение удалить свои данные в любой момент до 17-й недели с даты начала исследования.

Что ещё мне нужно знать об этом исследовании?

Мы рекомендуем Вам обсудить Ваше участие в этом исследовании с человеком с БАС, за которым Вы ухаживаете.

Жалобы

Если у вас появятся жалобы, касающиеся этого исследования, пожалуйста, сначала свяжитесь с нами:

- **Алиса Апрелева-Коломейцева**, ведущий исследователь, электронный адрес: alisa.apreleva@pgr.anglia.ac.uk
- **Лев Вадимович Брылев**, медицинский руководитель исследования в Москве; электронный адрес: lev.brylev@gmail.com
- **Дежурный координатор** Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия, электронный адрес: post.alsmoscow@gmail.com и info@alsfund.ru; телефоны: 8 (903) 625-54-52, 8 (901) 593-60-00

Если проблема не будет разрешена, Вы можете обратиться в Секретариат Университета Англия Раскин. Электронные адреса: paul.bogle@anglia.ac.uk и complaints@anglia.ac.uk. Почтовый адрес: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ. Если Вы пишете на русском языке, начните свое сообщение фразой: «This is a complaint about a postgraduate research study at Anglia Ruskin University, ALSS department. The following message is in Russian». Пошлите копию сообщения доктору Александру Стрит, научному руководителю в Кембридже, Великобритания, по электронному адресу: alex.street@anglia.ac.uk. Ваша жалоба будет рассмотрена в течение 5 рабочих дней, ответ будет предоставлен в кратчайшие возможные сроки после этого.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ УЧАСТНИКА ИССЛЕДОВАНИЯ (для ухаживающих)

Ф.И.О УЧАСТНИКА: ____

НАЗВАНИЕ ПРОЕКТА: Измерение эффекта протокола музыкальной терапии на дыхательные и бульбарные функции пациентов с ранней и средней стадией бокового амиотрофического склероза: смешанный метод анализа серии ситуационных исследований.

ВЕДУЩИЙ ИССЛЕДОВАТЕЛЬ: Алиса Апрелева-Коломейцева, магистр, сертифицированный музыкальный терапевт (США), сертифицированный неврологический музыкальный терапевт, аспирант Университета Англия Раскин, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. Электронный адрес: alisa.apreleva@pgr.anglia.ac.uk

НАУЧНОЕ РУКОВОДСТВО: доктор Александр Стрит (Alexander Street) и доктор Йорг Фахнер (Jörg Fachner), исследователи исследователи Кэмбриджского Института Исследований Музыкальной Терапии, Университет Англия Раскин, Young Street, Cambridge, CB1 2LZ, UK (Кэмбридж, Великобритания) (Кэмбридж, Великобритания), к.м.н. Лев Вадимович Брылёв, медицинский руководитель Выездной паллиативной службы помощи людям с БАС при АНО ЦКБ Святителя Алексия (Москва, Россия).

- ☐ Я согласен (согласна) принять участие в вышеупомянутом исследовании. Я прочитал(а) Информационный лист участника (версия 1.1, 10 февраля 2018 года) этого исследования. Я понимаю, в чем заключается мое участие в исследовании, и получил(а) удовлетворительные ответы на все мои вопросы.

- Я понимаю, что я могу отказаться от участия в исследовании в любое время, без объяснения причин.

- Я могу задать любой вопрос в любое время до и во время исследования.

- Я понимаю, что произойдет с моими данными, собранными для исследования.

- Мне была предоставлена копия этой формы Информированного согласия и Информационный листок участника.

- Я понимаю, что цитаты из моих опросов будут использованы при распространении исследования.

Защита данных: я согласен (согласна) с тем, чтобы Университет Англия Раскин и Выездная паллиативная служба помощи людям с БАС при АНО ЦКБ Святителя Алексия обрабатывали предоставленные мною персональные данные. Я согласен (согласна) на обработку этих данных для любых целей, связанных с исследовательским проектом, как это было мне разъяснено.

Ф.И.О. участника ______________________________Подпись_________ Дата _________

Ф.И.О. свидетеля______________________________ Подпись _________ Дата _________

Дата 10.02.2018

Версия 1.1.

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Я ХОЧУ ОТКАЗАТЬСЯ ОТ УЧАСТИЯ В ЭТОМ ИССЛЕДОВАНИИ

Если Вы хотите отказаться от участия в этом исследовании, пожалуйста, обратитесь к исследователю (Алисе Апрелевой-Коломейцевой) или напишите ей по электронному адресу alisa.apreleva@pgr.anglia.ac.uk. Вам не нужно указывать причину, по которой вы хотите отказаться. Пожалуйста, сообщите исследователю, разрешаете ли Вы использовать те данные о Вас, которые уже собраны, в описании и распространении результатов исследования.

Appendix F. Participant information sheet, consent and withdrawal form (for participants – persons with ALS, English translation)

Anglia Ruskin University

PARTICIPANT INFORMATION SHEET (for people with ALS)

Version 1.1, February 10 2018

<u>Section A: The Research Project</u>

Study title

Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series

An invitation to participate in the study

We invite you to participate in a clinical research on the effect of music therapy treatment on breathing, cough, swallowing and speech of people diagnosed with amyotrophic lateral sclerosis. It is important that you understand what this research involves and what your role in it may be.

Please carefully read the following information. Make sure you understand all of it before you make your decision. Ask questions if you need more information or if something is not clear. You may discuss this information with others. Take your time and carefully consider all the details before you decide if you want to take part in this study.

The purpose of the study

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a rare disease that affects nerve cells in the brain and the spinal cord. When the motor neurons in the brainstem are affected, the muscles used in breathing, cough, swallowing and speech are impaired. This may result in difficulty breathing ("dyspnoea"), disordered cough ("dystussia"), difficulty swallowing ("dysphagia") and difficulty speaking ("dysarthria"). The details of these conditions will have been explained to you by your ALS care team.

We are looking to find out if music therapy exercises, such as relaxation, light stretching, breathing and singing, may help people with ALS to maintain natural breathing, swallowing, cough and speech for longer. We are also looking to see what is the best way to measure the effect music therapy may have on these functions and to understand if people with ALS are motivated to participate in music therapy research.

Data from this research will allow to later design a larger study to continue exploring the effects of music therapy on breathing, swallowing, cough and speech of people living with ALS. The ultimate goal of this research is to create a safe set of exercises to be used by music therapists working with people affected by ALS worldwide.

This research is conducted in partial fulfillment of PhD research programme at Anglia Ruskin University (Cambridge, UK). We collaborate with ALS Centre Moscow on this research project.

The principal researcher for this study is **Ms. Alisa Apreleva-Kolomeytseva**, certified music therapist (USA), certified neurologic music therapist, PhD researcher at Anglia Ruskin University, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. E-mail: alisa.apreleva@pgr.anglia.ac.uk

The supervisors for the study are **Dr. Alexander Street** and **Dr. Jörg Fachner**, researchers at The Cambridge Institute for Music Therapy Research, Anglia Ruskin University, Young

Street, Cambridge, CB1 2LZ, UK and **Dr. Lev Brylev**, the medical director at ALS Centre Moscow (Moscow, Russia).

Why am I being asked to participate? Who else is invited?

Recently diagnosed patients from ALS Moscow Centre (Moscow, Russia) are invited to participate in this study, with the permission from the medical director of the Centre. We are looking for no more than eight participants in this study.

Caregivers of the people with ALS participating in the study will also be invited for brief interviews. If you do not have a caregiver, if they do not wish to participate or if you do not want them to share information about you, you can still take part in our study.

Can I refuse to take part?

We recognize that participation in this research will require additional effort and time commitment on your behalf. As we offer you to take part in the research, we would like to make clear that you can choose to refuse this offer without providing a reason.

Your care at ALS Centre Moscow will not be affected by this decision.

What are the likely benefits of taking part in this study?

As a participant of this study, you will receive twelve individual home-based music therapy sessions with a certified music therapist, free of charge, instructions for simple daily exercises with accompanying music files, and voice health guidelines leaflet.

Your breathing, swallowing, cough and speech will be assessed several times during the study.

If you choose so, you can receive this additional information during the course of this research.

Most importantly, your participation and feedback will provide valuable, unique information about music therapy effects in ALS and will help to advance the research on rehabilitative treatment for people diagnosed with ALS.

Has the study got ethical approval?

This study has ethical approval from an ethics committee at Anglia Ruskin University (Cambridge, UK) and from Moscow Municipal Independent Ethics Committee (Moscow, Russia).

Source of funding

This study is partially sponsored by The Stephen Hawking Foundation (UK).

What will happen to the results of this study?

The results of this study will be **presented in Alisa Apreleva-Kolomeytseva's doctoral thesis, and disseminated through scientific journal publications, conference presentations and media.**

As soon as we have the results, the summary of the research findings will be emailed to you.

Section B: Your Participation in the Research Project

What will I be asked to do?

This study will take 16 consecutive weeks. During these weeks you will

- participate in tests, measurements and interviews to assess you breathing, swallowing, cough and speech: most of these will be at your home, but you will also have to travel to the laboratory three times during the sixteen weeks;
- take part in twelve individual music therapy session at your home;
- if you choose so, practice similar daily exercises for 30 minutes each day in between your music therapy sessions.

Continue reading to find out more.

PARTICIPATING IN ASSESSMENTS

Your breathing, swallowing, cough and speech will be assessed by a research nurse and research assistant from ALS Centre Moscow at your home during weeks 1, 6, 12 and 16; and by a qualified medical professional at the laboratory in Moscow (week 1, 6, 12). Each assessment will take no longer than one hour. Most of these tests are routinely performed in ALS care. You will also be asked to participate in two brief interviews (week 5 and week 13). Each interview will take no more than half an hour. Here is the full list of assessments with brief descriptions.

Respiration assessments

- **Maximal Inspiratory Pressure (MIP)** and **Maximal Expiratory Pressure (MEP)** are standard tests to evaluate maximal strength of respiratory muscles. In order to measure these, you will be instructed to inhale and to exhale several times through a mouthpiece (tube) of a portable spirometer.

- **Forced Vital Capacity (FVC)** measures how much air can you forcibly exhale after taking the deepest breath possible. You will be instructed to forcefully exhale into a spirometer mouthpiece for this test.

Cough assessments

- **Peak Cough Flow (PCF)** is an indicator of cough effectiveness. You will be instructed to forcefully cough into the small device called peak flow meter during this test.

Swallowing assessment

- **Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Swallowing Score** is a 7-item questionnaire that assesses swallowing. You will be asked to score each question from “1” (does not apply) to “5” (applies most of the time).

- **Video fluoroscopic swallowing study (VFSS)** or **Fiberoptic Endoscopic Evaluation of Swallowing (FEES)** are the tests to evaluate your ability to swallow safely and effectively. These tests are the only ones that will require visits to a laboratory in Moscow, and will be administered three times (week 1, week 6, week 12). You will only have to do one type of the test – either VFSS or FEES, depending on the laboratory availability. **VFSS** is done in the radiology department. You will be given different foods and drinks mixed with barium. Barium makes the food and liquid show up on the x-ray. It is not harmful and won't stay in your body. During the study you may be instructed to try soft and hard foods, and thin and thick liquids. X-ray images will be made as you swallow. You should not have this test done if you think you may be pregnant. **FEES** serves the same purpose, but is performed in a different way. The flexible, very thin tube called endoscope is used, which has a tiny camera and light attached to it. Trained specialist will pass the endoscope through your nose and into your pharynx (upper part of the throat). Before the test, your nose and throat will be sprayed to help numb the area so you do not feel the tube being gently inserted. The endoscope will allow the parts of your larynx, pharynx, and trachea to be seen on a video screen. As with VFSS, you will be instructed to swallow foods and liquids of varied textures.

Speech assessment

- **Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Speech Score** is a 7-item questionnaire that assesses speech. You will be asked to score each question from “1” (does not apply) to “5” (applies most of the time).

- **Acoustic assessment of recorded voice samples** allows to objectively assess such speech parameters as speed, articulation, vowel quality, lip closure, loudness and more. Research assistant will visit you at home and ask you to read aloud a short text, to pronounce several words, certain syllables (for example, *pa-ta-ka*), and to keep a brief conversation. You will wear the lightweight Shure WH20XLR Dynamic Headset Microphone, so that these voice samples will be recorded for future analysis. To measure speech nasality (the amount of air that passes through your nose when you speak), you will be asked to put on a special nasal mask and to pronounce /pa/ syllable several times; this sample will be recorded for future analysis as well.

- Before and after each music therapy session the therapist will ask you **two questions about your breathing and speech**.

Interviews

- You will be asked to participate in a brief **interview** before you start music therapy treatment (week 5) and right after the treatment ends (week 13). The interview will include several simple questions, such as: “What do you expect in music therapy sessions?” The research assistant will write down your responses and then will read them back to you to make sure that your thoughts will have been written down correctly. The interviews will not be recorded in audio or video format.

- If there is a person who helps you with your daily routines (a caregiver), we will also approach them for a brief **caregiver interview** at the same time (week 5 and week 13). The interview will include several questions about music therapy treatment and its effects, for example: “How, you think, may music therapy affect speech, breathing and swallowing of (the person with ALS)?”

PARTICIPATING IN MUSIC THERAPY SESSIONS

You will participate in twelve home-based music therapy sessions during six "treatment weeks" (weeks 7 through 12). Professional, certified music therapist will visit you at home two times a week for one hour session. Each time you will participate in a set of light stretching, relaxation, breathing, swallowing and vocal exercises. The session will look very much like a vocal lesson, where you will learn appropriate posture, muscle relaxation, effective breathing and voice production techniques. The music therapist will describe and model each exercise, and support some of the exercises with the guitar accompaniment, specifically composed for these exercises. The speed and level of the accompaniment will be adjusted to suit your voice range and breathing.

Ample opportunities for rest and relaxation will be provided throughout the session, to make sure that you do not get tired. You will not have to perform any exercises that feel tiring, too difficult of simply "not right", for any reason. At the end of the session you will have a chance to practice singing one of your favorite songs, with the guitar accompaniment, to put together all the skills gained during the session.

Here are some examples of the exercise. The music therapist will demonstrate how to perform each exercise.

- Breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way, and no rib action should occur. Place one hand on the abdomen and the other on the chest as you practice diaphragmatic breathing. The front and the side of the abdominal wall expand as the diaphragm contracts and pulls down during breath in, while no visible movement of the chest or shoulders occurs.

- Rub your hands together or to warm them otherwise and place the palms over closed eyes for several seconds. Massage the face with gentle circular motions of the pads of the fingers, using both hands, moving from hairline downwards to cheeks, lips and chin, spending more time on areas that feel tight. When the cheeks are being massaged, let your jaw to hang slack. The face has to become void of any expression during this exercise.

- With the help of therapist, pick a comfortable tone from your voice midrange. Starting from this tone on "mah" syllable, slide up a maj3 interval and sustain this tone till the end of the measure (repeat after the therapist: you do not have to learn music theory to practice these exercises!). This singing pattern is repeated for three more measures, as the harmony in the live guitar accompaniment changes. Four measures on "mee" and then four measures on "moo" follow.

PERFORMING DAILY EXERCISES

The music therapist will suggest some of simple exercises from music therapy sessions for your daily exercise routine. The recorded accompaniment will be provided. Completing the set of exercises will take about 30 minutes of your time. You will choose if you would like to do these exercises and how often your will do that. You will have an opportunity to regularly discuss your progress with the music therapist.

Will my participation in the study be kept confidential?

Yes, we will make every attempt to ensure confidentiality.

In the course of this research you will come in contact with members of our research team, who will collect data about your breathing, swallowing, cough and speech, as well as conduct interviews. We will receive some limited information from your medical records – such as your diagnosis, and test results – to make sure that you meet the criteria to be included in this study. General information (sex, age) will also be recorded.

As soon as you enter the study, you will be assigned a unique number that will replace your name, for example: "Participant 1". All the data received, including the quotes from your interviews and voice samples, will then become the information about "Participant 1", so that when the study results are shared no one will be able to identify you. If we conduct interviews with your caregiver and quote them, your name will be replaced with the number.

The members of the research team who work at ALS Centre Moscow will still have access to your named medical records at ALS Centre Moscow, but those members of the research team who do not work at the Moscow Centre – supervisors, statistician and other staff at Anglia Ruskin University – will only see information about "Participant 1". All the members of our research team restricted by professional standards from sharing your personal information, which means they will not discuss or share it with anyone outside of the team.

As much as we try to minimize the chances for your to be recognized as a study participant, we have to let you know that there is still a chance that you may be identified. ALS is a rare group of diseases, with about 950 people diagnosed with ALS residing in Moscow region, and only 110 patients at ALS Centre Moscow. ALS Moscow Centre will be mentioned as the study results are shared in publications and presentations. Quotes from your interviews may be cited, and your voice samples may be attached.

Please carefully consider these risks as you decide if you wish to take part in our study.

What will happen to any information that is collected from me?

Your personal identifiable information (consent form, assigned participant number) will be separated from confidential data (medical information, test results, interviews) at the earliest opportunity.

All the collected information will be protected by password and stored securely at ALS Centre Moscow computer system and at Anglia Ruskin University server. The consent form and your assigned participant number will be stored separately from the study data, in a locked cabinet at ALS Centre Moscow.

The analysis of your individual data (for example, changes in test results from week 1, week 6, week 12 and week 16) and data from other participants will be presented in Alisa Apreleva's doctoral thesis and shared in publications and presentations. After the study is completed, the data will not be used for purposes other than dissemination of the results.

You may choose to receive the individual data from the tests and measurements. You will have to contact your care team for interpretation of the results, as the research team is not qualified to provide such interpretation.

Will I be reimbursed travel expenses?

Your transportation expenses for the three laboratory visits will be reimbursed or free transportation will be provided.

Are there any possible disadvantages or risks to taking part?

This study will require *time commitment* on your part, with about 8 hours of total testing time, 12 hour-long music therapy sessions and recommended daily exercises. If you think this may present a difficulty for you, this study may be not a good fit for you.

Music therapy exercises developed for this study are gentle and safe. However, you may experience mild physical discomfort or tiredness as your muscles are working while you are learning new breathing and vocalization techniques. In the beginning of every session the music therapist will remind you to stop if you feel tired or uncomfortable. You will be able to rest as needed throughout the sessions. You will not have to do any exercise that causes discomfort for you.

Discussing your breathing, swallowing, cough and speech functions during music therapy session and assessments may sometimes cause emotional upset or anxiety. The therapist and the research assistants are professionally trained and prepared to support you if such situation arises. You do not have to participate in discussions or answer interview questions that may be upsetting to you.

Finally, you may experience minor physical discomfort during assessment, such as swallowing test in the laboratory. You can ask the medical professional to stop the test if you feel uncomfortable.

Can I withdraw at any time and how?

Yes, you can withdraw from this study at any point, and you do not have to explain the reasons. If you wish to withdraw, please speak to the researcher (Alisa Apreleva Kolomeytseva) or email them at alisa.apreleva@pgr.anglia.ac.uk.

If you withdraw, you may consent for your data to still be used in the research, or you may choose to withdraw all your data from the study. You can decide to withdraw your data at any point up to week 17 from the start date of the study.

Anything else I should know about this study?

Please note that you cannot receive any other experimental treatment for breathing, swallowing, cough or speech as long as you are involved in this study. You will still receive the standard care at ALS Centre Moscow.

Please let the research team know if you are pregnant or may be pregnant so that we make alternative arrangements for the Video fluoroscopic swallowing study (VFSS).

Complaints

If you have any complaints about the study, please first contact us:

- **Ms. Alisa Apreleva**, principal researcher; e-mail: alisa.apreleva@pgr.anglia.ac.uk
- **Dr.Lev Brylev**, supervisor in Moscow, Russia, e-mail: lev.brylev@gmail.com
- **ALS Centre Moscow** on-duty coordinator, e-mail: info@alsfund.ru; phone: 8 (903) 625-54-52, 8 (901) 593-60-00

If the problem is not resolved, please contact **The Secretary and Clerk at Anglia Ruskin University**. E-mail: paul.bogle@anglia.ac.uk and complaints@anglia.ac.uk. Postal address: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ. If you are writing in Russian, precede your message by the phrase: “This is a complaint about a postgraduate research study at Anglia Ruskin University, ALSS department. The following message is in Russian”. Copy **Dr. Alexander Street**, supervisor in Cambridge, UK, on this e-mail: alex.street@anglia.ac.uk. Normally complaints will be acknowledged within 5 working days and answered as soon as possible thereafter.

PARTICIPANT CONSENT FORM (for people with ALS)

NAME OF THE PARTICIPANT: ____

TITLE OF THE PROJECT: Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series

MAIN INVESTIGATOR: Ms. Alisa Apreleva-Kolomeytseva, certified music therapist (USA), certified neurologic music therapist, PhD researcher at Anglia Ruskin University, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. E-mail: alisa.apreleva@pgr.anglia.ac.uk

SUPERVISORS: Dr. Alexander Street and Dr. Jörg Fachner, researchers at The Cambridge Institute for Music Therapy Research, Anglia Ruskin University, Young Street, Cambridge, CB1 2LZ, UK, and Dr. Lev Brylev, the medical director at ALS Centre Moscow (Moscow, Russia).

- ☐ I agree to take part in the above research. I have read the Participant Information Sheet (Version 1.1, February 10 2018) for the study. I understand what my role will be in research, and all my questions have been answered to my satisfaction.
- ☐ I understand that I am free to withdraw from the research at any time, without giving a reason.
- ☐ I am free to ask any question at any time before and during the study.
- ☐ I understand what will happen to the data collected from me for the research.
- ☐ I give permission for my personal records to be looked at by the members of the research team working at ALS Centre Moscow where it is relevant to my taking part in this research.
- ☐ I have been provided with a copy of this form and the Participant Information Sheet.
- ☐ I understand that quotes from me will be used in the dissemination of the research.
- ☐ I understand that my voice samples may be used in the dissemination of the research.

- ☐ I give permission to the research team to conduct interviews with my caregiver.
- ☐ I wish to receive individual data from the assessments

Data protection: I agree to the Anglia Ruskin University and ALS Centre Moscow processing personal data which I have supplied. I agree to the processing of such data for any purposes connected with the Research Project as outlined to me.

Name of participant (print) ________________________ Signed _________ Date _________

Name of person

witnessing consent (print) _________________________ Signed _________ Date _________

Date 10.02.2018

Version 1.1.

I WISH TO WITHDRAW FROM THIS STUDY

If you wish to withdraw from the research, please speak to the researcher or email them at alisa.apreleva@pgr.anglia.ac.uk. You do not have to give a reason for why you would like to withdraw. Please let the researcher know whether you are / are not happy for them to use any data from you collected to date in the write up and dissemination of the research.

Appendix G. Participant information sheet, consent and withdrawal form (for caregivers of persons with ALS, English translation)

PARTICIPANT INFORMATION SHEET (for caregivers)

Version 1.1, February 11 2018

Section A: The Research Project

Study title

Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series

An invitation to participate in the study

We invite you to participate in a clinical research on the effect of music therapy treatment on breathing, cough, swallowing and speech of people diagnosed with amyotrophic lateral sclerosis. It is important that you understand what this research involves and what your role in it may be.

Please carefully read the following information. Make sure you understand all of it before you make your decision. Ask questions if you need more information or if something is not clear. You may discuss this information with others. Take your time and carefully consider all the details before you decide if you want to take part in this study.

The purpose of the study

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a rare disease that affects nerve cells in the brain and the spinal cord. When the motor neurons in the brainstem are affected, the muscles used in breathing, cough, swallowing and speech are impaired. This may result in difficulty breathing ("dyspnoea"), disordered cough ("dystussia"), difficulty swallowing ("dysphagia") and difficulty speaking ("dysarthria").

We are looking to find out if music therapy exercises, such as relaxation, light stretching, breathing and singing, may help people with ALS to maintain natural breathing, swallowing, cough and speech for longer. We are also looking to see what is the best way to measure the effect music therapy may have on these functions and to understand if people with ALS are motivated to participate in music therapy research.

Data from this research will allow to later design a larger study to continue exploring the effects of music therapy on breathing, swallowing, cough and speech of people living with ALS. The ultimate goal of this research is to create a safe set of exercises to be used by music therapists working with people affected by ALS worldwide.

This research is conducted in partial fulfillment of PhD research programme at Anglia Ruskin University (Cambridge, UK). We collaborate with ALS Centre Moscow on this research project.

The principal researcher for this study is **Ms. Alisa Apreleva-Kolomeytseva**, certified music therapist (USA), certified neurologic music therapist, PhD researcher at Anglia Ruskin University, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. E-mail: alisa.apreleva@pgr.anglia.ac.uk

The supervisors for the study are **Dr. Alexander Street** and **Dr. Jörg Fachner**, researchers at The Cambridge Institute for Music Therapy Research, Anglia Ruskin University, Young Street, Cambridge, CB1 2LZ, UK), and **Dr. Lev Brylev**, the medical director at ALS Centre Moscow (Moscow, Russia).

Why am I being asked to participate? Who else is invited?

Recently diagnosed patients from ALS Moscow Centre (Moscow, Russia) are invited to participate in this study, with the permission from the medical director of the Centre.

Caregivers of the people with ALS participating in the study are also invited for brief interviews. A person with ALS who participates in the study has identified you as their caregiver and has given us permission to contact you. We are inviting you to take part in the interviews as we think that you can provide valuable input for this study.

Other caregivers of the persons with ALS participating in the study will be contacted as well.

Can I refuse to take part?

We recognize that participation in this research will require additional effort and time commitment on your behalf. As we offer you to take part in the research, we would like to make clear that you can choose to refuse this offer without providing a reason.

What are the likely benefits of taking part in this study?

People with ALS participating in this study will receive twelve individual home-based music therapy sessions with a certified music therapist, free of charge, instructions for simple daily exercises with accompanying music files, and voice health guidelines leaflet. Their breathing, swallowing, cough and speech will be assessed several times during the study, and the results will be reported to them if they choose so.

Most importantly, your participation and feedback will provide valuable, unique information about music therapy effects in ALS and will help to advance the research on rehabilitative treatment for people diagnosed with ALS.

Has the study got ethical approval?

This study has ethical approval from an ethics committee at Anglia Ruskin University (Cambridge, UK) and from Moscow Municipal Independent Ethics Committee (Moscow, Russia).

Source of funding

This study is partially sponsored by The Stephen Hawking Foundation (UK).

What will happen to the results of this study?

The results of this study will be **presented in Alisa Apreleva-Kolomeytseva's doctoral thesis, and disseminated through scientific journal publications, conference presentations and media.**

As soon as we have the results, the summary of the research findings will be emailed to you.

<u>Section B: Your Participation in the Research Project</u>

What will I be asked to do?

You will be asked to participate in a brief **interview** before the person with ALS participating in this study starts music therapy treatment and again in eight weeks, right after the treatment ends. The interview will include several questions about music therapy treatment and its effects, for example: “How, you think, may music therapy affect speech, breathing and swallowing of (person with ALS)?” The research assistant will write down your responses and then will read them back to you to make sure that your thoughts will have been written down correctly. The interviews will not be recorded in audio or video format. The interview will take place at your home or other place where you may feel comfortable talking with the interviewer.

Will my participation in the study be kept confidential?

Yes, we will make every attempt to ensure confidentiality.

As soon as the person with ALS enters the study, they will be assigned a unique number that will replace their name, for example: “Participant 1”. All the data received, including the quotes from your interviews, will then become the information about “Participant 1”, so that when the study results are shared no one will be able to identify the participant.

When we conduct interviews with you as a caregiver and write down the results, the name of the person with ALS will be again replaced with the number. Your name or any personal details, other than those you wish to share in the interview, will not be recorded except than on this consent form.

As much as we try to minimize the chances for your to be recognized as a study participant, we have to let you know that there is still a chance that you may be identified. ALS is a rare group of diseases, with about 950 people diagnosed with ALS residing in Moscow region, and only 110 patients at ALS Centre Moscow. ALS Moscow Centre will be mentioned as the study results are shared in publications and presentations. Quotes from your interviews may be cited, and your caregiver status will be mentioned.

Please carefully consider these risks as you decide if you wish to take part in our study.

What will happen to any information that is collected from me?

Your personal identifiable information (consent form) will be separated from confidential data (interviews) at the earliest opportunity.

All the collected information will be protected by password and stored securely at ALS Centre Moscow computer system and at Anglia Ruskin University server. The consent form will be stored separately from the study data, in a locked cabinet at ALS Centre Moscow.

Quotes from your interviews may be used in Alisa Apreleva Kolomeytseva's doctoral thesis and shared in publications and presentations. After the study is completed, the data will not be used for purposes other than dissemination of the results.

Are there any possible disadvantages or risks to taking part?

This study will require *time commitment* on your part, of about one hour total for the two interviews.

Discussing your role as a caregiver for a person diagnosed with ALS may cause emotional upset or anxiety. The research assistants are professionally trained and prepared to support you if such situation arises. You do not have to participate in discussions or answer interview questions that may be upsetting to you.

Can I withdraw at any time and how?

Yes, you can withdraw from this study at any point, and you do not have to explain the reasons. If you wish to withdraw, please speak to the researcher (Alisa Apreleva Kolomeytseva) or email them at alisa.apreleva@pgr.anglia.ac.uk.

If you withdraw, you may consent for your data to still be used in the research, or you may choose to withdraw all your data from the study. You can decide to withdraw your data at any point up to week 17 from the start date of the study.

Anything else I should consider about this study?

You may want to discuss your participation in this study with the person diagnosed with ALS who you provide care for.

Complaints

If you have any complaints about the study, please first contact us:

- **Ms. Alisa Apreleva**, principal researcher; e-mail: alisa.apreleva@pgr.anglia.ac.uk
- **Dr.Lev Brylev**, supervisor in Moscow, Russia, e-mail: lev.brylev@gmail.com
- **ALS Centre Moscow** on-duty coordinator, e-mail: info@alsfund.ru; phone: 8 (903) 625-54-52, 8 (901) 593-60-00

If the problem is not resolved, please contact **The Secretary and Clerk at Anglia Ruskin University**. E-mail: paul.bogle@anglia.ac.uk and complaints@anglia.ac.uk. Postal address: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ. If you are writing in Russian, precede your message by the phrase: “This is a complaint about a postgraduate research study at Anglia Ruskin University, ALSS department. The following message is in Russian”. Copy **Dr. Alexander Street**, supervisor in Cambridge, UK, on this e-mail: alex.street@anglia.ac.uk. Normally complaints will be acknowledged within 5 working days and answered as soon as possible thereafter.

PARTICIPANT CONSENT FORM (for caregivers)

NAME OF THE PARTICIPANT: ____

TITLE OF THE PROJECT: Measuring the effects of a music therapy protocol on respiratory and bulbar functions in patients with early and mid-stage amyotrophic lateral sclerosis: mixed methods single case study series

MAIN INVESTIGATOR: Ms. Alisa Apreleva-Kolomeytseva, certified music therapist (USA), certified neurologic music therapist, PhD researcher at Anglia Ruskin University, Cambridge Campus, East Rd, Cambridge CB1 1PT, UK. E-mail: alisa.apreleva@pgr.anglia.ac.uk

SUPERVISORS: Dr. Alexander Street and Dr. Jörg Fachner, researchers at The Cambridge Institute for Music Therapy Research, Anglia Ruskin University, Young Street, Cambridge, CB1 2LZ, UK, and Dr. Lev Brylev, the medical director at ALS Centre Moscow (Moscow, Russia).

- ☐ I agree to take part in the above research. I have read the Participant Information Sheet (Version 1.1, February 11 2018) for the study. I understand what my role will be in research, and all my questions have been answered to my satisfaction.
- ☐ I understand that I am free to withdraw from the research at any time, without giving a reason.
- ☐ I am free to ask any question at any time before and during the study.
- ☐ I understand what will happen to the data collected from me for the research.
- ☐ I have been provided with a copy of this form and the Participant Information Sheet.
- ☐ I understand that quotes from me will be used in the dissemination of the research.

Data protection: I agree to the Anglia Ruskin University and ALS Centre Moscow processing personal data which I have supplied. I agree to the processing of such data for any purposes connected with the Research Project as outlined to me.

Name of participant (print) ________________________ Signed _________ Date

Name of person
witnessing consent (print) _________________________ Signed _________ Date

Date 11.02.2018

Version 1.1.

I WISH TO WITHDRAW FROM THIS STUDY

If you wish to withdraw from the research, please speak to the researcher or email them at alisa.apreleva@pgr.anglia.ac.uk. You do not have to give a reason for why you would like to withdraw. Please let the researcher know whether you are / are not happy for them to use any data from you collected to date in the write up and dissemination of the research.

Appendix H. Voice care guidelines for research participants – persons with ALS (Russian original and English translation)

10 ПРАВИЛ ЗАБОТЫ О ГОЛОСЕ

1. Не говорите слишком долго. **Если голос устал,** обязательно **сделайте перерыв**.

2. **Не разговаривайте в шумной обстановке** (при включенном телевизоре, в автомобиле, в общественном транспорте). Разговаривайте только с людьми, находящимися рядом с вами. **Не кричите.** Чтобы привлечь внимание, воспользуйтесь колокольчиком или другим сигналом.

3. Поддерживайте **ровную осанку** и **говорите «от диафрагмы»**.

4. **Пейте** достаточно воды в течение дня.

5. **Отдыхайте**. Если вы устали, постарайтесь не разговаривать. Высыпайтесь.

6. **Замедляйте свою речь и растягивайте звуки,** особенно на концах слов, **как будто вы поете.**

7. **Говорите легко** – в удобном для вас диапазоне (не слишком низко и не слишком высоко) и с удобной громкостью (не кричите и не шепчите).

8. Регулярно **расслабляйте мышцы лица, шеи и плеч**.

9. **Если говорить больно, не говорите.** Не пользуйтесь леденцами от кашля для того, чтобы снять боль в горле и продолжать говорить: это лишь маскирует симптомы, и вы можете повредить свой голос.

10. **Радуйте себя**: наши эмоции влияют на наши голос и дыхание. Делайте всё возможное, чтобы уменьшить стресс в вашей жизни и регулярно получать позитивные впечатления.

Алиса Апрелева, MT-BC, NMT, музыкальный терапевт

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10 RULES OF VOICE CARE

1. Do not talk for too long. **If your voice is tired, be sure to take a break**.

2. **Do not talk in a noisy environment** (with the TV turned on, in the car, in public transport). Only talk to those who near you. **Do not shout**. Use a bell or other signal to attract attention.

3. Maintain **even posture** and **speak "from the diaphragm".**

4. **Drink enough water** throughout the day.

5. **Rest**. If you are tired, try not to talk. Get enough sleep.

6. **Slow down your speech** and stretch sounds, especially at the ends of words, as if you were singing.

7. **Speak lightly** - in a range convenient for you (not too low and not too high) and with a comfortable volume (do not scream or whisper).

8. Regularly **relax the muscles of the face, neck and shoulders**.

9. **If speaking causes pain, do not speak.** Do not use cough drops to relieve a sore throat and keep talking: this only masks the symptoms and you can damage your voice.

10. **Take care of yourself**: our emotions affect our voice and breath. Do everything you can to reduce stress in your life and get positive experiences regularly.

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Appendix I: Numerical rating scale for current perceived ease of respiration (Russian, English)

In Russian:

Насколько легко Вам дышать?

Отметьте по шкале от 1 (очень трудно) до 10 (очень легко).

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Очень трудно Нормально Очень легко

English translation:

How easy is it to breathe for you now?

Please indicate on the scale from 1 (very difficult) to 10 (very easy).

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Very difficult Normal Very easy

Appendix J: Numerical rating scale for current perceived ease of speech (Russian, English)

In Russian:

Насколько легко Вам говорить?

Отметьте по шкале от 1 (очень трудно) до 10 (очень легко).

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Очень трудно Нормально Очень легко

English translation:

How easy is it to speak for you now?

Please indicate on the scale from 1 (very difficult) to 10 (very easy).

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Very difficult Normal Very easy

Appendix K. CNS-BFS Speech subscale and CNS-BFS Swallowing subscale (English, Russian)

CNS-BFS Speech subscale

Participants are asked to score each question from “1” (does not apply) to “5” (applies most of the time), as each item has applied to them during the past week. Participants unable to speak are assigned a value of 6 for the speech domain questions.

In English (original):

CNS-BFS Speech	**Does not apply**	**Rarely applies**	**Occasionally applies**	**Frequently applies**	**Applies most of the time**
1. My speech is difficult to understand	1	2	3	4	5
2. To be understood I repeat myself	1	2	3	4	5
3. People who understand me tell other people what I said	1	2	3	4	5

4. To communicate I write things down or use devices such as a computer	1	2	3	4	5
5. I am talking less because it takes so much effort to speak	1	2	3	4	5
6. My speech is slower than usual	1	2	3	4	5
7. It is hard for people to hear me	1	2	3	4	5

Translated into Russian:

CNS-BFS Речь	**Никогда**	**Редко**	**Иногда**	**Часто**	**Почти всегда**
1. Мою речь трудно понять	1	2	3	4	5
2. Чтобы меня поняли, я повторяю сказанное	1	2	3	4	5

3. Люди, которые понимают мою речь, говорят другим, что я сказал(а)	1	2	3	4	5
4. Чтобы общаться, мне приходится записывать слова на бумаге или пользоваться устройствами, такими, как компьютер	1	2	3	4	5
5. Я говорю меньше, потому что требуется так много усилий, чтобы говорить	1	2	3	4	5
6. Моя речь медленнее, чем обычно	1	2	3	4	5
7. Людям трудно слышать меня	1	2	3	4	5

CNS-BFS Swallowing subscale

Participants to be asked to score each question from "1" (does not apply) to "5" (applies most of the time), as each item has applied to them during the past week.

In English (original):

CNS-BFS Swallowing	**Does not apply**	**Rarely applies**	**Occasionally applies**	**Frequently applies**	**Applies most of the time**
1. Swallowing is a problem	1	2	3	4	5
2. Cutting my food into smaller pieces makes it easier to chew and swallow	1	2	3	4	5
3. To get food down I have switched to a soft diet	1	2	3	4	5
4. After swallowing I gag or choke	1	2	3	4	5
5. It takes longer to eat	1	2	3	4	5

6. My weight is dropping because I can't eat normally	1	2	3	4	5
7. Food gets stuck in my throat	1	2	3	4	5

Translated into Russian:

CNS-BFS Swallowing	**Никогда**	**Редко**	**Иногда**	**Часто**	**Почти всегда**
1. Глотание это проблема	1	2	3	4	5
2. Разрезание еды на маленькие кусочки облегчает жевание и глотание	1	2	3	4	5
3. Чтобы еда проходила в желудок, я перешёл(-шла) на еду,	1	2	3	4	5

измельченную блендером					
4. Когда я глотаю, я давлюсь или поперхиваюсь	1	2	3	4	5
5. Требуется больше времени, чтобы поесть	1	2	3	4	5
6. Мой вес снижается, потому что я не могу есть нормально	1	2	3	4	5
7. Еда застревает у меня в горле	1	2	3	4	5

Appendix L. Text for oral reading task (Russian)

The excerpt marked in bold was recorded as a voice sample for acoustic analysis.

Дом, в котором я живу, расположен на окраине маленького городка, у самой подошвы горы. Здесь мягкий климат и редко идут дожди. Ночью небосвод бывает так густо усеян звездами, что кажется, будто все миллиарды их из нашей галактики разбросаны вверху над моей головой. Летним утром, как только я открываю окно, моя большая комната наполняется запахом цветов. Ветки черешен смотрят мне в окна, и легкий теплый ветер усыпает мой письменный стол белыми лепестками.

Я слушаю щебет птиц. Вот с искрометным задором пропел зяблик. Где-то дятел устраивает дупло. А это черные дрозды — поют не хуже соловьев. Прямо передо мной внизу — пестрый узор из крыш городских домов, а вдалеке, на краю горизонта, тянется серебряная цепь снеговых вершин... Весело жить в такой земле! Отрадное чувство разливается в жилах: вокруг величественные горы, воздух чистый и свежий, солнце яркое, небо синее — чего еще желать?.. Бьют настенные часы над камином: пять, шесть, семь, восемь, девять... Нужно торопиться в бюро. Минуты две-три ищу в шкафу электрическую схему, привезенную французским коллегой. Наконец заглядываю в портфель, нахожу ее внутри и вкладываю в книгу. После этого плотно закрываю жалюзи, однако сквозь щелки все равно пробивается солнечный свет. Выхожу на крыльцо и запираю ключом дверь. Спустившись ниже к центру города, иду бульваром. Часть дороги проходит по пешеходному мосту через реку. Гибкие стальные тросы держат невысокий мост. Они привязаны к специальным тяжелым якорям, врытым в землю. Останавливаюсь в начале мостика у ограды, чтобы полюбоваться рельефными склонами горных хребтов, всматриваюсь в речную рябь. Под мостом с шумом плещутся мелкие рыбешки, возмущая водную гладь. Откуда-то доносится музыка: ноктюрн Шопена — позывные местной радиостанции.

Вдруг позади себя я слышу: „Сережа, неужели это ты? Вот так встреча!“. Я узнаю этот низкий голос. Оборачиваюсь — так и есть: Андрей Сафонов!

Очень радостно видеть его вновь. С Андреем мы знакомы с конца восьмидесятых — служили вместе в армии. Его, энергичного и общительного, всегда на помощь готового прийти, любили все. Меня покорили его честность и недюжинная сила. Мы были дружны, но потом, мало-помалу, связь наша оборвалась.

— Здравствуй, Андрюша! Как ты тут оказался? — Командировка в архив: предлагают снять сюжет про судоверфь. Вчера приехали — сегодня уезжаем. Вернее, улетаем — к четырем в аэропорт. — Так скоро? И куда? — Следующим пунктом Уфа. Прямой рейс. А ты, значит, теперь здесь живешь? Давно? — Два года будет в феврале. Обменял свою городскую квартиру на бревенчатую избу. — Серьезно? Не жалеешь? В глазах моего приятеля мелькнул веселый огонек. — Нисколько. Отдыхаю от километровых пробок, сутолоки и пыли. — По-прежнему плывешь против течения? Счастливый ты человек, Сергей. — Ладно, расскажи лучше о себе. Мы тысячу лет не виделись. Как жизнь? Как семья? — Все у нас хорошо, все здоровы. Мы с женой работаем, дочь гимназию заканчивает. — Ну а Федор как? Учится? — Он в этом году поступил в медицинский. — Какой молодец! Поздравляю вас! — Спасибо. — Кстати, ты позавтракал? — Немного кофе выпил в гостинице. С удовольствием бы съел что-нибудь. — Недалеко отсюда есть кафе. Мы привыкли там есть. Пойдем, провожу тебя. Вполне приличный сервис, разнообразное меню. Одно из их „фирменных“ блюд — рыба по-бенгальски. Рекомендую: вкус необыкновенный — для настоящих гурманов. — Звучит слишком изысканно. Попроще ничего нет? — Как насчет яичницы с грибами? — В самый раз. А ты торопишься? Может быть, составишь мне компанию? За разговорами и воспоминаниями незаметно пролетел завтрак. Приближалось время сказать „до свидания“. Мы расстались в твердом намерении больше не терять друг друга из виду.

Source:

Smirnova N.S., Khitrov M.V. 2013. Foneticheski predstavitelnyi tekst dla fundamentalnykh I prikladnykh issledovanii russkoi rechi. Metodicheskie I algoritmicheskie osnovy obrabotki I analiza rechevykh I zvukovykh signalov. *Izvestiya Vysshykh Uchebnykh Zavedenii “Priborostroeniya”*, 56 (2), pp.6-10

Appendix M: Outcome measures and data collection summary table

Outcome measure	**Outcome measure description**	**Data collection points**
Feasibility outcome measures		
Recruitment	All newly diagnosed patients at ALS Moscow Centre living in Moscow city limits and meeting the inclusion and exclusion criteria were invited to participate, until the desired sample size (n=8) was achieved or the cut-off recruitment date occurred. Target recruitment over 80% was considered the marker of a successful feasibility trial.	Prior to the cut-off recruitment date.
Retention	The total number of participants recruited was compared with the total number of participants who completed the study. Retention rate over 70% at the end of follow-up period was considered the marker of a successful feasibility trial.	Week 1, Week 16.
Adherence	The number of music therapy sessions attended by each participant was recorded as an adherence measure for this study. Mean adherence across all participants who completed the study was calculated. Mean adherence for the group calculated at over 75% music therapy sessions delivered was considered the marker of a successful feasibility trial.	Each music therapy session (total of 12), throughout therapy phase (Weeks 6 – 12)
Tolerance	Short-term tolerability of the music therapy treatment protocol was assessed by measuring change in ratings on self-reported Ease of Respiration Visual Analogue Scale and change in ratings on self-reported Ease of Speech Visual Analogue Scale before and after every music therapy session. The outcome could range from "1" (very difficult) to "10" (very easy). Recorded by the music therapist.	Before and after each music therapy session (total of 12), throughout therapy phase (Weeks 6 – 12)

Self-motivation	Self-reported adherence to a suggested independent exercise routine was recorded to assess levels of self-motivation that participants demonstrated with regard to music therapy treatment. Any attempt to practice was recorded. The number of independent exercises sets performed, in proportion to the number of days when no visit from music therapist was scheduled, recorded during the sessions from 4 to 12 during the 6-week treatment phase, was calculated, measured in percent.	Each music therapy session starting at session 4 (total of 9), throughout therapy phase (Weeks 7 – 12)
Treatment experience of participants – persons with ALS	Semi-structured interviews with research participants – persons with ALS – were conducted pre-treatment (week 5) and at the end of the follow-up period (week 16). Participant's answers to open questions in regards to expectations for and impressions of music therapy treatment, were written down during a home visit by a trained research assistant. Interpretative phenomenological analysis was applied to find prominent common themes across the semi-structured interviews.	Week 5, Week 16
Caregiver's experience	Semi-structured interviews with caregivers were conducted prior to treatment (week 5) and at the end of the follow-up period (week 16). Primary caregivers, if identified by participants – persons with ALS – and only with their permission, were approached for the interviews. The caregivers' answers to open questions in regards to expectations for and impressions of music therapy treatment, were written down during a home visit by a trained research assistant. Interpretative phenomenological analysis was applied to find prominent common themes across the semi-structured interviews.	Week 5, Week 16
Music therapist's perspective	Individual treatment notes taken after each session and generalized "field notes" taken twice a week, after completion of each consequent session by all the participants, were submitted by the music therapist. Thematic narrative analysis of the notes was conducted.	Each music therapy session (total of 12), throughout therapy phase (Weeks 7 – 12)

Biomedical outcome measures		
Outcome measures to assess the long-term changes in respiration		
Change of Forced Vital Capacity (FVC) from baseline at Week 6, Week 12, Week 16	Forced Vital Capacity (FVC) is a standard spirometry test which measures the volume of air that can forcibly be blown out after full inspiration; measured in %. Measured during a home visit by a nurse.	Week 1, Week 6, Week 12, Week 16
Change of Maximal Inspiratory Pressure (MIP) from baseline at Week 6, Week 12, Week 16	Maximal Inspiratory Pressure (MIP) is the inspiratory pressure generated against a completely occluded airway; used to evaluate inspiratory respiratory muscle strength; measured in cm H_2O. Measured during a home visit by a nurse.	Week 1, Week 6, Week 12, Week 16
Change of Maximal Expiratory Pressure (MEP) from baseline at Week 6, Week 12, Week 16	Maximal Expiratory Pressure (MEP) is a measure of the strength of respiratory muscles, obtained by having the patient exhale as strongly as possible against a mouthpiece; measured in cm H_2O. Measured during a home visit by a nurse.	Week 1, Week 6, Week 12, Week 16
Outcome measures to assess the long-term changes in cough		
Change of Peak Expiratory Flow (PEF) from baseline at Week 6, Week 12, Week 16	Peak Expiratory Flow (PEF) is a measure of cough effectiveness, portable peak flow meter was used; measured in %. Measured during a home visit by a nurse.	Week 1, Week 6, Week 12, Week 16
Outcome measures to assess the long-term changes in speech		
Change of Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Speech	The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) consists of three domains (swallowing, speech, and salivation), each of which is	Week 1, Week 6, Week 12, Week 16

subscore from baseline at Week 6, Week 12, Week 16	assessed with a 7-item, self-report questionnaire. Each question is scored from "1" (does not apply) to "5" (applies most of the time). Speech domain subscore can range from "7" (best outcome) to "35" (worst outcome). The result was recorded during a home visit by a trained research assistant.	
Change in acoustic assessment parameters of recorded voice from baseline at Week 6, Week 12, Week 16	Voice samples were recorded during a home visit by a trained research assistant digitally in .wav format, using a Shure WH20XLR Dynamic Headset Microphone, Alesis iO Dock audio interface, Apple iPad 2 tablet and GarageBand software. Acoustic analysis of the voice samples was conducted using the Praat linguistic computer program to calculate the following outcome measures: - Maximum Phonation Time (MPT), sound /a/, measured in seconds, - Maximum Repetition Rate – Alternating (AMR), /pataka/ sequence, measured in total number of syllables uttered as fast and as clear as possible on one breath, - Maximum Repetition Rate – Sequential (SMR), /ba/ syllable, measured in total number of syllables uttered as fast and as clear as possible on one breath, - Jitter, local, sound /a/, measured in percent, - Shimmer, local, sound /a/, measured in percent, - Harmonics-to-Noise Ratio (HNR), measured in Db, sustained /a/ - Vowel Space Area (VSA), separate vowels /a, e, i, o, u/, measured in squared Hz, - Fundamental frequency (F0), oral reading, measured in Hz, - Speaking rate, oral reading, measured in words per minute, - Speech-pause ratio, oral reading, measured in seconds per minute,	Week 1, Week 6, Week 12, Week 16

	- Pause frequency, oral reading, measured in number of pauses per minute, - Fundamental frequency (F0), spontaneous speech, measured in Hz, - Speaking rate, spontaneous speech, measured in words per minute, - Speech-pause ratio, spontaneous speech, measured in seconds per minute, - Pause frequency spontaneous speech, measured in number of pauses per minute.	
Change in perceptual assessment parameters of recorded voice from baseline at Week 6, Week 12, Week 16	Voice samples were recorded during a home visit by a trained research assistant digitally in .wav format, using a Shure WH20XLR Dynamic Headset Microphone, Alesis iO Dock audio interface, Apple iPad 2 tablet and GarageBand software. Perceptual analysis of the voice samples was performed by three qualified speech-language specialists to assess change in hypernasality level of spontaneous speech, measured in points. Interrater reliability was calculated for the perceptual analysis results.	Week 1, Week 6, Week 12, Week 16
Outcome measures to assess the long-term changes in swallowing		
Change of Center for Neurologic Study Bulbar Function Scale (CNS-BFS) Swallowing subscore from baseline at Week 6, Week 12, Week 16	The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) consists of three domains (swallowing, speech, and salivation), each of which is assessed with a 7-item, self-report questionnaire. Each question is scored from "1" (does not apply) to "5" (applies most of the time). Swallowing domain subscore can range from "7" (best outcome) to "35" (worst outcome). The result was recorded during a home visit by a trained research assistant.	Week 1, Week 6, Week 12, Week 16

Change in videofluoroscopic swallowing study (VFSS) results from baseline at Week 6, Week 12	VFSS (videofluoroscopic swallowing study), an x-ray-based method of evaluating a person's swallowing ability, was performed by a trained specialist during a visit to a laboratory using a BV Pulsera Mobile C-arm fluoroscope, pulsing at 30 pulses per second and recorded on built-in Medical DVD Recorder at 30 frames per second. Each participant swallows 10mL of nectar and pudding-thick liquid boluses, thickened with a xanthan gum-based thickener (i.e., Nestle Thicken-Up Clear®) and mixed to 40% weight-to-volume concentration with BarVIPS powder. VFSS video clips were reviewed and scored by a trained speech-language pathologist, using frame-by-frame analysis following operational definitions outlined by (Steele et al, 2019). The following outcome parameters were calculated from VFSS video clips, recorded at three time points, to assess long-term changes in swallowing: - Time-to-Laryngeal Vestibule Closure, nectar 10 mL, measured in ms, - Time-to-Laryngeal Vestibule Closure, pudding 10 mL, measured in ms, - Maximum Pharyngeal Constriction Area, nectar 10 mL, measured in % $C2\text{-}4^2$, - Maximum Pharyngeal Constriction Area, pudding 10 mL, measured in % $C2\text{-}4^2$, - Peak position of the Hyoid Bone, nectar 10 mL, measured in % C2-4, - Peak position of the Hyoid Bone, pudding 10 mL, measured in % C2-4, - Penetration-Aspiration Scale Score (worst), nectar 10 mL, measured in points, - Penetration-Aspiration Scale Score (worst), pudding 10 mL, measured in points, - Total Pharyngeal Residue C24area, nectar 10 mL, measured in % C2-4,	Week 1, Week 6, Week 12

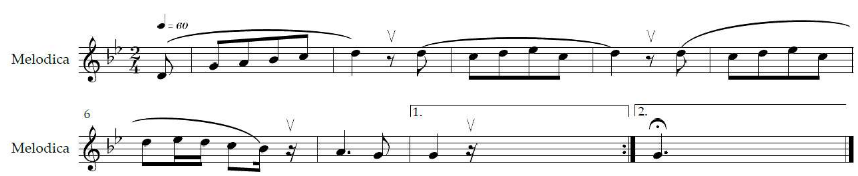
	- Total Pharyngeal Residue C24area, pudding 10 mL, measured in % C2-4, - Laryngeal vestibule closure, nectar 10 mL, described as complete, partial, or incomplete, - Laryngeal vestibule closure, pudding 10 mL, described as complete, partial, or incomplete.	

Appendix N. Experimental music therapy treatment protocol to support bulbar and respiratory functions of persons with early and mid-stage amyotrophic lateral sclerosis

Exercise	**Time** (approx.)	**Therapy objective**	**Description and participant instructions** (Music therapist verbally describes and models every exercise before inviting the patient to participate)	**Materials and equipment**
I. Session opening and assessment	5 min	Assessment.	Music therapist (MT) and participant exchange salutations. MT assesses participant's physical and emotional state through observation and conversation, and reestablishes the rapport through a brief conversation to ensure psychological comfort of the participant entering the session. The following information is recorded: 1) VAS for current perceived ease of respiration, 2) VAS for current perceived ease of voice production, 3) information about the adherence to the assigned independent exercises routine: frequency, duration, difficulties, comments (starting at session 4). Participant is reminded that he/she is going to be guided through all the exercises and is welcome to participate to his/her comfort, to ask clarifying questions and make comments, to stop doing an exercise at any point if he/she feels uncomfortable or tired, and to pause, rest and hydrate as needed.	VAS (respiration) and VAS (voice) sheets; VAS data sheet; notebook for note taking. Two sturdy chairs situated facing each other, approximately 1.5 m apart. Optional: wheelchair, small table, pillow for participant's comfort.

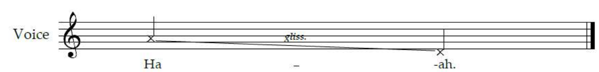
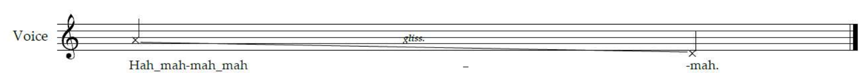
II. Body alignment exercise	3 min	To learn the proper body alignment and its role in respiration, voice production and swallowing.	II.1. Body awareness Participant is encouraged to become aware of the physical sensation of his/her body, to pay close attention to any muscle tension, strain or stiffness and to gently move, stretch or self-massage to release those. II.2. Body alignment Participant is encouraged to become aware of his/her body alignment and to find a good sitting posture by maintaining the spinal alignment from the hips up. Suggested steps to achieve this are: a. both feet are on the ground, shoulder-width apart, forming a 90-degree angle with the thighs; b. the pelvis is adjusted so there is slightly less curve in the lower back, and the spine feels extended both upwards and downwards; c. the rib cage is now more upward and "open" (not collapsed); d. the shoulders are suspended exactly over the rib cage (rather than pulled back or rolled forward); e. the head is balanced at the top of the spine and feels almost weightless, with the front half of the skull is balanced in front of Altanto-occipital joint, and its hind half is balanced behind Atlanto-occipital joint; f. the upper body is poised and aligned, yet flexible and ready to move: the images of the whole body as a marionette suspended by a rope extending from the top of the skull, or of the head as a water lily flower resting on water surface may be helpful; g. to check for the proper spinal alignment: stretch arms above the head and bend them down so that fingertips of one hand touch the elbow of the opposite arm; sustain this position for several seconds, then let the arms drop down gently to the sides of the body, but keep the posture.	Visual aids for anatomy of singing.

			The anatomy and physiology of respiration, voice production and swallowing are briefly explained to the patient during these and following exercises in order to increase the patient's awareness and sense of control over these processes.	
III. Diaphragmatic breathing exercises	4 min	To become aware of diaphragmatic action, its role in respiration and benefits of diaphragmatic breathing.	III.1. Silent long diaphragmatic breathing (5-10 repetitions) Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way, and no rib action should occur. Participant is encouraged to place one hand on his/her abdomen and the other on his/her chest as he /she practices diaphragmatic breathing. The front and the side of the abdominal wall expand as the diaphragm contracts and pulls down during breath in, while no visible movement of the chest or shoulders occurs. III.2. Audible diaphragmatic breathing on [s] sound (3 repetitions) Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth making a continuous [s] sound until he/she runs out of air. The sound should not be forced, and no rib action should occur. III.3. Silent long diaphragmatic breathing (3 repetitions) – see III.1. III.4. Diaphragmatic breathing with audible sigh (3 repetitions) Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth making an audible, very breathy sigh on a vowel sound (for example, 'a'). The sound should not be forced, the throat should be relaxed, and no rib action should occur. Note: No background music or music accompaniment will be used, as this will allow the participants to fully concentrate on the physical sensation of diaphragmatic breathing. During the first several sessions the participant may experience slightly uncomfortable pulling sensation around posterior abdomen wall: this sensation is due to this group of muscles being more intensively worked than usual and will	Visual aids for anatomy of singing (Figures 3, 4, 5).

			subside. When it becomes habitual, diaphragmatic breathing may reduce the effort necessary for breathing.	
IV. Controlled breathing and lip seal exercise	3 min	To practice controlled breathing in order to create sustained airflow necessary for speech; to improve oxygen and carbon dioxide exchange; to maintain lip seal (necessary for swallowing and for decreasing salivation).	IV.1. Pursed lip breathing (3 repetitions) Participant is instructed to take a diaphragmatic breath in through the nose and to breathe out very slowly through pursed lips ("as if blowing on a fire"). A piece of lightweight fabric held by MT in front of the participant can be used for visual feedback. IV.2. Controlled breathing and lip seal exercise Participant is instructed to blow into the tube mouthpiece of the melodica while MT plays on the keys of the melodica the first 16 measures from "Old French Song" from "Children's Album" (Op.39, No.16) by Tchaikovsky, at 60 bmp, with accompanying audible metronome click. Participant is advised to breathe in through the nose as necessary between the phrases, MT may provide conducting cues for inhale as necessary. The tempo is adjusted as needed (decreased for a longer exhale) to match participants' ability. IV.2. Controlled breathing and lip seal exercise "Old French Song" by P. Tchaikovsky, adapted from "Children's Album" Op.39, No.16 	37-key melodica; individual tube mouthpiece; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification). Optional: a small (approx. 15 cm x 15 cm) piece of lightweight fabric.
V. Music-assisted	8 min	To elicit the relaxation	Participant is reminded to maintain the aligned sitting posture, and to be gentle rather than forceful in releasing muscle tension.	Android smartphone;

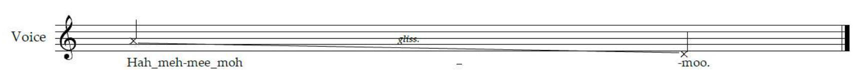
relaxation for voice production		response through music-assisted visualization technique (V.1) and to relax and stretch the muscles involved in voice production (V.2 – V.8).	V.1. Music-assisted visualization and relaxation (about 4 minutes) The recorded relaxing music is started in the background at the level allowing for a live narrative to be clearly heard. Maintaining the aligned sitting body position, participant is advised to close the eyes and to breathe deeply, as he/she is led by MT through a brief (about 3 minutes) music-assisted visualization for relaxation. At the end of the exercise, as the background music continues, participant is invited to gently open his/her eyes, first looking downwards and then gradually orienting him/herself to the surroundings. The background music continues through the rest of the exercise sets. V.2. The head and the neck muscles relaxation (2 repetitions) Maintaining the body alignment, participant is advised to let his/her head slowly fall forward under its weight, to feel the stretch on the spine, and then to bring the head back to the balanced position at the top of the spine. Participant may also sway the head gently side to side during this exercise, if it feels appropriate. V.3. The facial muscles relaxation Participant is advised to rub his/her hands together or to warm them otherwise and to place the palms over closed eyes for several seconds, then to gently massage the face with circular motions of the pads of the fingers, using both hands, moving from hairline downwards to cheeks, lips and chin, spending more time on areas that feel tight. When the cheeks are being massaged, participant is advised to let his/ her jaw to hang slack. Face massage may be performed by MT or a care provider if the patient’s hand function is impaired. V.5. The tongue muscles relaxation and stretch (3 repetitions) Participant is encouraged to let the tongue relax and fall forward slightly out of the mouth by releasing its muscles, then to gently stretch the tongue out of the mouth down toward the chin, and to release again allowing the tongue to rest on the lower	default music player for Android; Spotify application for Android (with subscription); Kinivo ZX120 Mini Portable Wired Speaker for amplification). Optional: lotion or oil for massage; Purell for hands disinfection (if MT touches participant’s face).

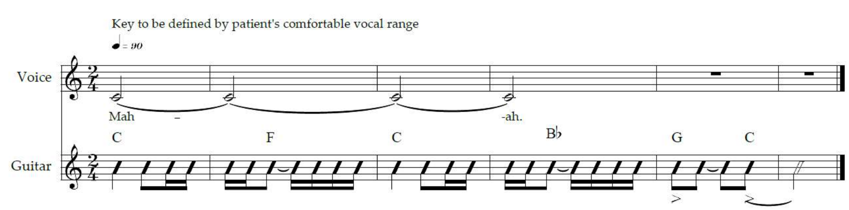
			lip. Participant is further advised to pull the tongue back into the mouth as far as possible, hold for a few seconds, and release. V.6. The mandible (jaw) relaxation and stretch Participant is assisted in finding his/her temporomandibular joints. With the fingers placed over the joints, the patient allows the jaw to drop without resistance. Participant is encouraged to take his/her jaw between the thumb and forefinger and to gently move the jaw up and down, at first slowly, then faster. The movement will be unrestricted if the jaw is relaxed. Participant is then advised to move the jaw as far forward as possible, hold, then release; then to move the jaw as far back and upwards as possible (chin tuck), hold, then release. This stretch may be repeated 2 or 3 times. V.7. The suprahyoid muscles relaxation Participant is assisted in finding his/her suprahyoid (digastric and mylohyoid) muscles under his/her chin (the muscles responsible for elevating the larynx during swallowing). Participant is advised to gently massage these muscles with his/her thumbs in slow, "kneading" motions, pushing vertically up and releasing down. V.8. The infrahyoid (strap) muscles relaxation Participant is assisted in finding his/her larynx by placing fingers flat against the front of his / her neck and swallowing, thumb and forefinger of one hand are used to gently move the larynx side to side several times.	
VI. "Ping pong" soft palate exercise	1 min	To tonicize the soft palate muscles involved in velopharyngeal function and to practice the proper soft	Participant is instructed to "yawn politely" (half yawn) in order to find the proper position for relaxed sound production (Woo, 2012). It may helpful to imagine there is a ping pong ball in the back of the mouth and to hold this position for several seconds. Repeat 5 times.	None.

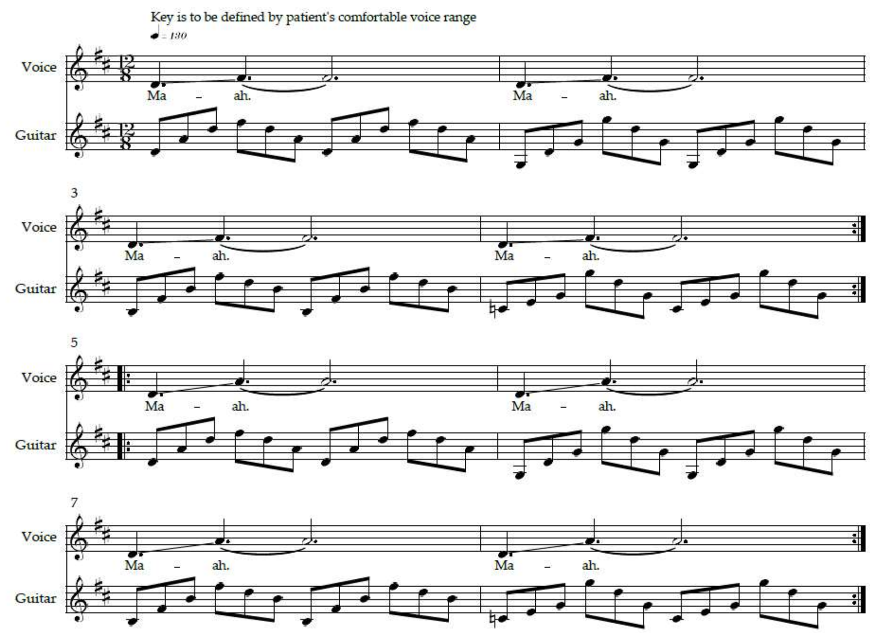
		palate position for phonation.		
VII. Phonation exercises	5 min	To facilitate proper engagement of arytenoid cartilages and vocal folds (VII.1 – VII.3), to increase the speech rate (tongue movement speed) (VII.3).	VII.1. “Hah” sigh exercise (2 repetitions) Participant is instructed to take a breath, to expel about half of it, then to add a light, “lazy” sigh (“hah”), starting in the voice midrange and inflecting downwards. The tongue rests in the limp position, the jaw is relaxed. VII.1. "Hah" sigh exercise voice pattern  VII.2. Interrupted “hah” sigh exercise (2 repetitions) Participant is instructed to repeat the previous exercise, allowing the lips to close and open several times at the beginning of the sigh, resulting in light humming sound (“hah-mah-mah-mah-mah”). The lips are not pressed firmly together like in the regular [m] sound. The tongue rests in the limp position, the jaw is relaxed. VII.2. Interrupted "hah" sigh exercise voice pattern  VII.3. Voiced consonant sigh exercise (2 repetitions for each consonant)	Visual aids for anatomy of singing Figures 9 and 10).

			Maintaining relaxation of facial and laryngeal muscles, participant is instructed to take a diaphragmatic breath, then to expel the air while making a continuous consonant sound, starting in the voice midrange and inflecting downwards. An accompanying short vowel sound has to be added to the stop consonants ('b', 'd', 'g'), e.g. "ba-ba-ba-ba-ba". The sound should not be forced. The jaw and tongue are relaxed. The sequence of the consonants for this exercise is: /v/, /z/, /z</, /l/, rolled /r/, /j/, /b/, /d/, /m/, /n/, /g/. Rolled /r/ may present a challenge for some people. This is not related to ALS and should not discourage the patient from attempting this exercise.	
VIII. Consonant range cantillation exercise	2 min	To facilitate the tongue movement ease and speed, to improve velopharyngeal function, to prevent (reduce) hypernasality.	Participant is instructed to take a diaphragmatic breath and say "Mah-nah-ng-ah" in cantillation once, then proceed saying "Mah-nah-ng-ah" 3 times on one exhalation, next – saying it 6 times on one exhalation, then 9 times on one exhalation, and, finally, 12 times on one exhalation. Participant is encouraged to maintain and note the freedom of tongue and jaw movement as he / she does this exercise. Note: The sequence of tongue movements required for this exercise involves fast progression from the resting position (/m/) to hard palate (/n/), to soft palate (/g/) (McClosky, 2011) . Besides facilitating the tongue movement ease and speed, this exercise has the potential to improve velopharyngeal function and, thus, to prevent (reduce) hypernasality, which also contributes to speech intelligibility (Rong et al., 2016).	None.
IX. Velopharyngeal port exercise	3 min	To improve velopharyngeal function, to prevent hypernasality.	Starting in the lower mid-range of his / her voice, participant is instructed to sing the syllables "Hun-ga" three times as a scale from *sol* to *do*. "Hun" corresponds with the offbeat, and "ga" falls on the beat. The exercise is then modulated gradually up by semitones, until it reaches the limit of the participant's comfortable range. After that it modulated down by semitones until it is three semitones below the starting key. The therapist models the exercise and provides the guitar accompaniment, and sings together with the participant. The patient is encouraged to notice the switching between nasal ("hun") and non-nasal sound ("ga"). Audible metronome click is set	Visual aids for anatomy of singing (Figure 10). Acoustic guitar; metronome (Android smartphone,

			up. The tempo of the accompaniment can be adjusted to the ability of the patient. Gradual increase to up to 90 bpm is advisable in later sessions. IX. Velopharyngeal port exercise voice pattern and guitar accompaniment 	Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).
X. Impulse diaphragmatic breathing exercise	2 min	To increase the efficiency and speed of relaxed diaphragmatic inhalation.	X.1. Impulse breathing with short "hah" exhale (2 repetitions) The exercise starts with participant listening to 8 beats of audible metronome click initially set at 4/4, 64 bpm. Participant is instructed to fully relax abdominal muscles, letting the air effortlessly enter the lungs, then to abruptly expel the air with a short, though deep and strong ("barking") "hah" sound and to immediately let the abdominal muscles relax again, letting the air into the lungs. Suggested sequence: 1) listen and rest for 8 beats, 2) 8 "hah" utterances for 8 beats, 3) listen and rest for 8 beats, 4) 8 "hah" utterances for 8 beats, 5) stop. The tempo should be slightly faster that the tempo most comfortable for the participant and may be increased gradually in subsequent sessions if the patient is ready. X.2. Impulse breathing with sustained "hah" exhales (4 repetitions) As in the previous exercise, participant is advised to fully relax the abdominal muscles, letting the air effortlessly enter the lungs. Then the air is expelled 3 times following the pattern: "Hah-hah-haaaaaaaah" (short-short-long), where /a/ vowel is very open, strong and deep, but is not forced. After each syllable, the abdominal muscles should relax again, letting the air into the lungs.	Acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

XI. Sustained vowels production exercises	5 min	To practice full diaphragmatic breathing and healthy vocal folds coordination for sustained, supported vowel production.	XI.1. Vowel shaping exercise (3 repetitions) With the mouth fully closed, participant is instructed to silently form vowel shapes in the following sequence: /a/, /e/, /i/, /o/, /u/, paying attention to position changes in tongue and facial muscles. MT model the vowels (with sound). XI.2. “Hah-meh-mee-moh-moo” sigh exercise (3 repetitions) Similar to exercise VII.3, participant is encouraged to take a breath, then expel it on a light, “lazy” sigh, starting in the voice midrange and inflecting downwards. During this exhale, participant forms the vowel shapes /a/, /e/, /i/, /o/, /u/ in a relaxed manner and allows the lips to close and open several times, resulting in light humming sound: “Hah-meh-mee-moh-moo”. The lips are not pressed firmly together like in the regular [m] sound, and the jaw is relaxed. XI.2. "Hah-meh-mee-moh-moo" sigh exercise voice pattern  XI.3 “Hah-eh-ee-oh-oo” sigh exercise (3 repetitions) The instructions for this exercise are the same as for the exercise IX.2., but the lip movement resulting in the light /m/ sound is now omitted: “Hah-eh-hee-oh-oo”. XI.3. "Hah-eh-ee-oh-oo" sigh exercise voice pattern 	Acoustic guitar; metronome (Android smartphone, Metronome Beats application for Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).

			XI.4. Sustained vowels exercise (2 repetitions, if tolerated well) Comfortable tone from participant's midrange is chosen for the exercise and becomes the tonal center (*do*). The patient sustains *do* for four measures (2/4, 90 bpm) on "mah" syllable, then rests for 2 measures. The next syllable ("meh") is then sustained is a similar manner, then "mee", "moh" and "moo". The therapist provides the guitar accompaniment, and sings together with the participant. Accompanying audible metronome is set up at 2/4, 90 bpm. The tempo is adjusted as needed (decreased for a longer exhale) to match participants' ability. The exercise may be performed twice, if tolerated well. XI.4. Sustained vowels exercise voice pattern and guitar accompaniment  Note: In case of excessive perceived nasality, participant may be advised to "adopt a pleasant facial expression", slightly lifting the zygomatic muscles ("lifting the cheeks").	
XII. Laryngeal elevation through vocalization (gliding vowels) exercise	5 min	To facilitate sustained laryngeal elevation.	MT models the exercise and sings together with the participant. A comfortable tone from the participant's midrange is chosen for the exercise. Starting from this tone on "mah" syllable, participant is instructed to slide up a major 3rd interval by beat 4 (the second dotted quarter) of the measure and to sustain this tone until the end of the measure. This singing pattern is repeated for 3 more measures, as the harmony changes. 4 measures on "mee" and then 4 measures on "moo" follow. If tolerated well, the whole exercise may be repeated once and major 3rd interval may be	Acoustic guitar; metronome (Android smartphone, Metronome Beats application for

			increased to perfect 5^{th} for increased laryngeal elevation. Live guitar accompaniment is provided by MT, in 12/8, 130 bmp, one harmony per measure, with accompanying audible metronome click. Repeat 2 times if tolerated well. XII. Gliding vowels exercise voice pattern and guitar accompaniment 	Android, Kinivo ZX120 Mini Portable Wired Speaker for amplification).
XIII. Vocal cords relaxation exercises	2 min	To relax vocal cords following the singing exercises.	Participant is instructed to use diaphragmatic or mixed type of breathing during these relaxation exercises. XIII.1. Vocal fry exercise	None.

			Participant is instructed to take a deep breath and to make vocal fry sound for the duration of the exhale. Can be repeated. XIII.2. Deep breathing (3 repetitions) Participant is instructed to breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way. Participant can choose to use diaphragmatic or mixed (diaphragmatic and chest) type of breathing. XIII.3. Exhale on hard [h] (3 repetitions) Participant is instructed to continue deep breathing and then to exhale of a “lazy”, long, uninterrupted hard [h] sound.	
XIV. Preferred song performance	5 min	To reinforce all the voice skills practiced in previous exercises (body alignment and posture, diaphragmatic breathing, proper phonation, soft palate elevation, relaxed consonant articulation, etc.), to provide a motivating reward at the end of the session.	Participant is invited to sing his / her preferred song in comfortable range, at comfortable tempo, with live guitar accompaniment provided by MT. MT may choose to sing together with participant to encourage participation and to model healthy singing technique. Both the participant and the MT provide brief feedback on the performance at the end of song. Selection of the song for this exercise will occur as follows. At recruitment, each participant will be asked to provide the list of his/her 3 to 5 favorite songs to sing. MT will choose one of these songs to include into the protocol, giving preference to the songs with simple melodic and harmonic structure, enough pauses for proper phrasing, moderate tempo, and emotionally neutral or “positive”.	Acoustic guitar. Optional: song lyrics printout.

XIV. Session closure and assessment	5 min	Assessment.	MT closes the session, acknowledges participant’s effort and reminds of the upcoming session(s) if any are left. The following information is gathered and recorded into the Patient’s individual data sheet: 1) VAS for current perceived ease of respiration, 2) VAS for current perceived ease of voice production. MT instructs (or reminds) the participant to practice Recommended daily exercises, if possible, always taking precautions to avoid strain and exhaustion (to “stop if somethings doesn’t feel right”). MT instructs (or reminds) the participant to follow the Voice health guidelines (Roman, 2014).	VAS (respiration) and VAS (voice) sheets; VAS data sheet; notebook for note taking.

Appendix O. Music therapy session data collection sheet

	VAS speech pre	VAS resp. pre	VAS speech post	VAS resp. post	Exercises	Session
1						
2						
3						
4						
5						
6						

7						
8						
9						
10						
11						
12						

Appendix P. Visual aids for anatomy and physiology of respiration, voice production, cough and swallowing

Figure I. Sitting posture. Source: (McClosky, 2011)

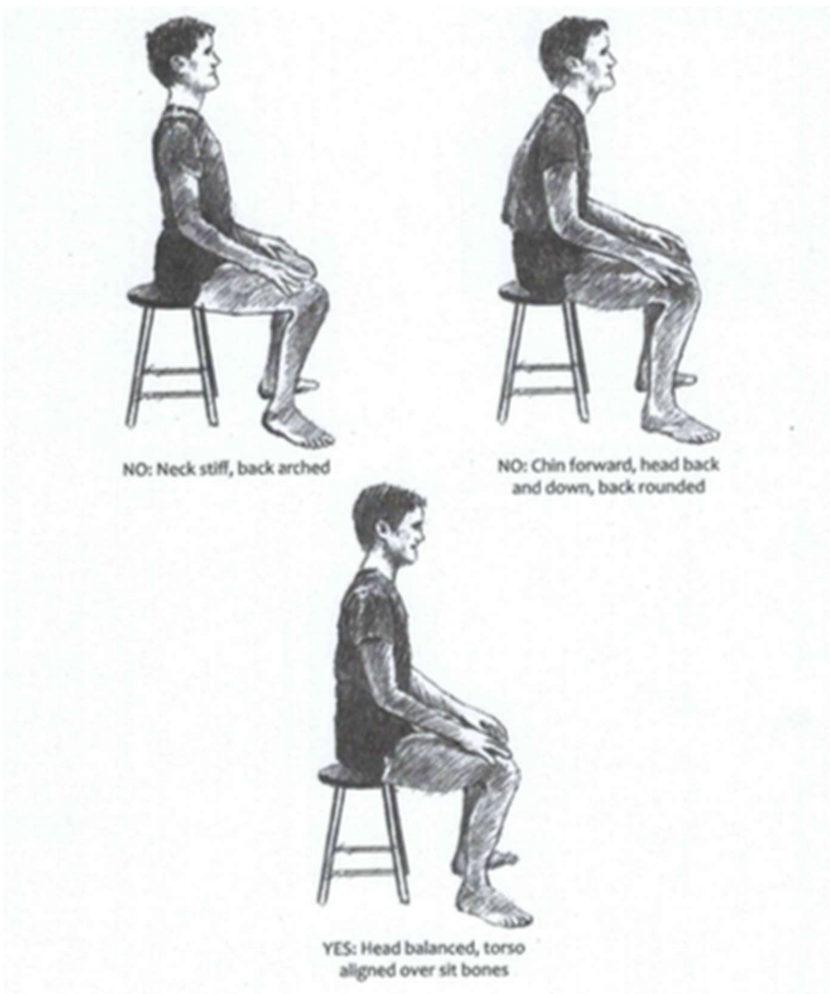


Figure II. Balance of the head and neck. Source: (McClosky, 2011)

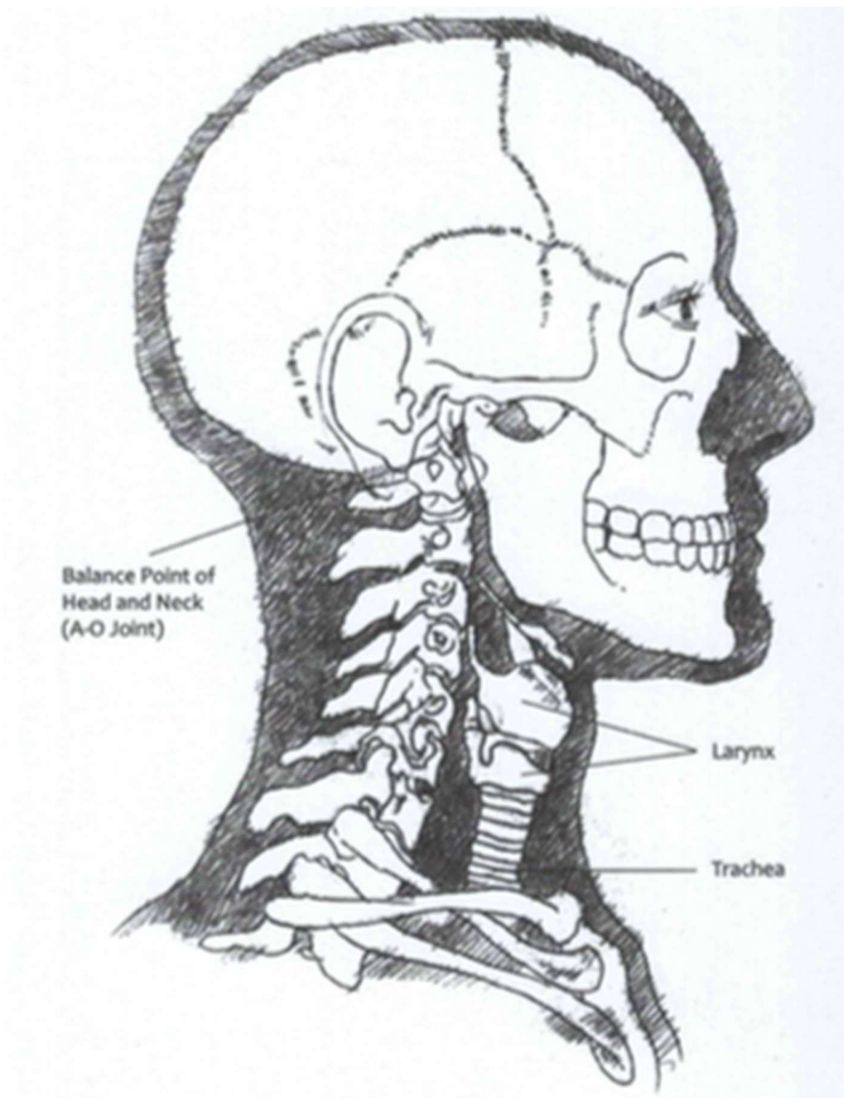


Figure III. Rib cage and abdominal muscles. Source: (Peckham, 2010)

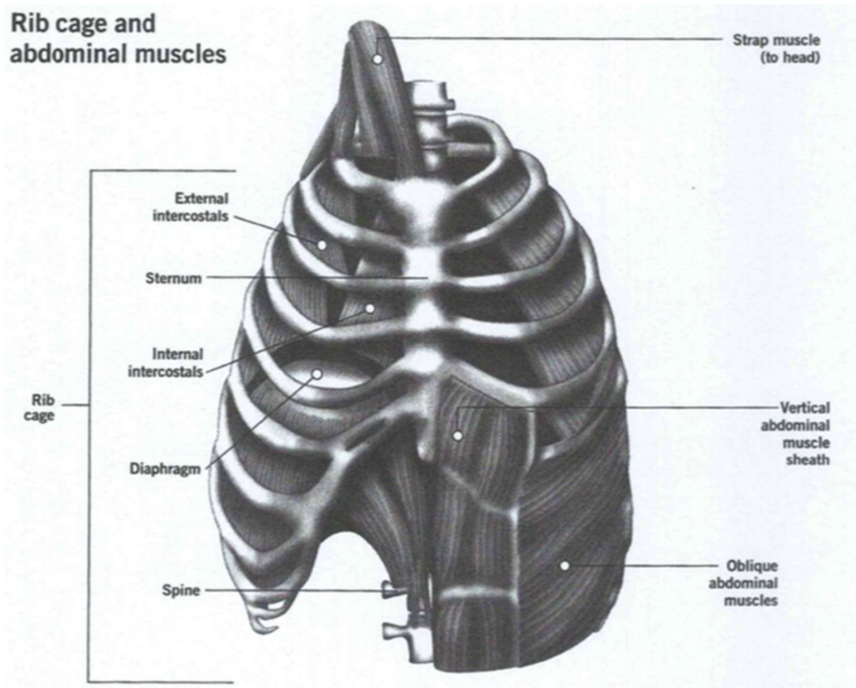


Figure IV. Diaphragm action (anterior view). Source: (Peckham, 2010)

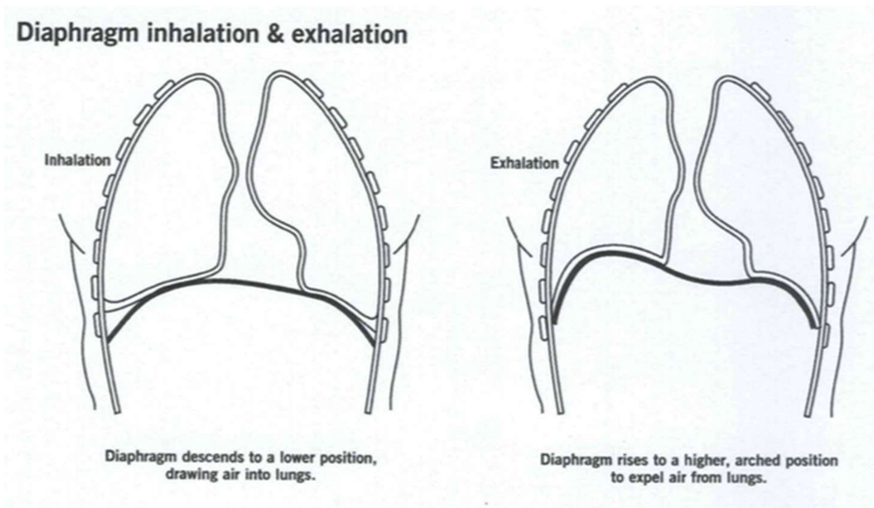


Figure V. Diaphragm action (lateral view). Source: (McClosky, 2011)

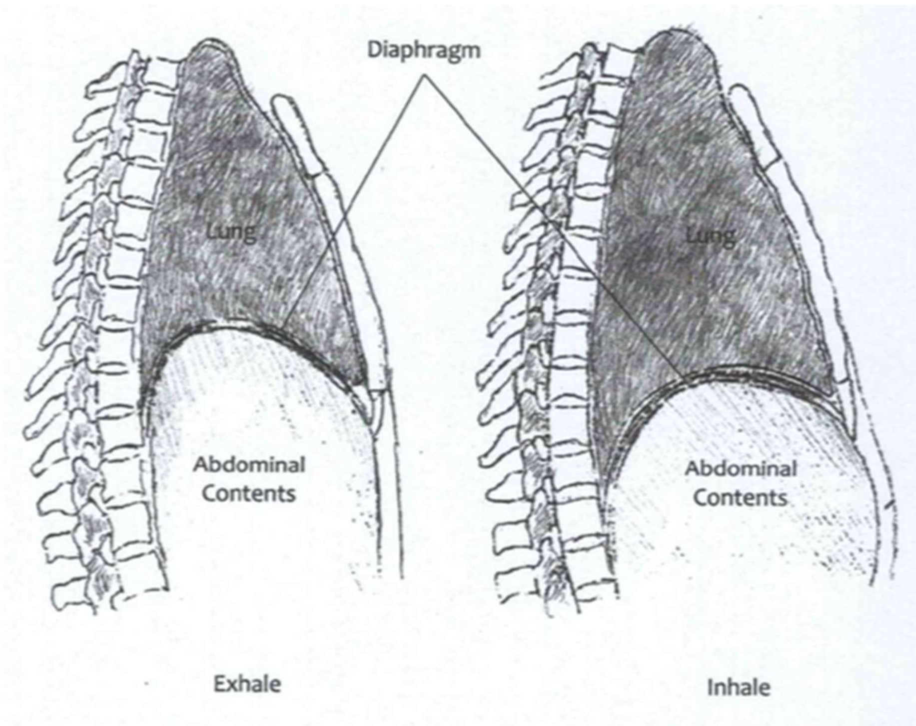


Figure VI. The larynx. Source: (Peckham, 2010)

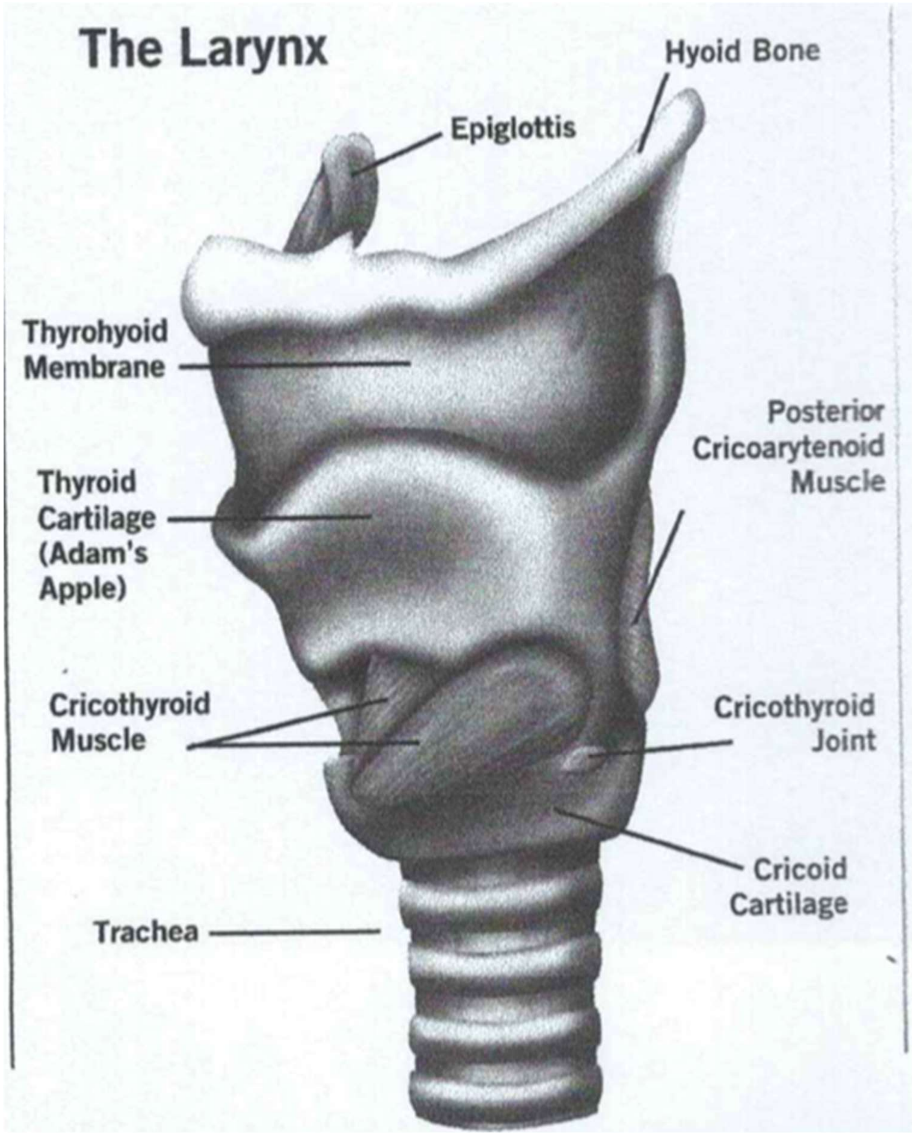


Figure VII. Cartilages of the larynx (anterior and posterior views). Source: (McClosky, 2011).

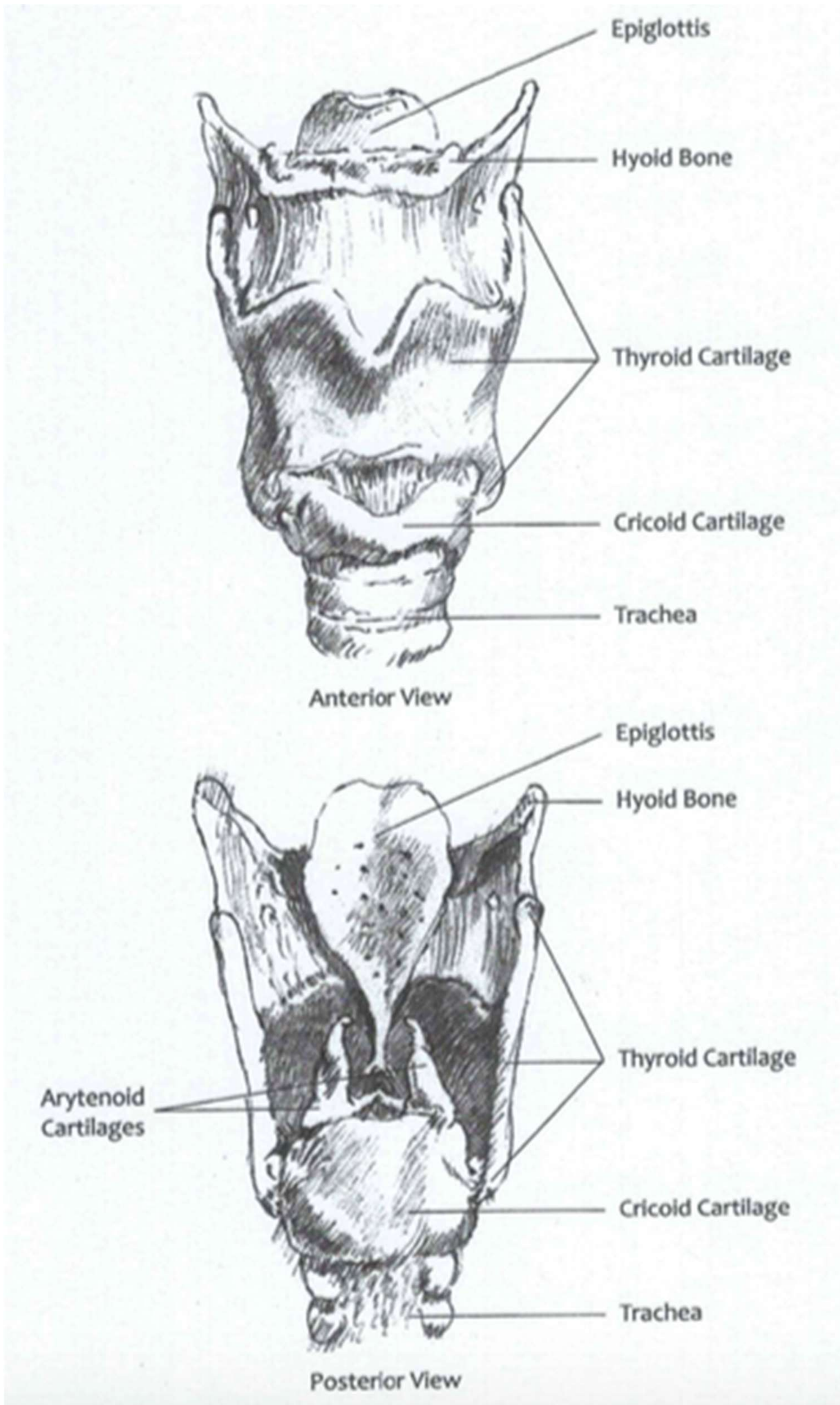


Figure VIII. Cartilages of the larynx (lateral view). Source: (McClosky, 2011).

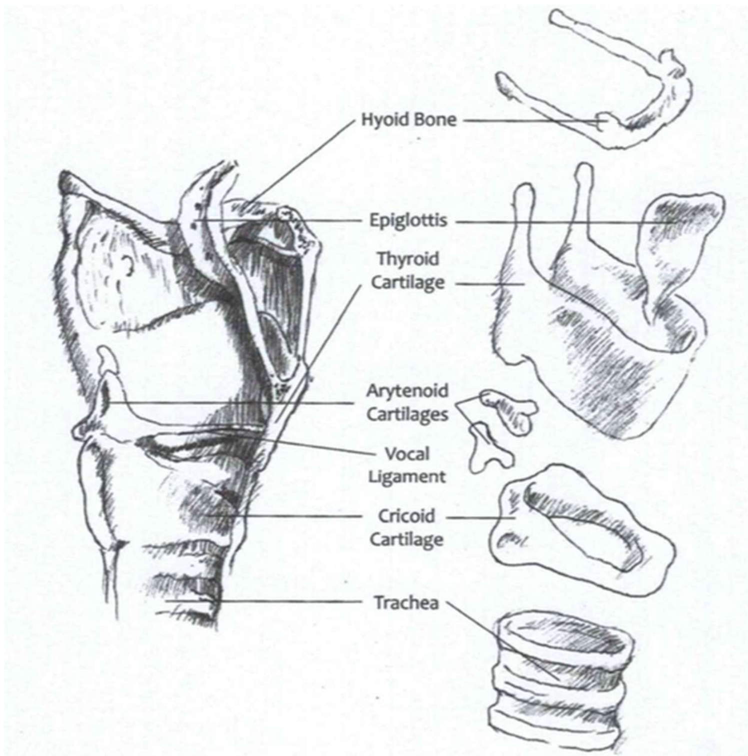


Figure X. Profile of vocal tract. Source: (Peckham, 2010)

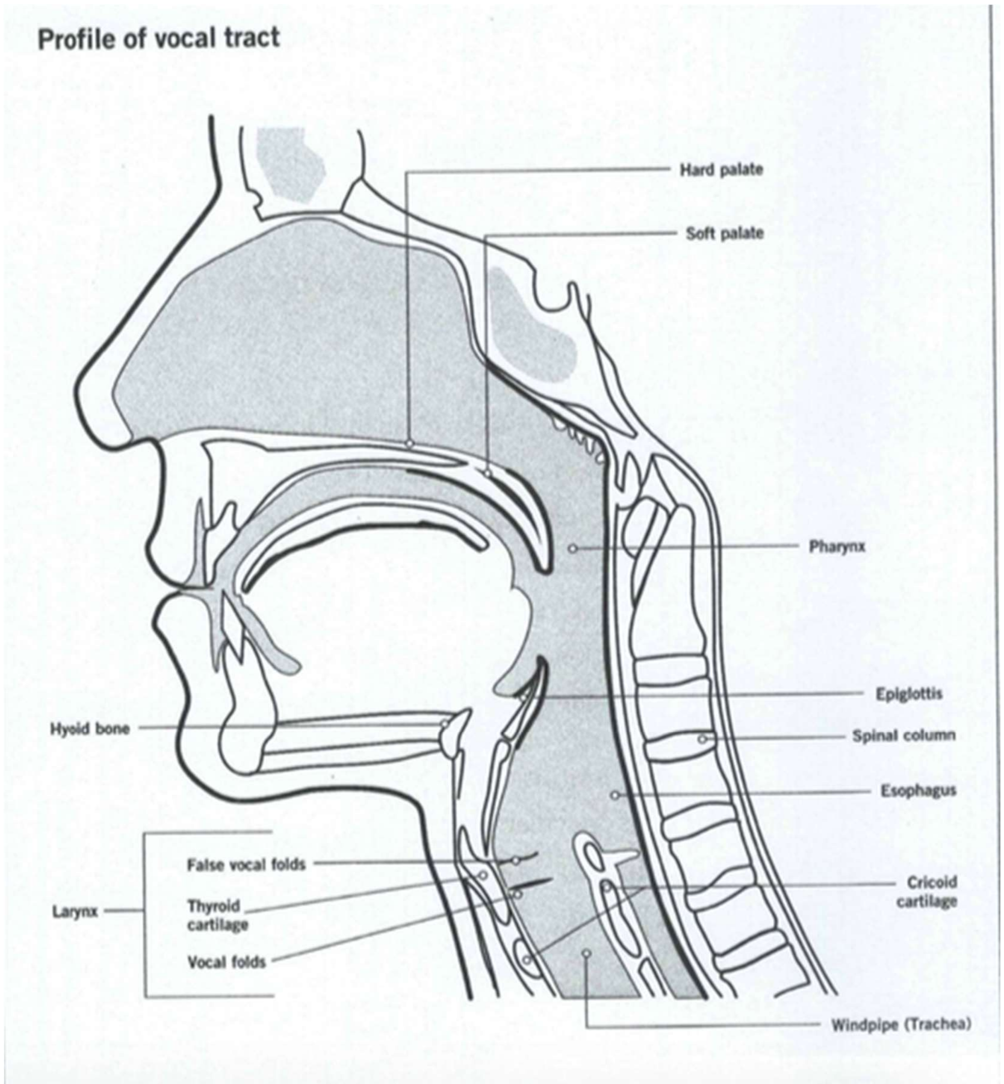
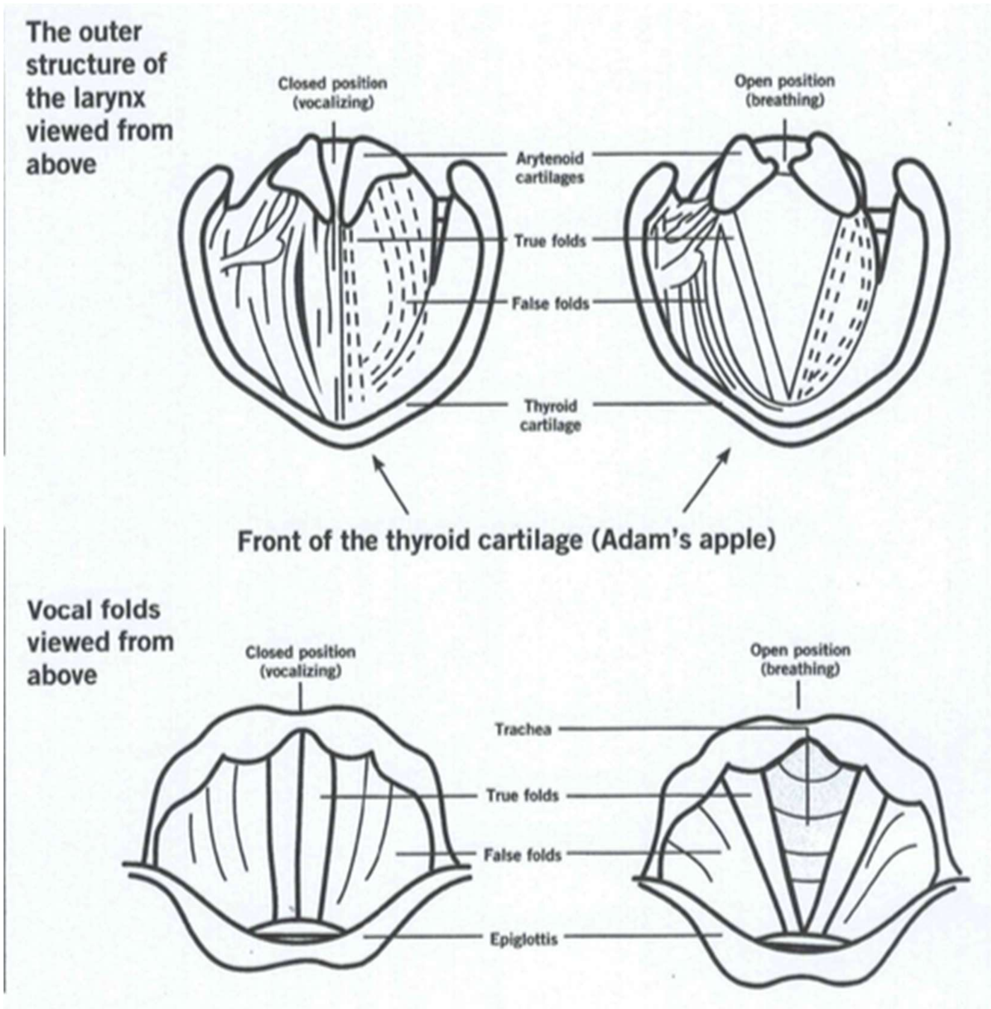


Figure XI. The structure of larynx and the vocal folds. Source: (Peckham, 2010)



The outer structure of the larynx viewed from above
Closed position (vocalizing)
Open position (breathing)
Arytenoid cartilages
True folds
False folds
Thyroid cartilage
Front of the thyroid cartilage (Adam's apple)
Vocal folds viewed from above
Closed position (vocalizing)
Open position (breathing)
Trachea
True folds
False folds
Epiglottis

Appendix Q. Sample narrative for Exercise V.1. Music-assisted visualization and relaxation, English translation

This is the English translation of a sample narrative for music-assisted visualization and relaxation exercise. Please note that the following narrative is for sample purposes only. It is important that the text is adjusted by a certified music therapist to individual preferences and physical capabilities of each patient.

Close your eyes and take a deep breath.

Concentrate on your breathing. Feel the air entering and leaving your body.

Feel the floor under your feet.

Feel the weight of your body. Let your hands become heavy.

Keep breathing deeply.

Move your shoulders slightly. Imagine standing under beautiful, warm waterfall. Water running down your shoulders, washing away all the tension, worries and fatigue, leaving you refreshed and balanced.

Feel the full length of your spine.

Take another breath. Feel the air filling up your lungs. Then let it go.

Now think of a space, real or imaginary, where you feel safe and content. It may be a beautiful forest with sunbeams coming through the green leaves, an open field full of wild flowers, an ocean shore with waves coming and going, or a quiet sunny room with a cozy chair.

Keep breathing. With each breath take in the energy of this place. Notice the colors, sounds, smells.

Stay in this place for several minutes.

Take this time for yourself.

While the music sounds, all the business and thoughts can wait. Let the music hold you.

(Let the participant enjoy one or two minutes of music).

It is time to go now. But as you leave this place, remember that you can return as often as you wish, whenever you need.

Take another deep breath. As you inhale, take in all the good, healing energy of this place. As you exhale, let go of the thoughts and sensations you do not need or want.

Feel your body. Feel the chair that supports you.

Feel your shoulders. Your arms.

Feel your feet on the floor. Let the floor surface supporting the weight of your feet.

Take another breath.

When you are ready, gently open your eyes.

It is time to start the muscle relaxation exercises.

Appendix R. Sample recommended daily exercises instructions (English translation)

This is English translation of sample recommended daily exercises instructions for the study participants. Please note that the following instructions are for sample purposes only. It is important that the exercises are adjusted by a certified music therapist to meet individual preferences and physical capabilities of each patient. In addition to an individualized printout in Russian, a corresponding individualized audio guide with the instructions in Russian and appropriate music tracks will be provided for each participant to make the exercise routine easier.

RECOMMENDED DAILY MUSIC THERAPY EXERCISES

These exercises are advised, but not required for you to perform on the days when you do not have a music therapy session. You have experienced all these exercises during your music therapy sessions with your therapist. Practice the assigned exercises ONCE DAILY. You will need about 30 minutes to do the exercises.

You may choose to use the separate music tracks or the accompanying audio guide provided by your music therapist. All the instructions and the music accompaniment have been tailored to meet your voice range, tempo and medical needs.

Remember to do these exercises when you are rested and hydrated. Wear comfortable clothes allowing for unrestricted movement and breathing. Find a comfortable space to sit. Minimize noise and distractions: turn off TV and radio, close the windows if you live on a busy street. As you do the exercises, you may want to take a little break, drink a glass of water or stop altogether if fatigue is a problem.

ALWAYS TAKE PRECAUTIONS TO AVOID STRAIN AND EXHAUSTION

IF IT HURTS OR SIMPLY DOES NOT FEEL RIGHT, STOP RIGHT AWAY

If you have any questions or concerns regarding these exercises or music therapy treatment, contact your therapist or the research assistant:

(Music therapist): phone#, email

(Research assistant): phone#, email

Step 1. POSTURE (2 minutes)

Firstly, let us work on body alignment. Proper body posture make breathing, speaking and swallowing more effective.

To start, sit down comfortably and pay attention to physical sensation of your body, any muscle tension, strain or stiffness. Then gently move, stretch or self-massage for about one minute to release those.

Now find your proper body alignment. In doing so, let us move from the feet up.

Place both FEET on the ground, shoulder-width apart, forming the right angle with the thighs.

Adjust the PELVIS so there is slightly less curve in the lower back, and the spine feels extended both upwards and downwards.

Your RIB CAGE is now more upward and “open” (it is not collapsed).

Your SHOULDERS are suspended exactly over the rib cage (rather than pulled back or rolled forward).

Your HEAD is balanced at the top of the spine and feels almost weightless.

Your UPPER BODY is poised and aligned, yet flexible and ready to move (like a marionette suspended by a rope extending from the top of your head, or like the head of a water lily flower resting on water surface).

Step 2. BREATH (2 minutes)

Maintaining body posture and flexibility, start diaphragmatic breathing.

JUST BREATHE. Breathe in through the nose, with the mouth slightly open, then breathe out through the mouth, without sound. The air enters and escapes from the lungs with no effort: it is not forced in any way, and no rib action should occur. You may place one hand on your abdomen and the other on the chest: feel your diaphragm working as your abdomen expands with each breath, while no visible movement of the chest or shoulders occurs. Repeat two more times.

EXHALE ON [S]. Now let us make sound. Continue breathing in the same way, then, on the outbreath, make a continuous [s] sound until you run out of air. The sound should not be forced, and no rib action should occur. Repeat two more times.

EXHALE ON [A]. Let us continue. This time, as you breathe out, make an audible, very breathy sigh on a vowel sound (for example, [a]). The sound should not be forced, the throat should be relaxed, and no rib action should occur. Repeat two more times.

"BLOW ON THE FIRE". And the last one. Breathe in through the nose, then breathe out very slowly through pursed lips ("as if blowing on the fire"). Repeat two more times.

Step 3. RELAXATION (10 minutes)

It is most beneficial to do these exercises to music. If possible, start the relaxation music provided to you by your music therapist in the background. Make sure you can hear the music well, but it is not too loud. Remember to maintain the aligned sitting posture and to breathe abdominally during this exercise. Be gentle rather than forceful releasing muscle tension. Let us begin[1].

Close your eyes and take a deep breath.
Concentrate on your breathing. Feel the air entering and leaving your body.
Feel the floor under your feet.
Feel the weight of your body. Let your hands become heavy.
Keep breathing deeply.
Move your shoulders slightly. Imagine standing under beautiful, warm waterfall. Water running down your shoulders, washing away all the tension, worries and fatigue, leaving you refreshed and balanced.
Feel the full length of your spine.
Take another breath. Feel the air filling up your lungs. Then let it go.
Now think of a space, real or imaginary, where you feel safe and content. It may be a beautiful forest with sunbeams coming through the green leaves, an open field full of wild flowers, an ocean shore with waves coming and going, or a quiet sunny room with a cozy chair.
Keep breathing. With each breath take in the energy of this place. Notice the colors, sounds, smells.
Stay in this place for several minutes.
Take this time for yourself.
While the music sounds, all the business and thoughts can wait. Let the music hold you.

(Enjoy 1 or 2 minutes of music).

[1] Please note that the following narrative is for sample purposes only. It is important that the text is adjusted to individual preferences and physical capabilities of each patient.

It is time to go now. But as you leave this place, remember that you can return as often as you wish, whenever you need.
Take another deep breath. As you inhale, take in all the good, healing energy of this place. As you exhale, let go of the thoughts and sensations you do not need or want.
Feel your body. Feel the chair that supports you.
Feel your shoulders. Your arms.
Feel your feet on the floor. Let the floor surface supporting the weight of your feet.
Take another breath.
When you are ready, gently open your eyes.

It is time to start the muscle relaxation exercises.

HEAD. Let your head slowly fall forward under its weight, feel the stretch on the spine, and then bring the head back to the balanced position at the top of the spine. Repeat 2 or 3 times. You may also sway the head gently side to side during this exercise, if it feels appropriate.

FACE. Rub your hands together or warm them otherwise and place the palms over closed eyes for several seconds. Gently massage the face with circular motions of the pads of the fingers, using both hands, moving from hairline downwards to cheeks, lips and chin, spending more time on areas that feel tight. Let your jaw to hang slack ("as if only thing stopping your jaw from falling further was the skin on your face"). The face has to become void of any expression during this exercise.

TONGUE. Release your tongue muscles and let the tongue relax and fall forward slightly out of the mouth. Gently stretch the tongue out of the mouth down toward the chin, and release again allowing the tongue to rest on the lower lip. Then pull the tongue back into the mouth as far as possible, hold for a few seconds, and release. Make 2 or 3 repetitions.

JAW. Allow your jaw to drop without resistance. Take your jaw between the thumb and forefinger and gently move it up and down, at first slowly, then faster. The movement will be unrestricted if the jaw is relaxed. Now move the jaw as far forward as possible, hold, then release; then move the jaw as far back and upwards as possible (so that it looks like you have a “double chin”), hold, then release. Repeat this stretch two or three times, if it feels appropriate.

UNDER CHIN. Gently massage the muscles under your chin with your thumbs in slow, “kneading” motions, so that they go up and down. This movement should not be painful.

LARYNX. Place your fingers flat against the front of your and swallow: you can feel you larynx move. Now use your thumb and forefinger to gently move the larynx side to side several times.

<u>Step 4. CONSONANTS</u> (8 minutes)

As you start this set of exercises, remember to maintain the aligned posture and to practice diaphragmatic breathing.

YAWN. Pretend you are yawning with your mouth closed – or imagine there is a ping-pong ball in the back of your mouth. Feel a light stretch in your soft palate. Repeat three times.

“HAH”. Take an abdominal breath, expel about half of it, then add a light, “lazy” sigh (“hah”), starting in the middle of your voice range and going downwards. The tongue should rest in the limp position, the jaw should be relaxed. *Raise your arm and let it fall down to accompany the sound, as practiced in music therapy sessions, if this helps you. Do it twice.

“HAH-MAH-MAH-MAH-MAH”. Repeat the previous exercise, but at the beginning of the sigh allow the lips to close and open several times so that it sounds like “hah-mah-mah-mah-mah”. Remember not to press lips too firmly together.

CONSONANTS. Remember to keep face and larynx muscles relaxed as you do this exercise. Take a deep diaphragmatic breath, then exhale making a continuous consonant sound. As before, start in the middle of your voice range and go downward. Repeat each consonant twice. Go in this order:

/V/

/Z/

/Z</

/L/

/R/

/J/

/M/

/N/

Remember to add a short vowel sound as you pronounce the following three consonants:

/B/

/D/

/G/

“MAN-NAH-NG-AH”. Take a deep diaphragmatic breath and slowly say “Mah-nah-ng-ah” in cantillation once as you breathe out. Take another breath and say “mah-nah-ng-ah” 3 times in a row, on the next breath – 6 times, on the next breath – 9 times, and, finally, try to say it 12 times on one exhalation. Note how freely move your tongue and jaw as you do this exercise.

“HUN-GA”. Now check your posture and make sure the muscles of you jaw, neck and shoulders are relaxed. Practice saying “hun-ga”. Feel the air coming through your nose on the first syllable and through your mouth on the second syllable. As you sing along the track provided to you by your music therapist, remember to breathe with your diaphragm and to not force the sound.

Step 5. IMPULSE BREATHING (2 minutes)

SHORT “HAH”. For this exercise you will need to fully relax abdominal muscles and let the air effortlessly enter your lungs, then to abruptly expel the air with a short, though deep and strong (“barking”) “hah” sound and then to immediately let the abdominal muscles relax again, letting the air back into the lungs. On the recording provided to you by your music therapist, listen to the metronome for 8 beats, then do 8 exhales on “hah” for the next 8 beats, then rest for 8 more beats, after which do 8 more exhalations on “hah” to the beat.

LONG “HAAAAH”. As in the previous exercise, fully relax the abdominal muscles and let the air effortlessly enter the lungs. Then pronounce two short and one long syllable: “Hah-hah-haaaaaaaah”. After each of the three syllables, the abdominal muscles should quickly relax again, letting the air into the lungs. /A/ sound should be very open and deep, but not forced. Repeat two more times.

Step 6. VOWELS (6 minutes)

VOWEL SHAPES. With the mouth fully closed, silently, form vowel shapes in the following sequence: /A/ - /E/ - /I/ - /O/ - /U/. Pay attention to position changes in tongue and facial muscles. Repeat the sequence two more times.

SUSTAINED VOWELS. Check your posture and make sure that muscles of your face, neck and shoulders are not strained. Remember to take deep diaphragmatic breath for each syllable you sing. As you sing along the track provided to you by your music therapist, sustain syllable «MAH» for four measures, and when you hear a brief stop in the guitar accompaniment, stop and take another deep breath. Repeat the exercise for syllables “MEH”, “MEE”, “MOH”, “MOO”.

GLIDING VOWELS. In this exercise you will sing along the music track again. Starting on “MAH” syllable slide up a major third interval as your music therapist models for you on the recording. Sustain this tone till the end of the measure or till you run out of air. The sound does not have to be loud. Repeat the slide three more times on “MAH”, as the harmony changes.

Continue with four slides on “MEE” and four slides on “MOO”. If it feels good and your voice is not tired, you can repeat the whole exercise making a larger (perfect fifth) slide, as demonstrated on the recording by your music therapist.

When you are finished with your daily exercises, rest for several minutes and drink enough water to keep hydrated. Remember to keep record of the days when you do your exercises. Try to notice how these exercises make you feel afterwards. Take a mental note on any difficulties, successes or changes. You will have the opportunity to discuss your daily exercise routine with your therapist during your next session. Remember to always follow the Vocal health guidelines provided to you by your music therapist.

Appendix S. Interviews with research participants – persons with ALS, conducted prior to treatment (week 5) (English translation and thematic analysis)

Question 1. How, you think, may music therapy affect your speech, breathing and swallowing?

Participant 1: In no way. Because I have tracheitis. I have had it for three years already. Muscles atrophied because I had sinus troubles.

Participant 2: I think, in a positive way, because breathing exercises and emotional tuning are beneficial.

Participant 3: It somehow affects vocal chords and the muscles responsible for swallowing and breathing. I have no idea what it is, how it will be, that is why my answers are so scanty.

Participant 4: I hope that any kinds of training – swallowing, breathing, speech – are useful for me when I have this disease. I know that when people are taught singing, the first things they get straight are breathing and vocal chords action. Both would be useful for me. The music itself has positive emotional effect, I know it firsthand. I come from a musical family and live with the music all my life.

Participant 5: I hope, beneficially. I do not understand the mechanism. Breathing exercises help to keep the speech.

Participant 6: I don't think at all. What's the use to think about things I have no idea about? If I had a practical experience… but I do not know, so I do not think.

Participant 7: To be honest, I do not quite believe in this. I agreed to help the science, I agree to all clinical trials. I will be happy it this helps me and, consequently, the others.

Question 2. How, you think, may music therapy affect you otherwise?

Participant 1: I have a lot of music, I love it, I have been singing my whole life. I listen (to the music) all the time, so I do not think music therapy will bring me more joy. I will not be able to sing, will not be able to manage.

Participant 2: Way out of depression, I am slipping away into depression. I would like to extend my communication circle. I corner myself into depression. I would like to have positive emotions and to learn how to support myself emotionally, and to support my loved ones more.

Participant 3: Mood improvement. I will have to set aside the time. My daughter knows that I have (some) disease, and I will be able to exercise in her presence.

Participant 4: It is difficult to say. I can manage my moods myself. I expect, in the first place, the therapeutic effect. From music, literature, communication with people I always receive psycho-emotional support. They always encourage me, and through music therapy there will be more opportunities for that. Already, because of this research, I have understood the mechanics of swallowing.

Participant 5: Positive emotions related to singing. I am ready to sing together with the children. New experiences. Because of cooperative work with the children, the time spent together, the relationship with the children will develop positively. If called for, (my husband) will sing too.

Participant 6: Fine pastime. “Let us sing, my friends”.

Participant 7: Emotional support. Despondency is absolutely contraindicated under our condition, only positive emotions.

Question 3. What do you expect in music therapy sessions?

Participant 1: Will it work out or not? I will try, will see what comes from it. I have issues with nasopharynx, but it is difficult to pronounce.

Participant 2: I do not expect difficulties. I need to communicate with the people who know and understand. I hope to extend my communication opportunities.

Participant 3: I think I will get positive effect from music, that is why I agreed. These sessions will slow down the disease progression.

Participant 4: Daddy used to sing well and he said that I had improper vocal chords closure, so I never used to sing like my relatives on my mother or my father side. Though my daughter says it is all well with my vocal chords. I am not going to learn how to sing. I have signed up and I will do my best to complete everything. I do not want to answer to this question any more.

Participant 5: Aside from finding the time – I am afraid, it may not work; not sure, but I assume: (that) joy (awaits) because of music, because of collaborative activities with the children.

Participant 6: I don't think at all. See the answer number one.

Participant 7: The regularity of the sessions will trouble me, but I will regard it responsibly, to help. I do not like to sing. I warned from the start that I will not sing. If I will be asked to sing, I will feel inhibited. But I like to listen to good singing. I joined without joy, only to help the researchers. For many (patients) it is difficult to travel. But I agreed.

Question 4. How, you think, will it be to independently do the assigned music therapy exercises between the sessions?

Participant 1: When I succeed, it will be joy. But because nasopharynx is blocked and begma collects, it is not possible. I do not know how to get rid of it. I had 48 sinus punctures.

Participant 2: I will try to make a hobby of it and to use it as an opportunity to prolong active living.

Participant 3: Positive expectations. I am ready to orderly perform all the exercises to sustain functioning.

Participant 4: I regard these with interest, curiosity and anticipation. I will try to exercise conscientiously.

Participant 5: I need to make myself work independently. I need to find the time and the energy and to work with the tenet that this will help me. I have not made efforts of such kind in my life yet. I have to force myself.

Participant 6: I am ready for everything. If (music therapist) will tell me to sing the song 32 times a day, I will try to sing. I used to love singing when I got married, but then wife would not let me. Now she will be making me sing. Dream has come true.

Participant 7: I am used to making regular efforts. I exercise and many other things, I try to make effort, to overcome laziness. I will endeavor to organize myself, not to laze.

Question 5. How, you think, may these music therapy exercises affect your speech, breathing and swallowing?

Participant 1: Exercises will do nothing for my speech, they can only help the lungs.

Participant 2: The mechanism behind it is strengthening of the movement muscles. These muscles atrophy, because I do not use them, I keep silent all day long. I used to talk all the time, and now the regular volume of movement is missing.

Participant 3: The muscles will strengthen, will become more elastic. And will be able to function longer. The emotional condition itself is very important. I believe that laughing is essential. There are “funsters” among my relatives. The relatives (of persons with ALS) and the patients say that the good mood is the main thing. The rescue is in not staying alone. Otherwise bad thoughts come.

Participant 4: Breathing is still good, it was compromised only when I had bronchitis and normalized when the sickness gave way. I hope that decline will slow down. I already do have some problems with swallowing. I expect that exercises will slow down the decline of these functions.

Participant 5: Structuring of the day. One may convince oneself that the exercises will affect the disease course, practice this mindset. I have experience when I attempted to calm myself down if I was unsettled.

Participant 6: See my reply to the first question. Will start, will see. I am a practical person.

Participant 7: Possibly, they will improve speech; don’t think they will affect breathing. There are no problems with swallowing: I eat everything that is not nailed down, I have even gained weight.

Question 6. Other comments.

Participant 1: No.

Participant 2: I feel my uselessness.

Participant 3: No.

Participant 4: No.

Participant 5: No.

Participant 6: No.

Participant 7: No.

Area of inquiry	Common themes	Quotations
Music therapy outcomes expected by PALS	Most PALS stated they expected that music therapy may have a positive effect on their bulbar and respiratory functions	• Participant 2 ("in a positive way", "breathing exercises… are beneficial", "exercises will do nothing for my speech, they can only help the lungs") • Participant 3 ("these sessions will slow down the disease progression", "the muscles will strengthen, will become more elastic, and will be able to function longer") • Participant 4 ("I hope that any kinds of training – swallowing, breathing, speech – are useful for me when I have this disease", "I hope that decline will slow down") • Participant 5 ("I hope, beneficially", "breathing exercises help to keep the speech", "one may convince oneself that the exercises will affect the disease course, practice this mindset") • Participant 7 ("Possibly, they will improve speech; don't think they will affect breathing")
	Most PALS stated they expected music therapy to have a positive effect on their psychological state	• Participant 2 ("emotional tuning (is) beneficial", "way out of depression", "I would like to have positive emotions and to learn how to support myself emotionally") • Participant 3 ("mood improvement") • Participant 4 ("the music itself has positive emotional effect") • Participant 5 ("positive emotions related to singing", "joy (awaits) because of music") • Participant 7 ("emotional support")
	Some PALS stated they expected increased communication as a result of music therapy	• Participant 2 ("to extend my communication circle", "I hope to extend my communication opportunities")

		• Participant 3 (“the rescue is in not staying alone, otherwise bad thoughts come”) • Participant 4 (“music, literature, communication with people <…> always encourage me, and through music therapy there will be more opportunities for that”) • Participant 5 (“I am ready to sing together with the children”, “new experiences”) • Participant 6 (“fine pastime”, “Let us sing, my friends”)
	Some PALS stated they expected positive change in their relationship with other family members as a result of music therapy	• Participant 2 (“I would like to learn how to support myself emotionally, and to support my loved ones more”) • Participant 5 (“Because of cooperative work with the children, the time spent together, the relationship with the children will develop positively”)
Music therapy process, as anticipated by PALS	Some PALS expected singing during music therapy to present a challenge	• Participant 1 (“I will not be able to sing, will not be able to manage”) • Participant 4 (“I am not going to learn how to sing”, “I will do my best to complete everything”) • Participant 7 (“if I will be asked to sing, I will feel inhibited”)
	Some PALS anticipated that consistent engagement in music therapy may require additional (organization) effort	• Participant 3 (“I will have to set aside the time”) • Participant 5 (“I need to find the time and the energy and to work with the tenet that this will help me”) • Participant 7 (“the regularity of the sessions will trouble me”, “I will endeavor to organize myself, not to laze”)
	Most PALS reported being motivated to participate in music therapy treatment	• Participant 1 (“Will it work out or not? I will try, will see what comes from it”, “When I succeed, it will be joy”) • Participant 2 (“I will try to make a hobby of it and to use it as an opportunity to prolong active living”)

		• Participant 3 ("Positive expectations. I am ready to orderly perform all the exercises to sustain functioning") • Participant 4 ("I regard these with interest, curiosity and anticipation. I will try to exercise conscientiously") • Participant 6 ("I am ready for everything")

Appendix T. Interviews with research participants – persons with ALS, conducted at the end of the follow-up period (week 16) (English translation and thematic analysis)

Question 1. Has music therapy affected your speech, breathing and swallowing? In which way?

Participant 1: Not swallowing, it is normal. Breathing – yes, speech became somewhat better.

Participant 2: Considering my swallowing is unimpaired, it has not been affected. Speech has become more intelligible. (Music therapist) taught me to use diaphragm and abdomen muscles for talking, it has become easier to speak. I have enough air to finish the phrase. It has become easier to breathe as well. I experience less gagging.

Participant 3: Nose breathing has become better, I do not notice other changes.

Participant 4: I think the two months of practice influenced my attention to diaphragmatic breathing. I did not use to pay attention to that before. Specific diaphragm training is very useful when one has this disease. As a person coming from a musical family, I always used to hum. It turned out that I could not really sing, and I was glad to learn some basic things. It turned out I did not sing properly. I familiarized myself with elements of voice training. It is useful for more accurate command of vocal chords. I am grateful for this experience.

Participant 5: I very much hope so. Because of this everyday practice (the disease) does not progress that fast.

Participant 6: No, time went by fast.

Participant 7: It has not affected, no changes. Everything would be the same without music therapy.

Question 2. Has music therapy affected you otherwise?

Participant 1: Simply pleasant therapy, that's all.

Participant 2: Yes, (music therapy affected me) benefited me emotionally. Positive state of mind. Communication with (music therapist), in the first place – the person who is not indifferent to our story. Considering the dynamics for speech and breathing, the ability to communicate again with the others stabilized my overall condition. It was easy to incorporate (music therapy) into my everyday routine. I knew that I had to be ready for (music therapist's) visit by 10 am, and this time continues to be my music therapy time after she has left.

Participant 3: I started to pay attention to myself, learned that it is better to talk softly and in a relaxed manner.

Participant 4: If we were to use a wider understanding of music therapy, not in a narrow technical sense, then I have been using music therapy my whole life, it is natural to me. Adding the technical details was important. I could only practice independently two times a week.

Participant 5: It was very pleasant to practice with (music therapist). She helped me with the exercises, left a CD to practice on my own. (Music therapist) sincerely wanted to help me, and I am very grateful to her.

Participant 6: Communication was pleasant. Everything else as well. I'm in my own right, the disease is in its own right. Might goes before right.

Participant 7: It was very pleasant to meet and communicate with (music therapist).

Question 3. How did it feel to participate in music therapy sessions?

Participant 1: It was very pleasant to work with (music therapist). There were some problems each time, for example I could not pronounce (rolled) R sound. I am able to pronounce lower (register) vowels, there are problems with others. Some exercises worked out, some not so, I can't roar.

Participant 2: Positive, pleasant, rewarding. I found motivation. Considering that it has become easier for me to speak and an opportunity emerged to express my thoughts, I now have desire and capacity to communicate with friends. Which has become a motivation for communication. And I can now help my former patients with advice, by answering their phone calls.

Participant 3: I liked everything. We found problems with vocal chords. I learned a lot of new and interesting things. I plan to continue practicing. Will set an appointment with a phoniatrist.

Participant 4: Practicing was pleasant and comfortable. I appreciate the help that therapy sessions brought in terms of breathing and speaking-and-singing skills. The sessions were well planned and organized. And were lead with great tact, understanding, pedagogic skills, did not bring any fatigue. Without patronizing. We worked with great pleasure. I endeavored to be attentive and experienced great pleasure from communication and satisfaction with the accomplishments.

Participant 5: It was good, comfortable, I liked it very much. I could not reach high notes. There were no other problems.

Participant 6: Communication was enjoyable. It was good to participate actively. I practice for an hour every day, under control of my wife. Sometimes it worsens. Altogether, it is the same now as it was before the (music therapy) sessions. If it has not worsened, it is a good thing already.

Participant 7: Overall, I enjoyed sessions with (music therapist). But at times it was difficult, because it did not go as I wanted.

Question 4. How was it to independently do the assigned music therapy exercises between the sessions?

Participant 1: You have to practice, that's all, work with pronunciation a lot. It was difficult to sustain notes, singing was most difficult. It has been very useful to exercise diaphragm, breathing. And I will continue to exercise. I have everything that I need for that, the set of exercises of a CD.

Participant 2: I practiced every day. If I was not feeling well, I shortened the exercise set. I was missing (music therapist). Very much. I practice every day and will continue to do so.

Participant 3: Practicing was fine. Everything on the CD is accessible, like with a teacher. I experienced no difficulties.

Participant 4: Performing exercises independently in between therapy sessions was made easy by the very detailed instructions which we used all the time. The set of exercises was recorded onto a CD, and we used it. I liked the CD most, and my wife read the (printed out) instructions, and so we worked together. The CD was very well thought through, in regards to timing as well. It has been easy to exercise with it, like with a teacher.

Participant 5: I practiced, it takes half an hour. I felt well. At first it did not turn out too well, but then I learned how to breathe abdominally. You have to get used to that. It helps you to exhale stronger.

Participant 6: I practiced every day, no issues. Of course, I will continue practicing.

Participant 7: I practiced. Sometimes it was difficult to perform (the exercises set in its) entirety. I divided (the set) into parts and practiced throughout the day. 30-40 minutes are not always available.

Question 5. Have these music therapy exercises affected your speech, breathing and swallowing?

Participant 1: It affected my speech. My doctor told me that my speech has become better, clearer, more comprehensive. My sister and my friend told me the same thing. I feel it myself. When I speak slower, my speech is normal.

Participant 2: Of course, the exercises affected these, positively.

Participant 3: It was quite alright even as we started. I learned to breath diaphragmatically, and to relax the muscles of tongue, face and larynx when they are tired.

Participant 4: I think they did. In my case the decline is slow, so it is hard to assess. I have become more attentive to voice vibration and articulation. I think it has become easier for my family and conversation partners to hear me, I have started to talk with more clarity. I feel that I have started articulating more thoughtfully. It is enjoyable and helpful.

Participant 5: I cannot say it became better. I think if I continue with the exercises that (music therapist) provided, it will not progress that rapidly.

Participant 6: No.

Participant 7: I do not think so, I do not feel it.

Question 6. Other comments.

Participant 1: No.

Participant 2: I would love to continue music therapy individually or in a group. When abdominal breathing was emphasized, I paid attention to the fact that I started to use abdominal muscles in everyday situations more often, which affected my chest breathing. I discussed this situation with (music therapist), and as a result started using mixed breathing.

Participant 3: The root of the tongue got tired. (Music therapist) commented that it was normal.

Participant 4: Music therapy for ALS is included into the whole system of medical and medico-psychological efforts of many charitable organizations that fight this nasty disease and improve quality of life for persons with this disease. The selfless efforts of all the people who help create special psychological climate for people with this disease, which is pleasing and aid us a lot. Communication with such people is very beneficial. One should wish that such people worked with other service organizations as well.

Participant 5: I am very grateful to (music therapist) for her appetence to help, for all help she provided. She even traveled to our summer house to continue the sessions. I hope these exercises help other ALS patients.

Participant 6: No comments. It is sad that (music therapist) went away. I feel that my speech is not always intelligible. It is not every time that my wife understands me.

Participant 7: The time period is too short (for music therapy) to have the effect. It would take about three months for the result to occur. I spoke with another (research participant) – (music therapy) helped her. I am happy. I will continue exercising on my own. Not sure that I will do that often, but I will practice.

Area of inquiry	Common themes	Quotations
Music therapy outcomes perceived by PALS	Most PALS reported they perceived music therapy to have a positive effect on their speech	• Participant 1 (“speech became somewhat better”, “When I speak slower, my speech is normal”) • Participant 2 (“speech has become more intelligible”, “it has become easier to speak. I have enough air to finish the phrase”) • Participant 4 (“I think it has become easier for my family and conversation partners to hear me, I have started to talk with more clarity. I feel that I have started articulating more thoughtfully”) • Participant 5 (“because of this everyday practice (the disease) does not progress that fast”) • Participant 6 (“Altogether, it is the same now as it was before the (music therapy) sessions. If it has not worsened, it is a good thing already”) • Participant 7 (“Everything would be the same without music therapy”)
	Most PALS reported they perceived music therapy to have no effect on their swallowing	• Participant 1 (“swallowing, it is normal”) • Participant 2 (“my swallowing is unimpaired”) • Participant 3 (“I do not notice other changes”) • Participant 6 (“No”) • Participant 7 (“No changes”)
	Most PALS reported they perceived music therapy to have a positive effect on their respiration	• Participant 1 (“breathing – yes, /became better/”) • Participant 2 (“it has become easier to breathe as well”) • Participant 3 (“nose breathing has become better”) • Participant 4 (“I think the two months of practice influenced my attention to diaphragmatic breathing… Specific diaphragm training is very useful when one has this disease”) • Participant 5 (“because of this everyday practice (the disease) does not progress that fast”)

	Some PALS reported they perceived music therapy to increase their opportunities for communication	• Participant 1 (”My doctor told me that my speech has become better, clearer, more comprehensive. My sister and my friend told me the same thing. I feel it myself”) • Participant 2 (“communication with (music therapist), in the first place (has been beneficial)”, “the ability to communicate again with the others stabilized my overall condition”, “Considering that it has become easier for me to speak and an opportunity emerged to express my thoughts, I now have desire and capacity to communicate with friends. Which has become a motivation for communication. And I can now help my former patients with advice, by answering their phone calls”) • Participant 6 (“Communication was enjoyable”)
	Most PALS reported they perceived music therapy to help them learn new vocal and breathing skills	• Participant 2 (“Music therapist) taught me to use diaphragm and abdomen muscles for talking”) • Participant 3 (“I learned a lot of new and interesting things”, “I learned to breath diaphragmatically, and to relax the muscles of tongue, face and larynx when they are tired”, “I started to pay attention to myself, learned that it is better to talk softly and in a relaxed manner”) • Participant 4 (“I appreciate the help that therapy sessions brought in terms of breathing and speaking-and-singing skills”, “I familiarized myself with elements of voice training. It is useful for more accurate command of vocal cords”) • Participant 5 (”At first it did not turn out too well, but then I learned how to breathe abdominally. You have to get used to that“)
Music therapy process, as perceived by PALS	Most PALS reported being moderately challenged by music therapy exercises	• Participant 1 (“There were some problems each time, for example I could not pronounce (rolled) R sound. I am able to pronounce lower (register) vowels, there are problems with others. Some exercises worked out, some not so,

		I can’t roar”, “It was difficult to sustain notes, singing was most difficult”) • Participant 3 (“The root of the tongue got tired”) • Participant 5 (“I could not reach high notes”, ”At first it did not turn out too well, but then I learned how to breathe abdominally. You have to get used to that“) • Participant 7 (“at times it was difficult, because it did not go as I wanted”)
	All PALS reported music therapy to be a pleasurable experience	• Participant 1 (“simply pleasant therapy”, “it was very pleasant to work with the music therapist”) • Participant 2 (“Positive, pleasant, rewarding”) • Participant 3 (“I liked everything”) • Participant 4 (“Practicing was pleasant and comfortable”, “We worked with great pleasure”, “I <…> experienced great pleasure from communication and satisfaction with the accomplishments”) • Participant 5 (“It was very pleasant to practice with (music therapist)”, “It was good, comfortable, I liked it very much”) • Participant 6 (“Communication was pleasant. Everything else as well”) • Participant 7 (“It was very pleasant to meet and communicate with (music therapist)”, “Overall, I enjoyed sessions with (music therapist)”)
	Most PALS reported music therapy independent exercises routine was easy to perform	• Participant 1 (“You have to practice, that’s all <…> I have everything that I need for that, the set of exercises on a CD”) • Participant 2 (“it was easy to incorporate (music therapy) into my everyday routine”, “I practiced every day. If I was not feeling well, I shortened the exercise set”) • Participant 3 (“Practicing was fine. Everything on the CD is accessible, like with a teacher. I experienced no difficulties”) • Participant 4 (“Performing exercises independently in between therapy sessions was made easy by the

		very detailed instructions which we used all the time. <…> It has been easy to exercise with (the CD), like with a teacher”). • Participant 5 (“I practiced, it takes half an hour. I felt well”) • Participant 6 (“I practice for an hour every day, under control of my wife”) • Participant 7 (“Sometimes it was difficult to perform (the exercises set in its) entirety. I divided (the set) into parts and practiced throughout the day”)
	Most PALS reported being motivated to continue performing independent music therapy exercises after the treatment ends	• Participant 1 (“I will continue to exercise”) • Participant 2 (“I found motivation”, “I would love to continue music therapy individually or in a group”) • Participant 3 (“I plan to continue practicing. Will set an appointment with a phoniatrist”) • Participant 5 (“I think if I continue with the exercises that (music therapist) provided, it will not progress that rapidly”) • Participant 6 (“Of course, I will continue practicing”) • Participant 7 (“I will continue exercising on my own. Not sure that I will do that often, but I will practice”)

Appendix U. Interviews with research participants – caregivers of persons with ALS, conducted prior to treatment (week 5) (English translation and thematic analysis)

Question 1. How, you think, may music therapy affect speech, breathing and swallowing of X (person with ALS)?

Participant 1: Muscles stretch and work, any exercise is beneficial. She needs to exercise to help the nerve-endings develop.

Participant 2: I do not know about swallowing, as for speech and breathing – as an exercise, positively.

Participant 3: N/A

Participant 4: I think it ought to have a positive effect. Currently there are sometimes problems: he speaks too softly. I wish he could speak more clearly. Breathing and swallowing will be freer.

Participant 5: I do not know. No one in the world knows how to treat this disease, the government does not provide the money.

Participant 6: I hope that positively. It is like physical therapy. Muscles will be involved and the exercises will affect their strengthening.

Participant 7: I don't really know. Perhaps as an exercise.

Question 2. How, you think, may music therapy affect X (person with ALS) otherwise?

Participant 1: Emotional energy, positivity, mood. Mom is positive, giggler, she has no problems with humor.

Participant 2: Not a very easy question. Psychological aspect. Communication provides a positive outlook.

Participant 3: N/A

Participant 4: For some time, he will be in touch with music pieces. It is important for him, he lives and breathes music since childhood.

Participant 5: I do not know. Possibly, there will be benefit from (the patient) singing together with the children. It is always important. The children do everything together. That is psychology.

Participant 6: It will extend the period when he is able to communicate normally. Everything he does now, he does only with me. And the situation is not an easy one now, he is finishing an important work, and I am helping. I also have mother who needs help. I do not know what the reaction will be, my emotions are confused.

Participant 7: Joy of communication. It is important for her to be useful for the others.

Question 3. How, you think, X's engagement in music therapy may affect you as a primary caregiver?

Participant 1: My interest may affect her being interested, she will have stronger stimulus to practice. Then there will be energy and possibilities for a result. I will calm down a little bit, will receive emotional support.

Participant 2: When the person who has the disease feels better, depression goes away, and I feel more joyful. Goals emerge. It does not affect me immediately, but the indirect effect is important.

Participant 3: N/A

Participant 4: I am very pleased. I love music, too. In our family it is a thing to live with music, to watch it on TV, our daughters are professional musicians. We always had a good record library. Psychologically, we have decided, that (music therapy) would be very useful as a music practice, and as a stimulus.

Participant 5: Everything that the children do together always has a positive result. It is communication.

Participant 6: There will be a positive influence, because this is something new. I look forward to it. In any case, this will be interesting. It is better to do something than not to do. Everything possible needs to be done.

Participant 7: In no way.

Area of inquiry	Common themes	Quotations
Music therapy outcomes anticipated by caregivers of participants with ALS	Most caregivers suggested that music therapy may have a beneficial effect as an exercise to improve bulbar functions of participants with ALS.	• Caregiver of participant 1: “Muscle stretch and work. And exercise is beneficial” • Caregiver of participant 2: “As an exercise, positively” • Caregiver of participant 4: “I think it ought to have a positive effect. <…> Breathing and swallowing will be freer” • Caregiver of participant 6: “I hope that positively. <…> Muscles will be involved and the exercises will affect their strengthening” • Caregiver of participant 7: “As an exercise”
	Most caregivers suggested that music therapy may have a positive effect on the psychological state of participants with ALS.	• Caregiver of participant 1: “Emotional energy, positivity, mood” • Caregiver of participant 2: “Communication provides a positive outlook” • Caregiver of participant 5: “Possibly, there will be benefit from (the participant) singing together with the children. <…> That is psychology” • Caregiver of participant 7: “Joy of communication”
	Most caregivers suggested that participation of their family member affected by ALS in music therapy may have a positive effect on their own psychological state.	• Caregiver of participant 1: “I will calm down a little bit, will receive emotional support” • Caregiver of participant 2: “When the person who has the disease feels better, depression goes

		away, and I feel more joyful” • Caregiver of participant 4: “Psychologically, we have decided, that (music therapy) would be very useful <…> as a stimulus” • Caregiver of participant 6: “There will be a positive influence, because this is something new. I look forward to it”

Appendix V. Interviews with research participants – caregivers of persons with ALS, conducted at the end of the follow-up period (week 16) (English translation and thematic analysis)

Question 1. Has music therapy affected X's (person with ALS) speech, breathing and swallowing?

Participant 1: I cannot say for sure. (These functions have) not worsened, and there is some improvement – yes, rather than no.

Participant 2: Speech, yes, it is obvious and one can hear that. Swallowing is not impaired. Breathing can be assessed subjectively.

Participant 3: N/A

Participant 4: (Speech language specialist from the lab) will have better information about swallowing. After each session a fine sensation of lightness was obvious. But we did not practice (the independent exercises) quite regularly. Learning diaphragmatic breathing was helpful. Speech became clearer by the end of each session.

Participant 5: No, I think it had not affected anything.

Participant 6: I cannot unequivocally say that it had a very positive effect. However, I am very grateful. I hope that further exercises with the CD will help us. It is important that there was no regress.

Participant 7: I do not know, maybe.

Question 2. Has music therapy affected X (person with ALS) otherwise?

Participant 1: I think no. Our relationship is normal, behavior is stable, everything is fine, positive. She is happy, she liked it. If the mood was pessimistic, it is likely it would improve, but now it is all right, she is happy with life. They sang, she told me.

Participant 2: I remember responding that I expected (music therapy having an) indirect effect (on breathing, speech, swallowing), mediated by mental impact. Likely, this is how (music therapy) had positive impact. (My wife) anticipated (music therapy) sessions every time.

Participant 3: N/A

Participant 4: Overall, (music therapy) was very pleasant. Communication with (music therapist) brought joy. She is a very tranquil, serene person. Every lesson was like a holiday with new positive experiences.

Participant 5: No effect, the person feel worse and worse. She cannot walk already. And in December she could still took our son to afterschool. Nothing can stop the disease.

Participant 6: Communication, something new. (Participant) is a very optimistic person, loves people and communication is very important for him. So, the (music therapy) session affected him positively. At any rate, the sessions had positive effect.

Participant 7: No.

Question 3. Has X's (person with ALS) engagement in music therapy affected you as a primary caregiver?

Participant 1: It would not affect me, I am healthy. We now do everything for her. This work is not without the results, I am sure it brings benefits.

Participant 2: She feels better, and I feel relieved.

Participant 3: N/A

Participant 4: I liked (the sessions) very much, too. It was sheer positive emotions. (Music therapist) not only offered exercises, but we also sang songs. That affected me in a positive way.

Participant 5: Not in any way.

Participant 6: Yes, of course. I love communication. It is important to learn something new. It became a revelation that there is such field (music therapy), that people work there, altruists, trying to do something in such a hopeless situation. All this affected me very much.

Participant 7: No.

Question 4. Other comments.

Participant 1: If the sessions would continue, it would be great if we could participate. Music exercises have the effect, I am sure, they help. (Music therapist) is a clever person, way to go! I am grateful to everyone who participates in this work, who helps. I wish you all the best, let this work be appreciated.

Participant 2: I wish (music therapist) could come back.

Participant 3: N/A

Participant 4: (Music therapist) has become almost a family member. We will be waiting for her to visit us some day. It is wonderful, when there is not simply a distraction, but a distraction accompanied by a hope to change the situation for better.

Participant 5: The disease is frightful and no one knows how to deal with it.

Participant 6: I am very grateful to ALS Centre Moscow that we were included into this program. We use everything we can. I am ready to everything to slow down the disease. Meeting (music therapist) and other people who support and do not leave us is important in itself.

Participant 7: No.

Area of inquiry	Common themes	Quotations
Music therapy outcomes perceived by caregivers of participants with ALS	Most caregivers stated that music therapy improved or sustained bulbar functions of the participant with ALS.	• Caregiver of participant 1: “(These functions have) not worsened, and there is some improvement – yes, rather than no” • Caregiver of participant 2: “Speech, yes, it is obvious and one can hear that” • Caregiver of participant 4: “Learning diaphragmatic breathing was helpful. Speech became clearer by the end of each session” • Caregiver of participant 6: “It is important that there was no regress”
	Some caregivers stated that music therapy had a positive effect on the psychological state of the participant with ALS.	• Caregiver of participant 2: “…mental impact. Likely, this is how (music therapy) had a positive impact. (My wife) anticipated (music therapy) sessions every time” • Caregiver of participant 4: “Communication with (music therapist) brought joy. <…> Every lesson was like a holiday with new positive experiences” • Caregiver of participant 6: “Communication is very important for him. So, the (music therapy) session affected him positively”
	Some caregivers suggested that participation of their family member affected by ALS in music therapy had a positive effect on their own psychological state.	• Caregiver of participant 2: “She feels better, and I feel relieved” • Caregiver of participant 4: “It was sheer positive emotions. <…> That affected me in a positive way”

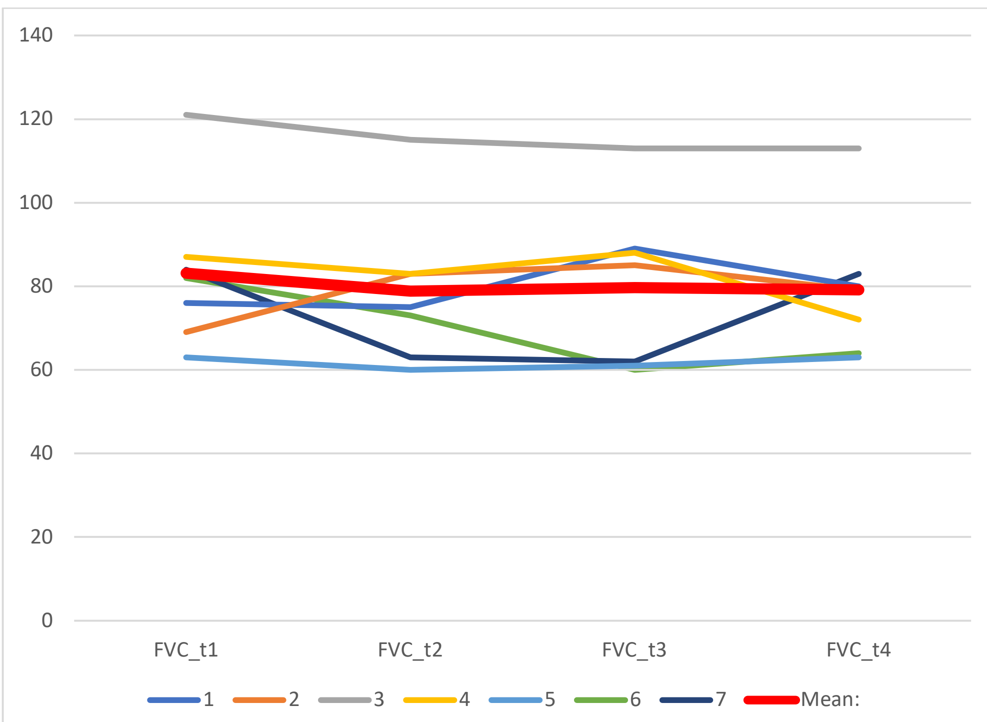
		• Caregiver of participant 4: "I love communication. It is important to learn something new. <…> All this affected me very much"

Appendix W. Individual and mean long-term changes for biomedical measurement outcomes over all available assessment time points

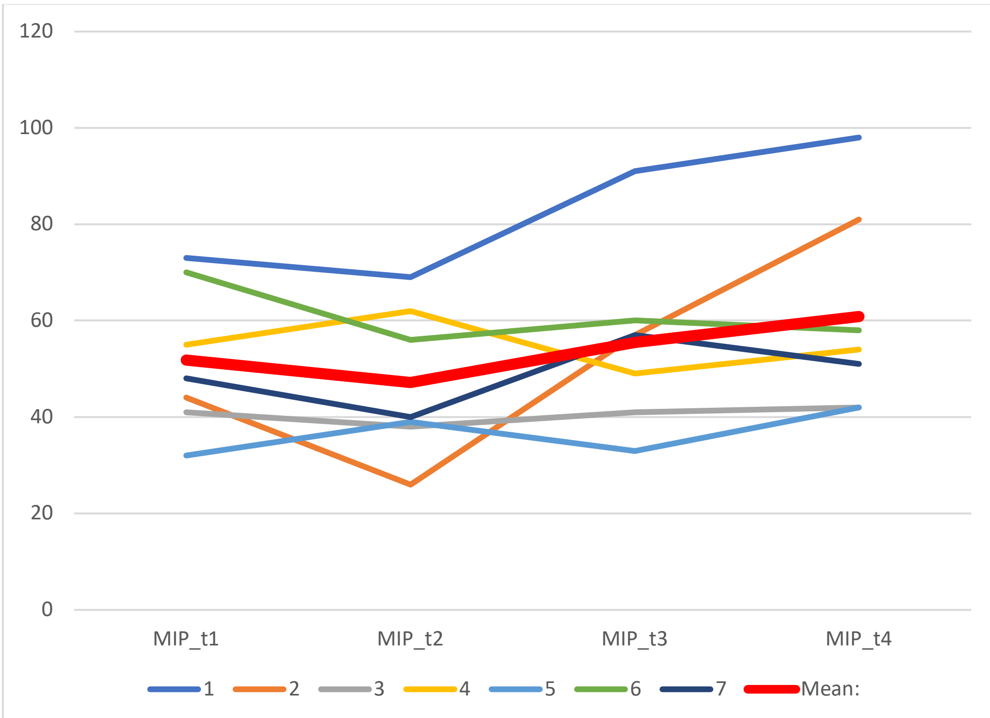
The following line graphs visualize changes of biomedical measurement outcomes over time for each participant (signified by lines of various colours), as well as the mean (signified by thick red line).

Respiration outcome measures:

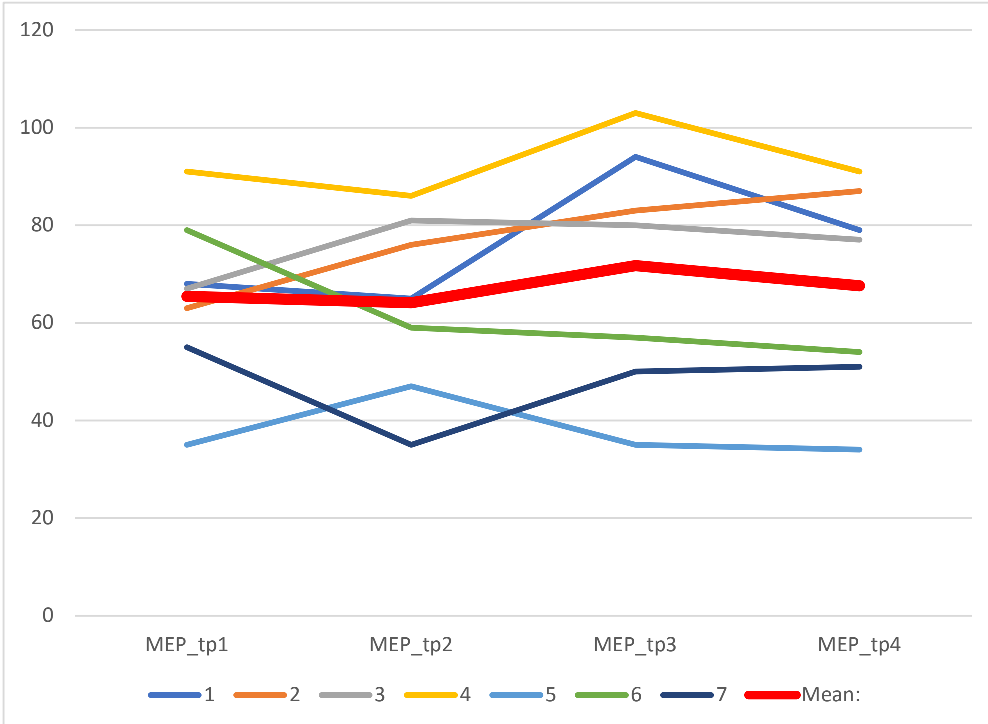
FVC (%) line graph for the pattern of change for all participants over four assessment time points. Higher score corresponds to better functioning.



MIP (cm H_2O) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.

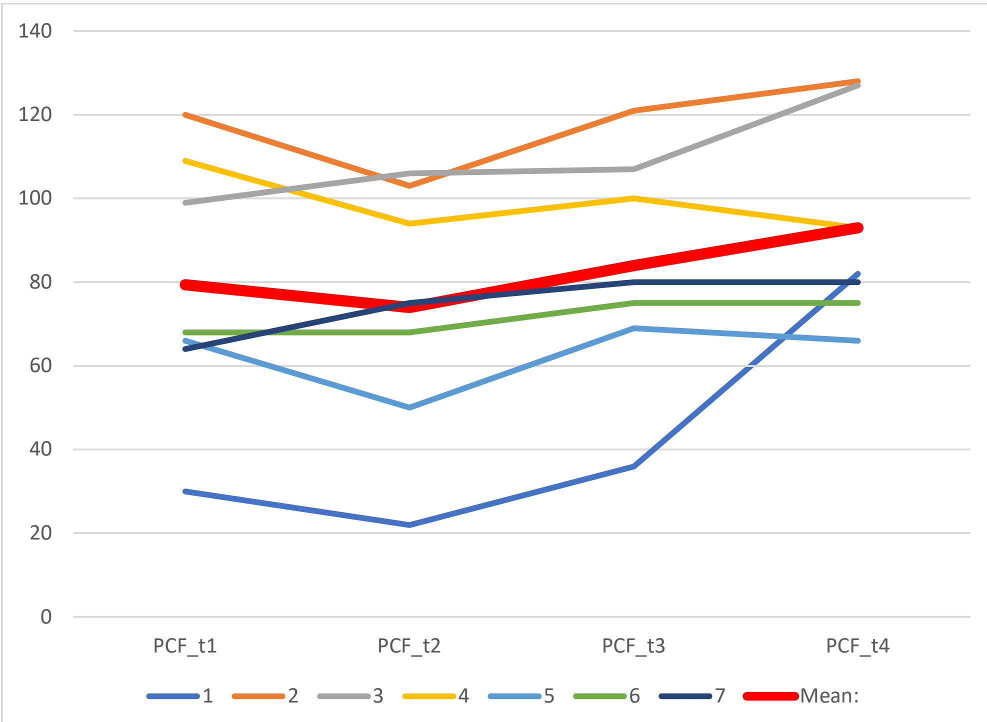


MEP (cm H_2O) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



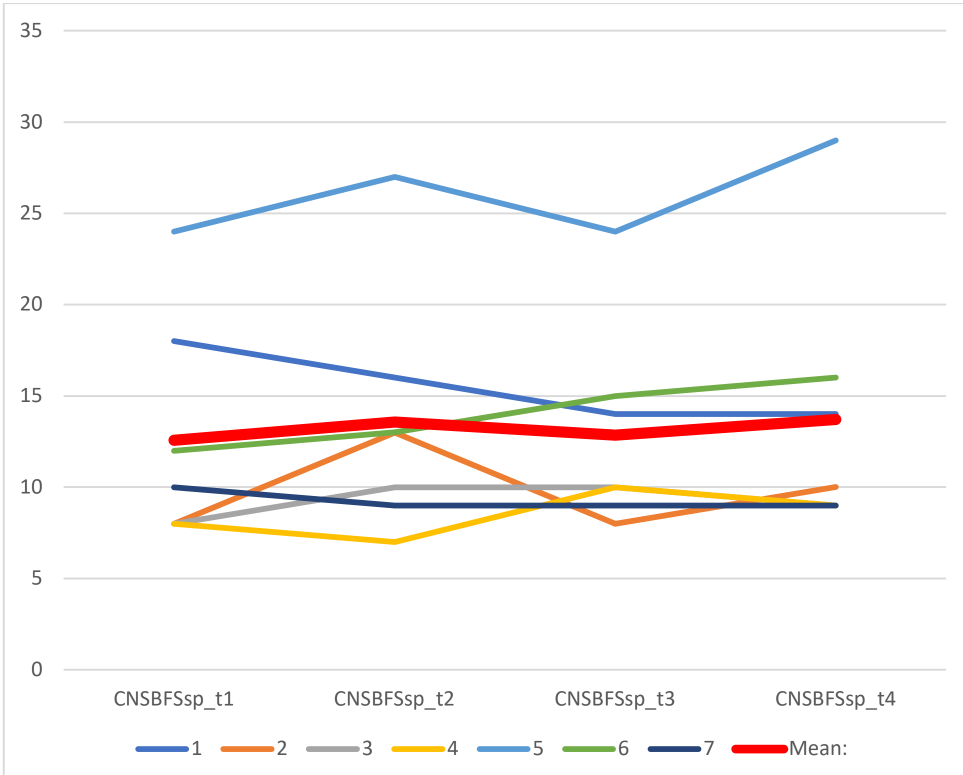
Cough outcome measure:

PEF (%) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.

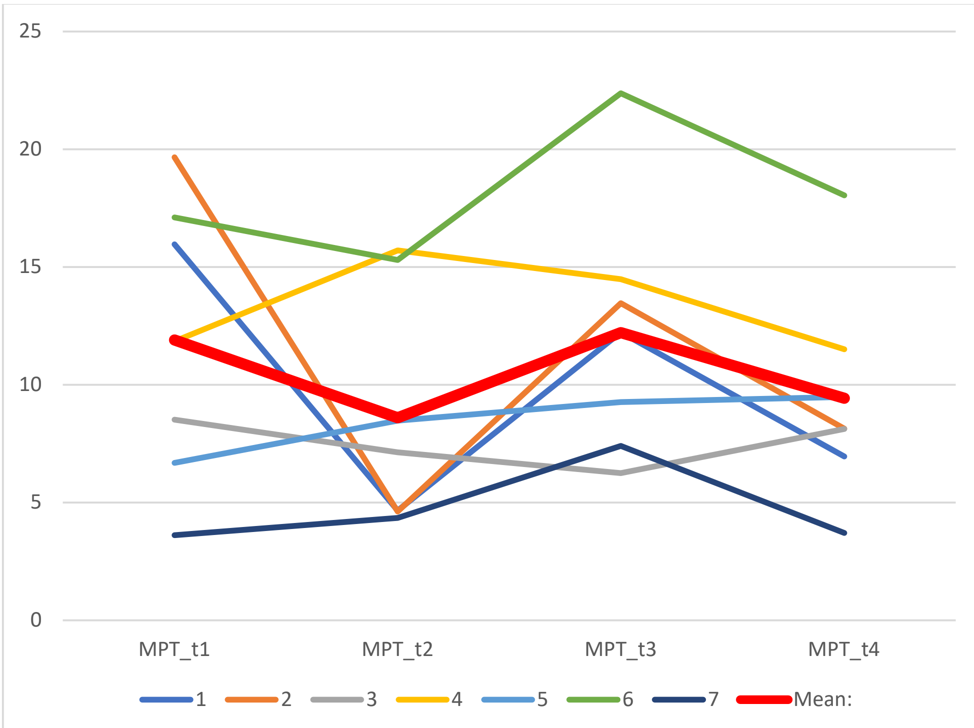


Speech outcome measures:

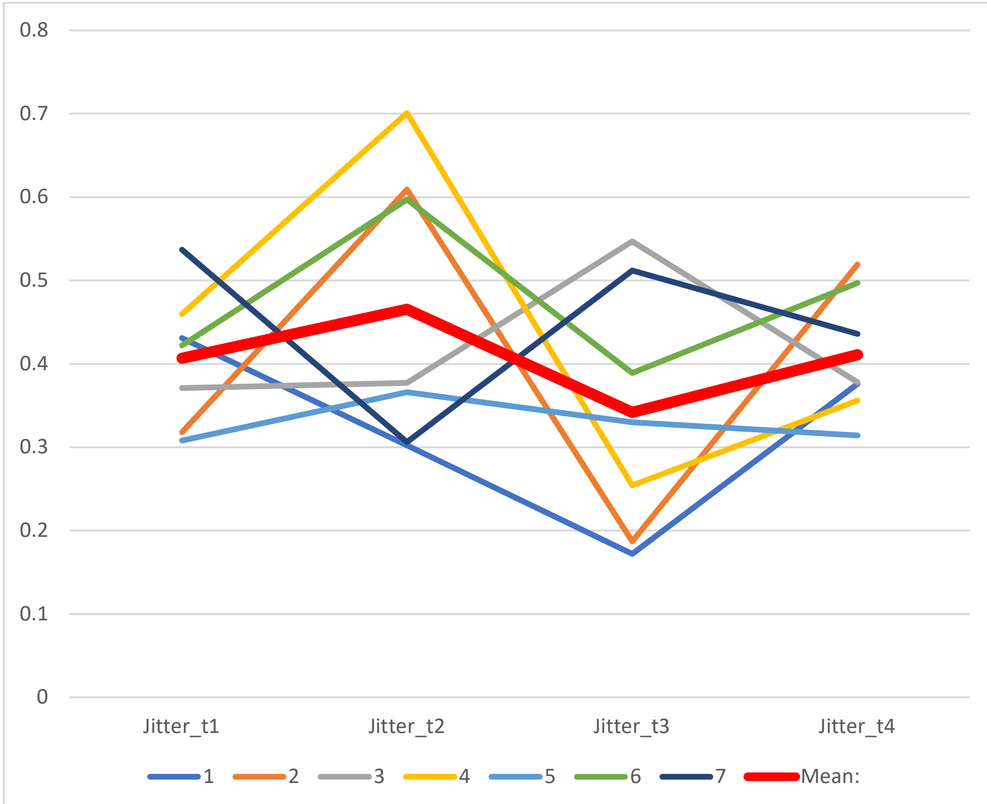
CNS-BFS speech subscore (points) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.



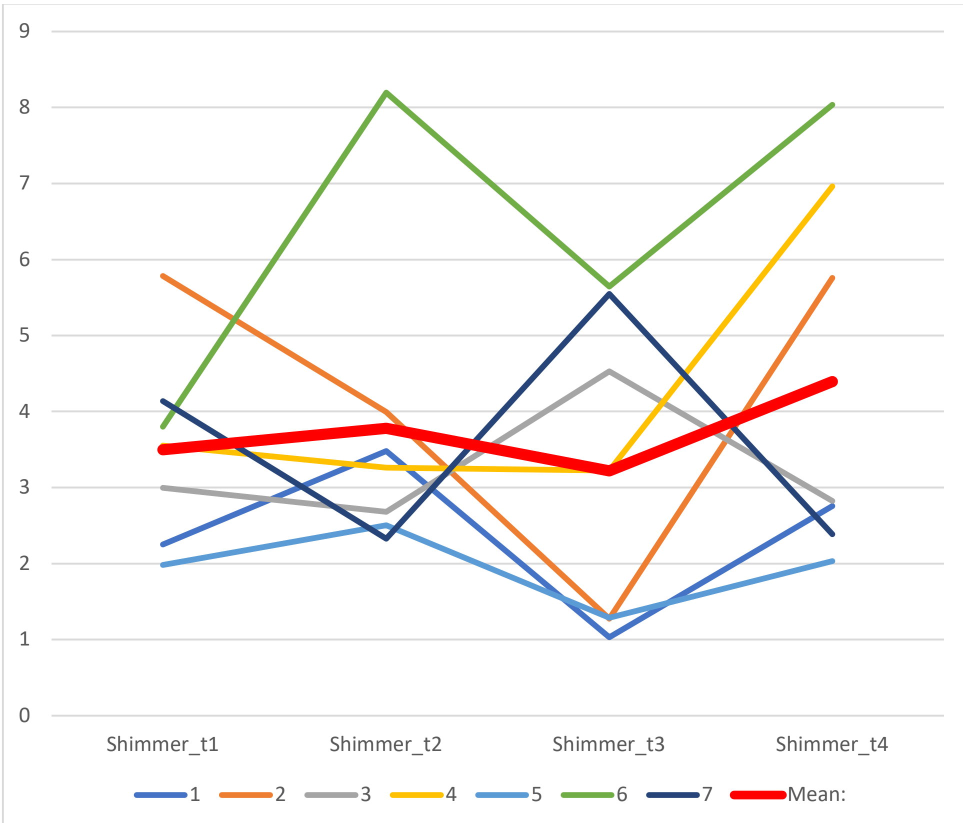
MPT (seconds) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



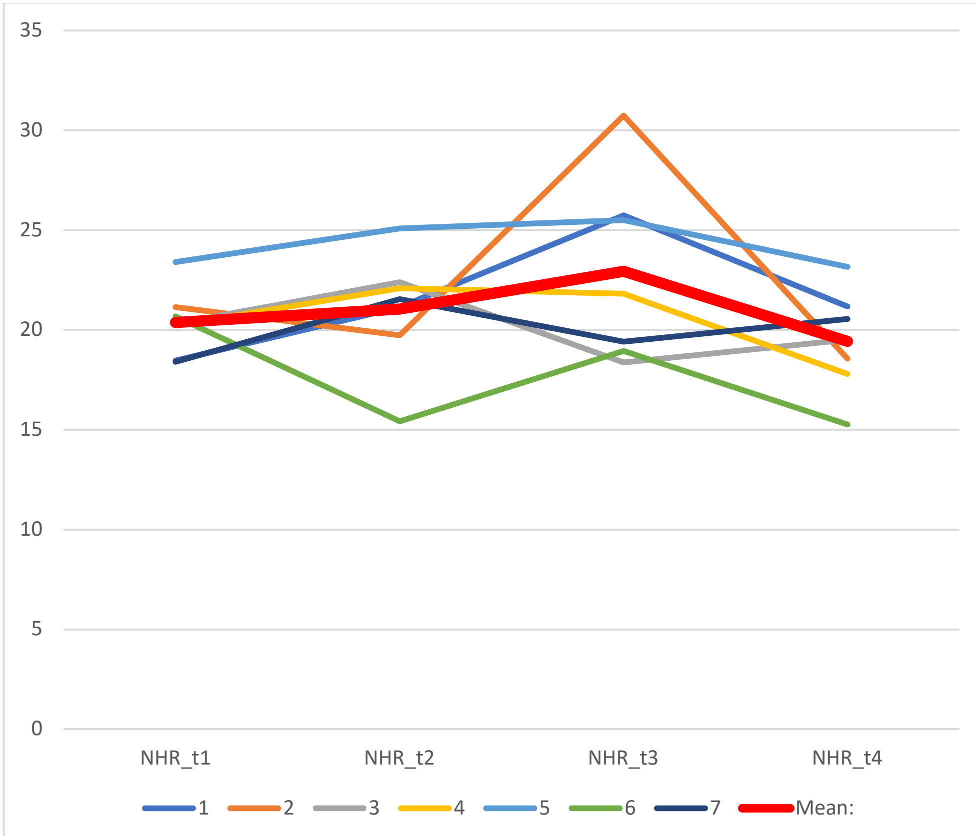
Jitter (local, %) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.



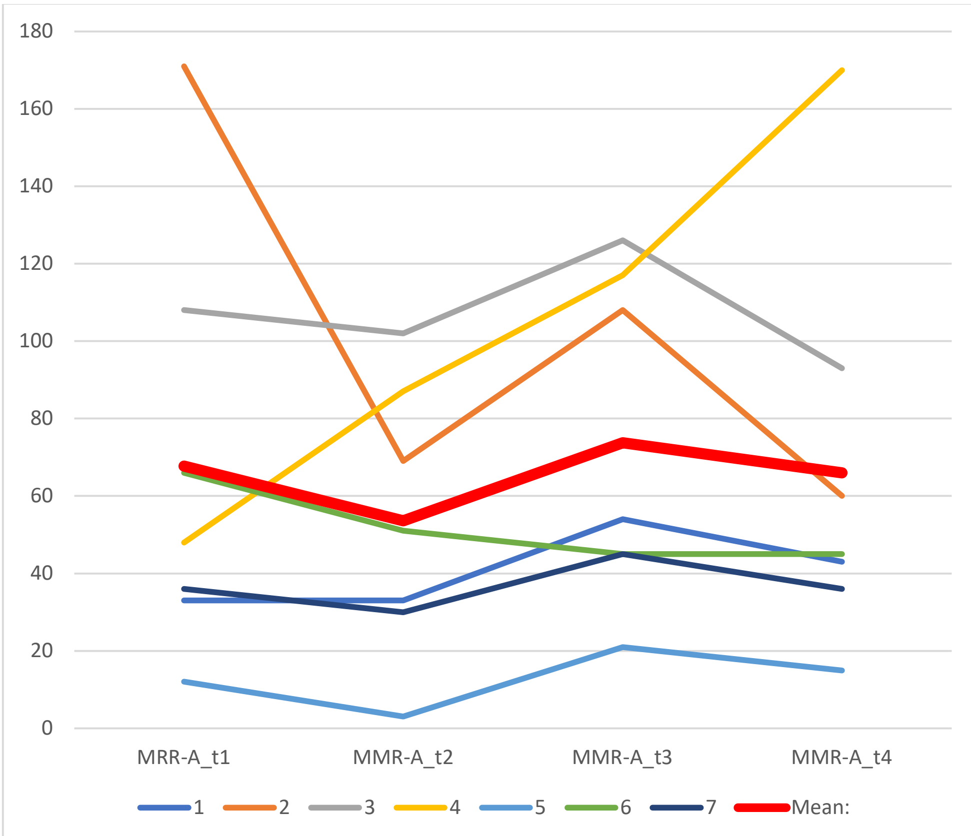
Shimmer (local, %) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.



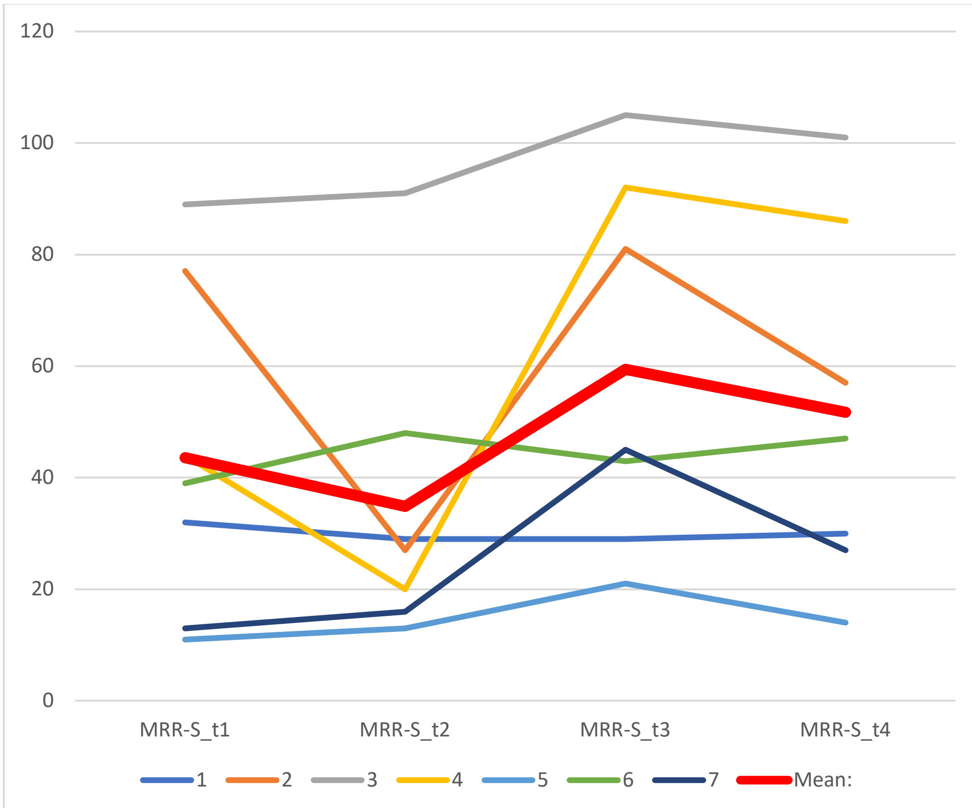
HNR (Db) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



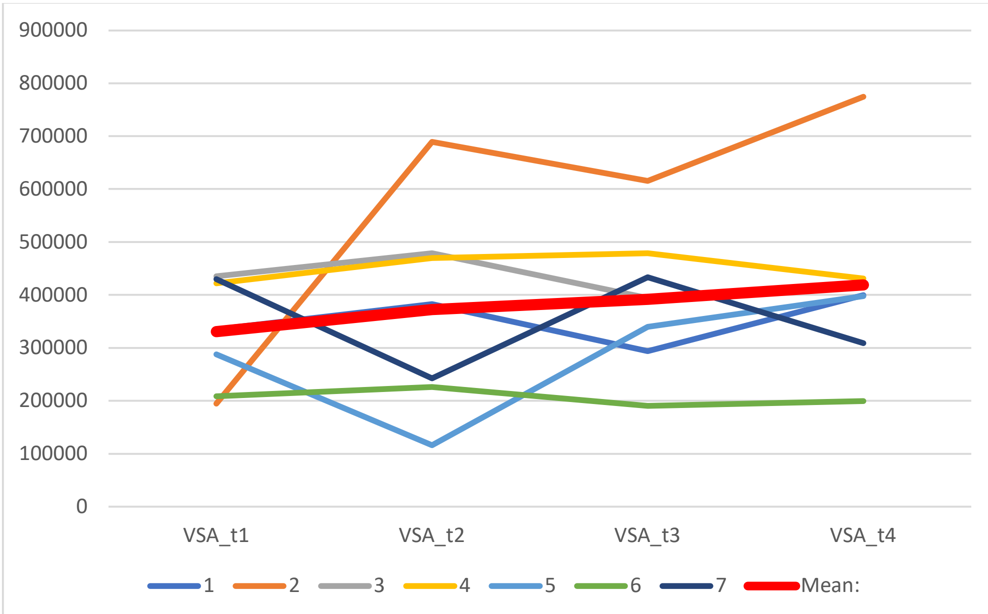
MRR-A (syllables, total) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



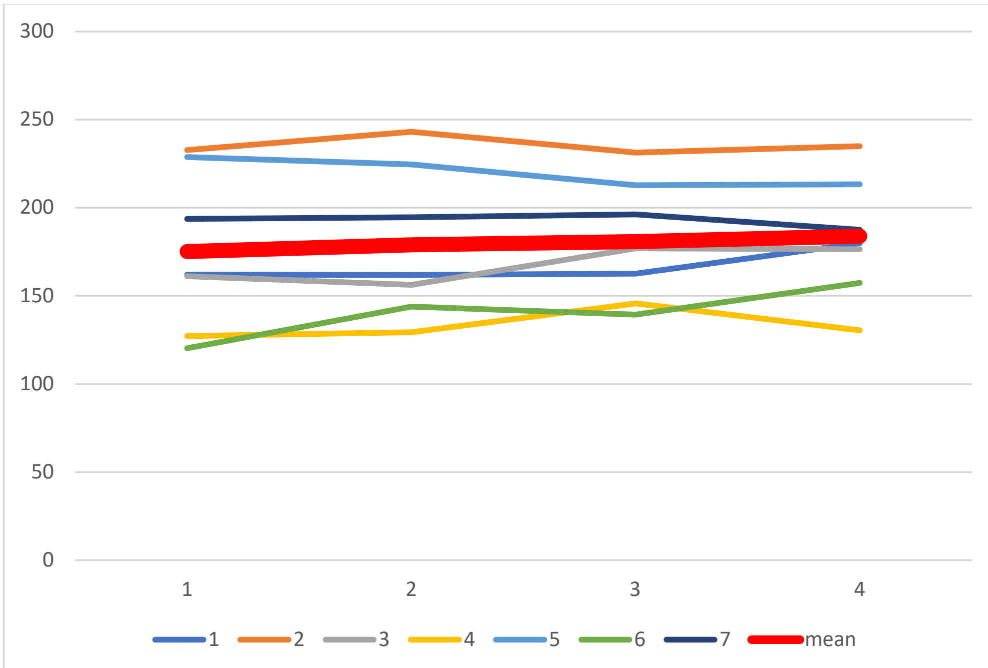
MRR-S (syllables, total) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



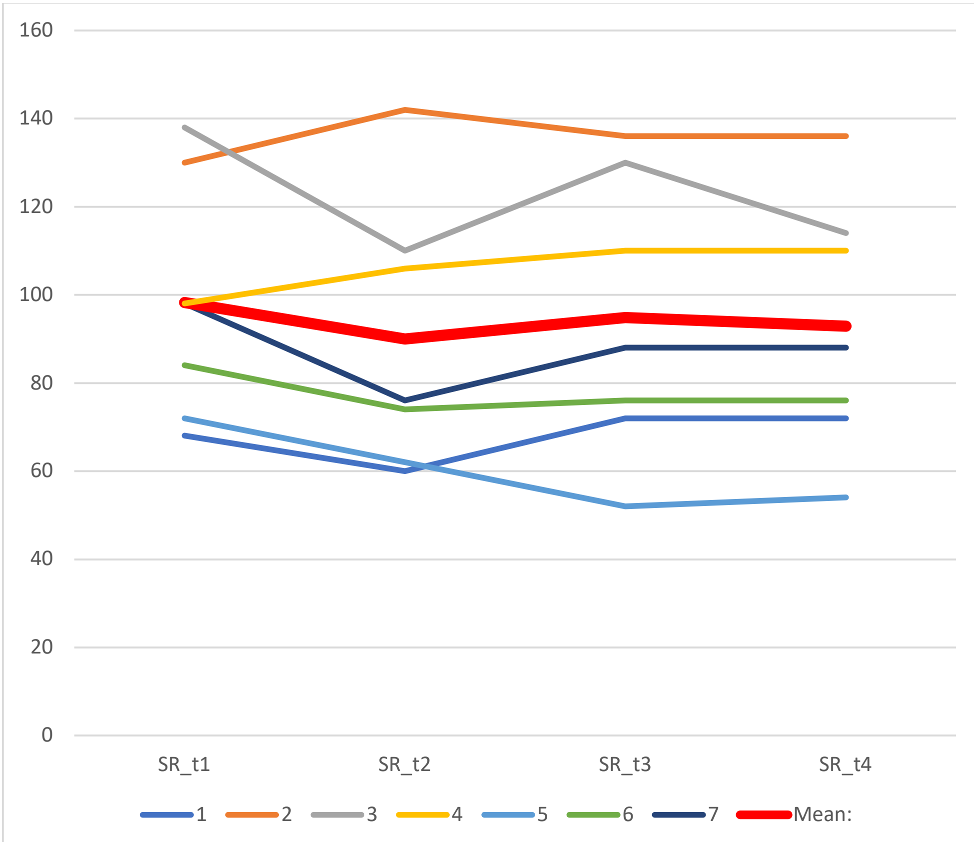
VSA (Hertz, squared) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



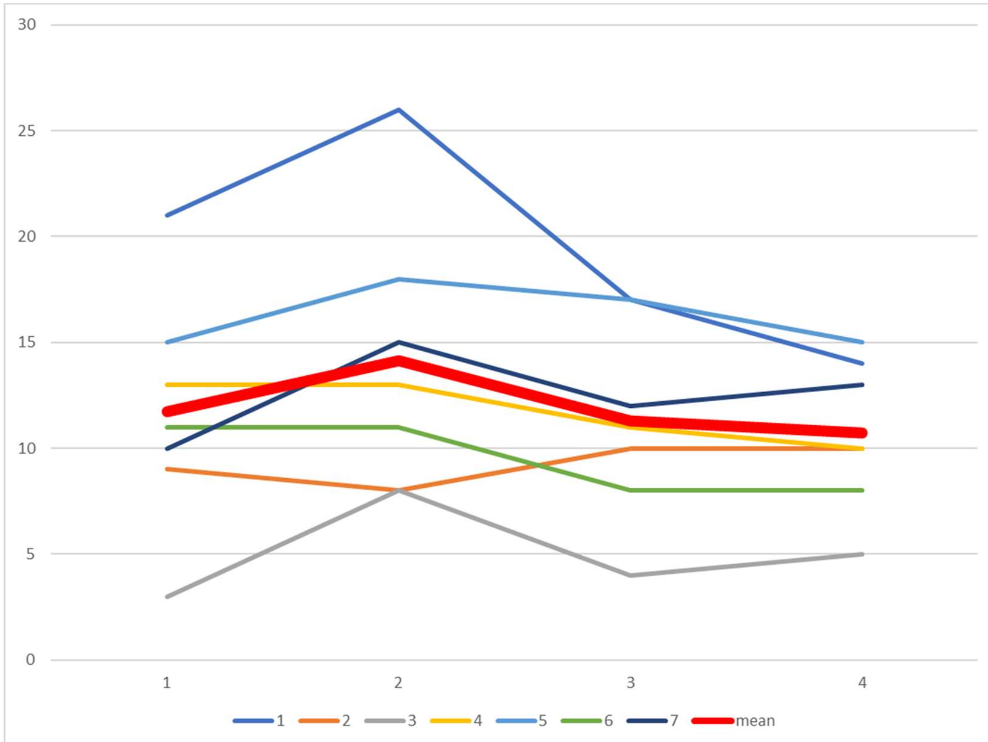
Fundamental frequency (Hz) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



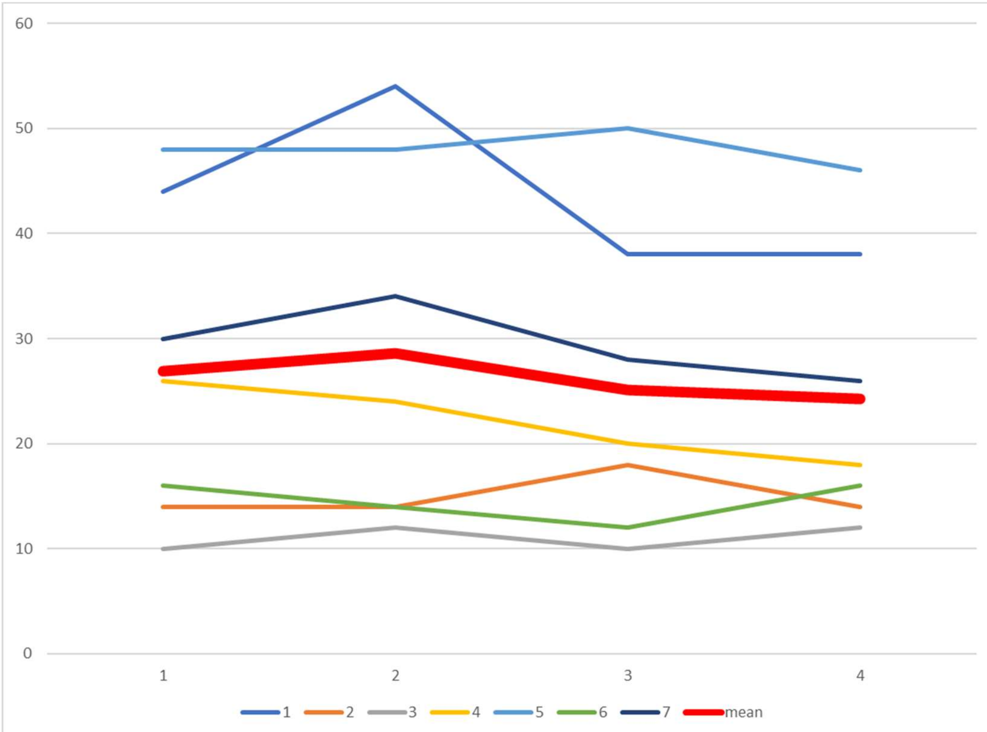
Speaking rate (words per minute) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.



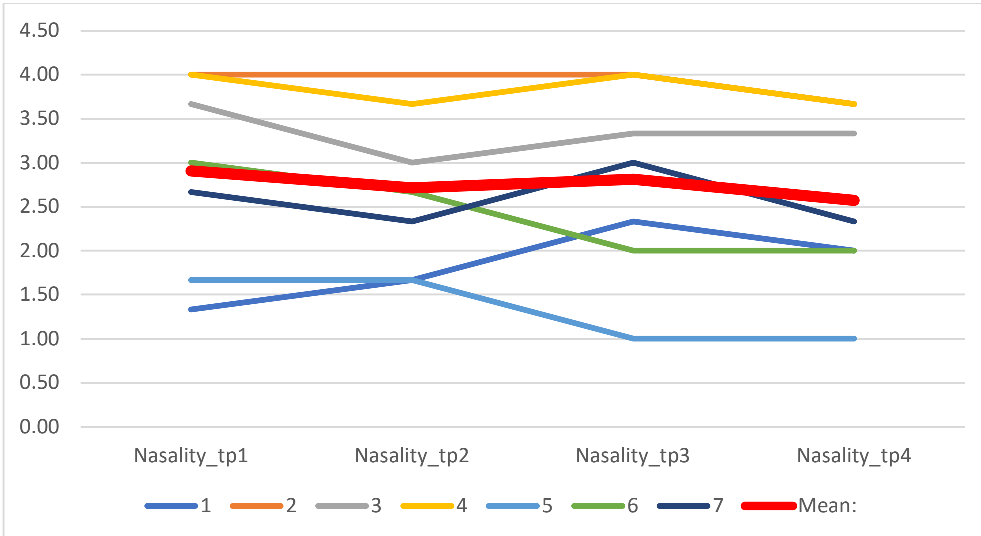
Speech-pause ratio (seconds per minute) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.



Pause frequency (total, per minute) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.

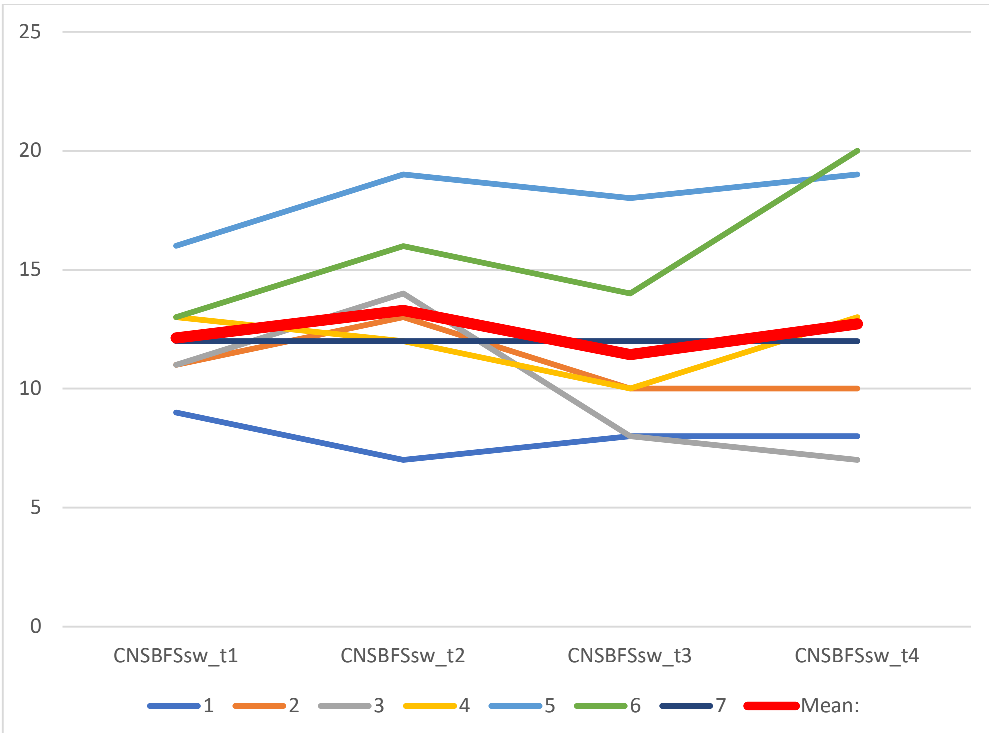


Hypernasality level (points) line graph for the pattern of change over four assessment time points. Higher score corresponds to better functioning.

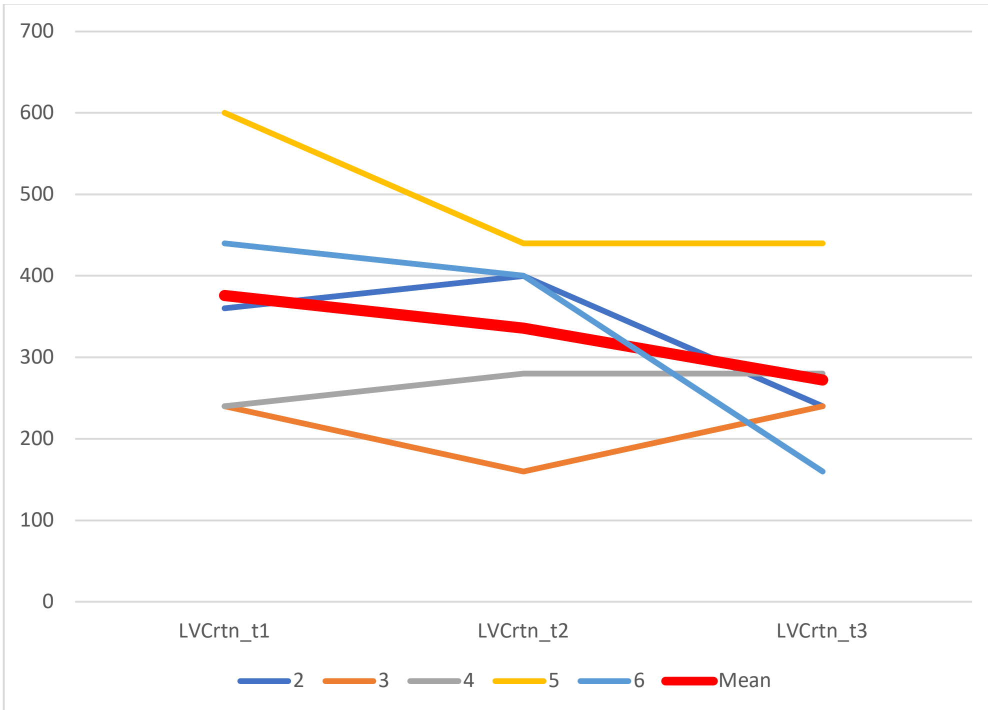


Swallowing outcome measures:

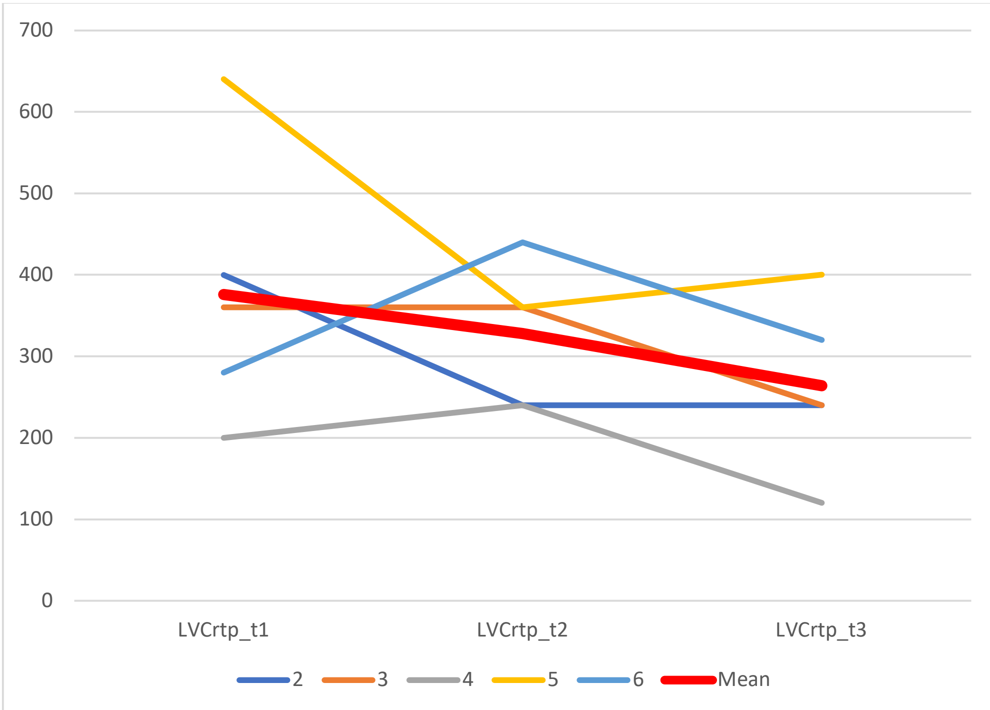
CNS-BFS swallowing subscore (points) line graph for the pattern of change over four assessment time points. Lower score corresponds to better functioning.



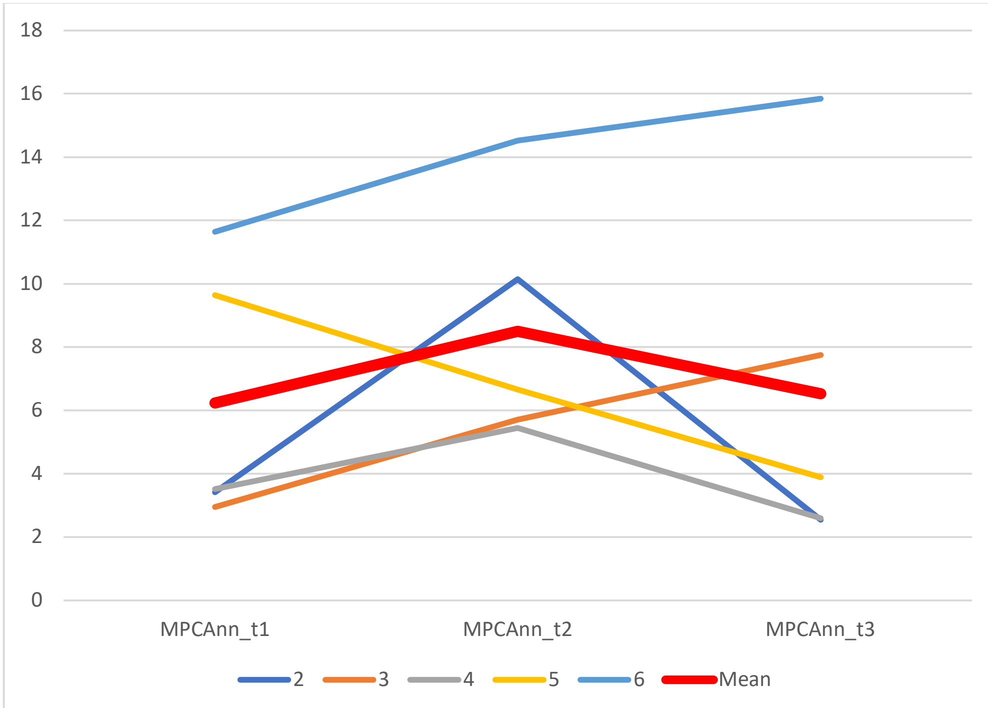
LVCrt, nectar 10 mL (ms) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



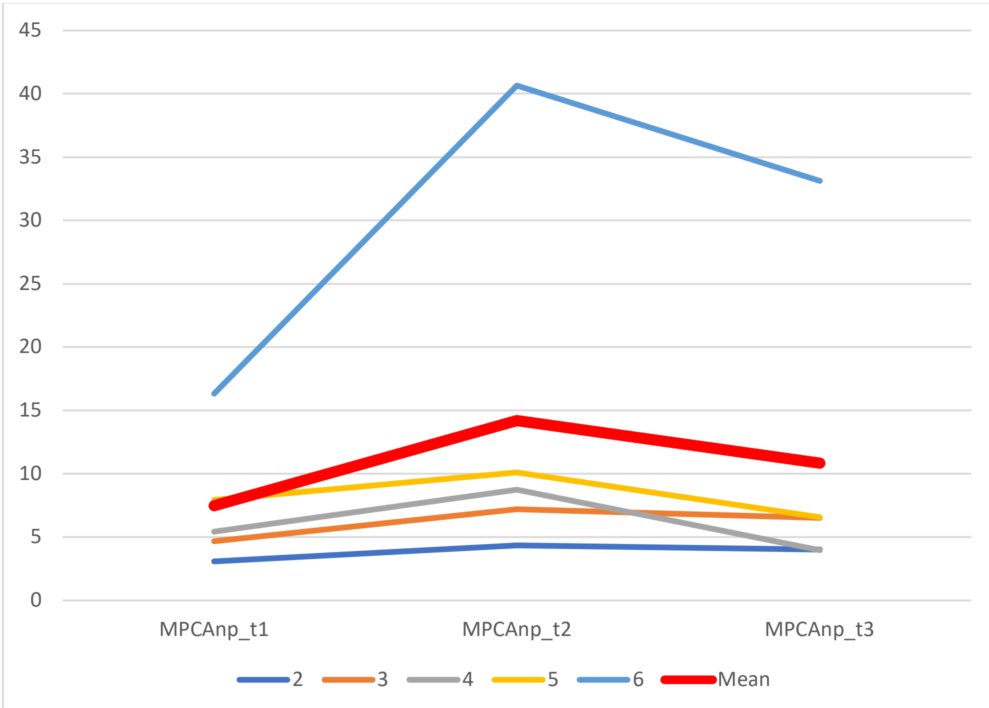
LVCrt, pudding 10 mL (ms) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



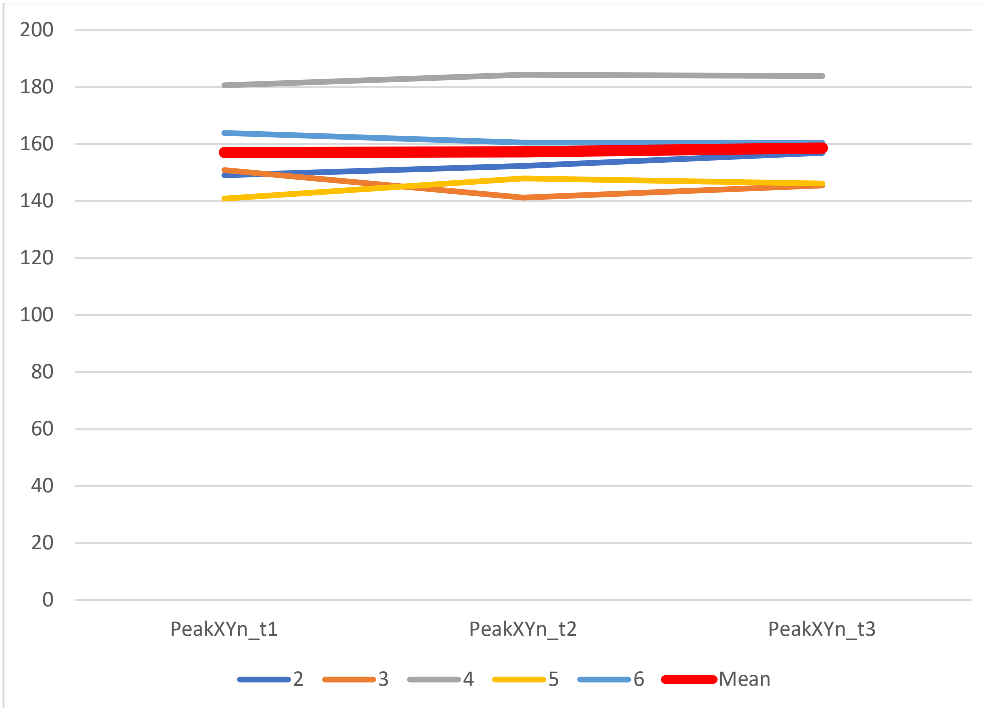
MPCAn, nectar 10 mL (% C2-4^2) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



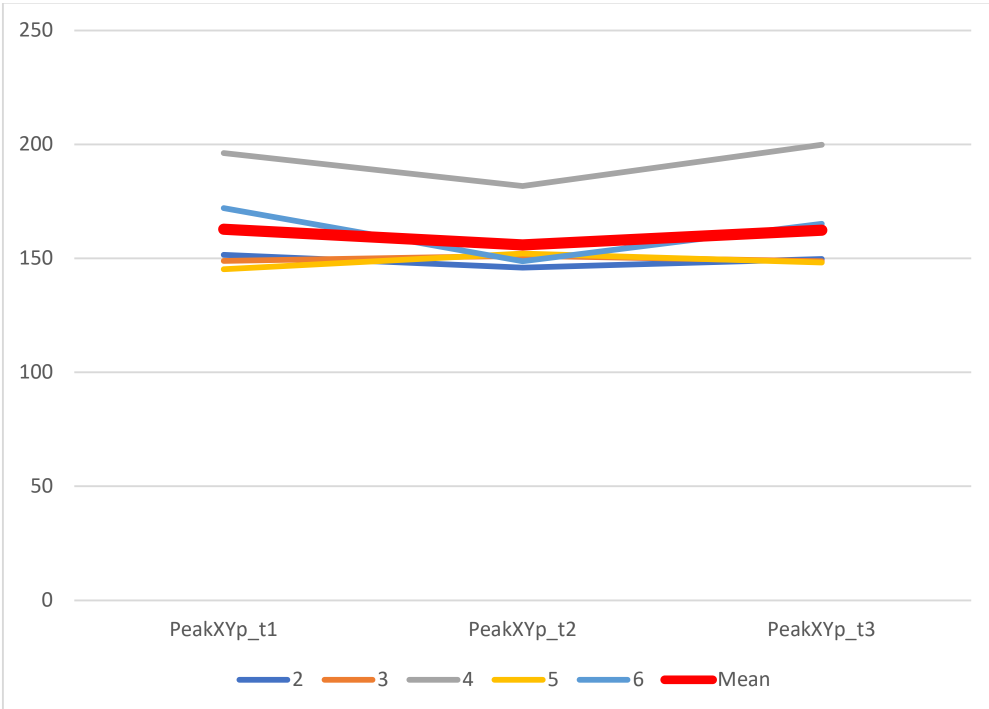
MPCAn, pudding 10 mL (% C2-4^2) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



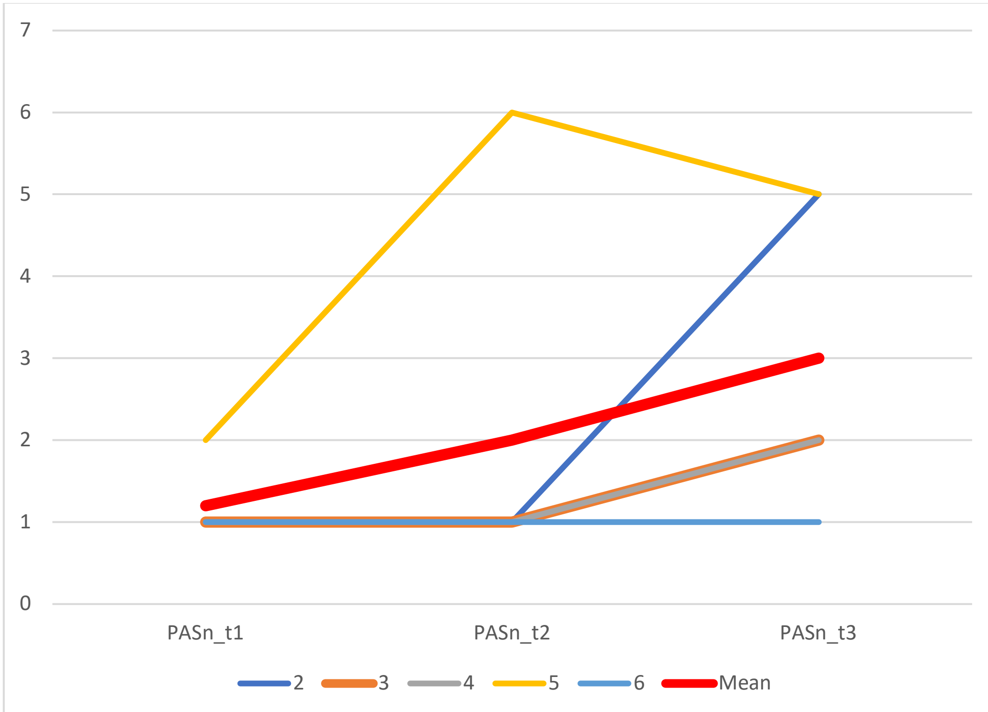
PeakXY, nectar 10 mL (% C2-4) line graph for the pattern of change over three assessment time points. Higher score corresponds to better functioning.



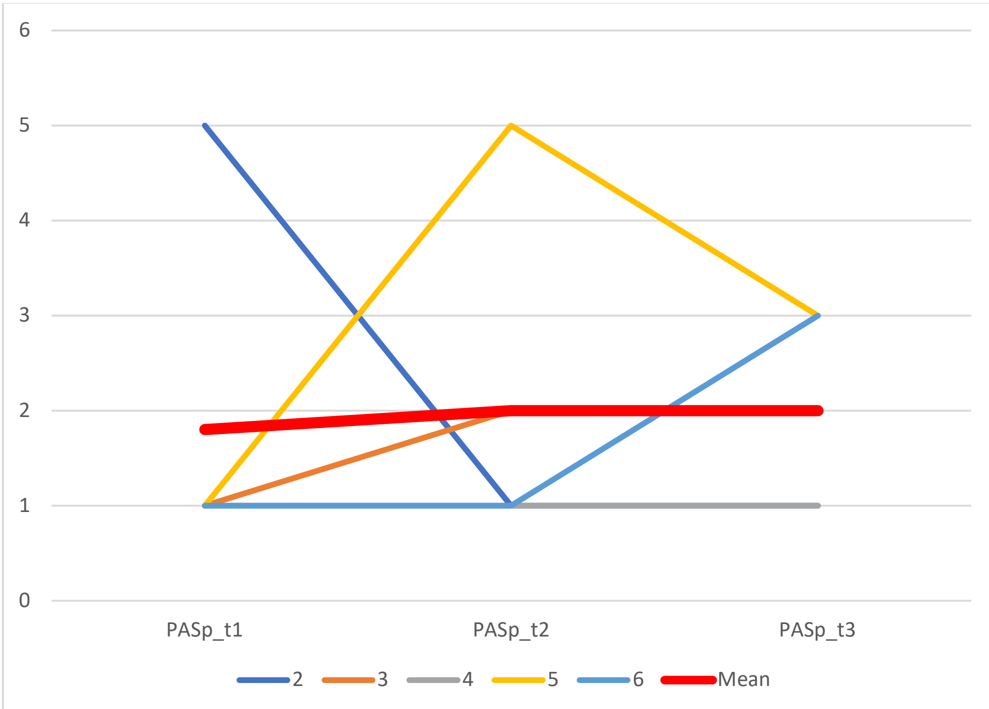
PeakXY, pudding 10 mL (% C2-4) line graph for the pattern of change over three assessment time points. Higher score corresponds to better functioning.



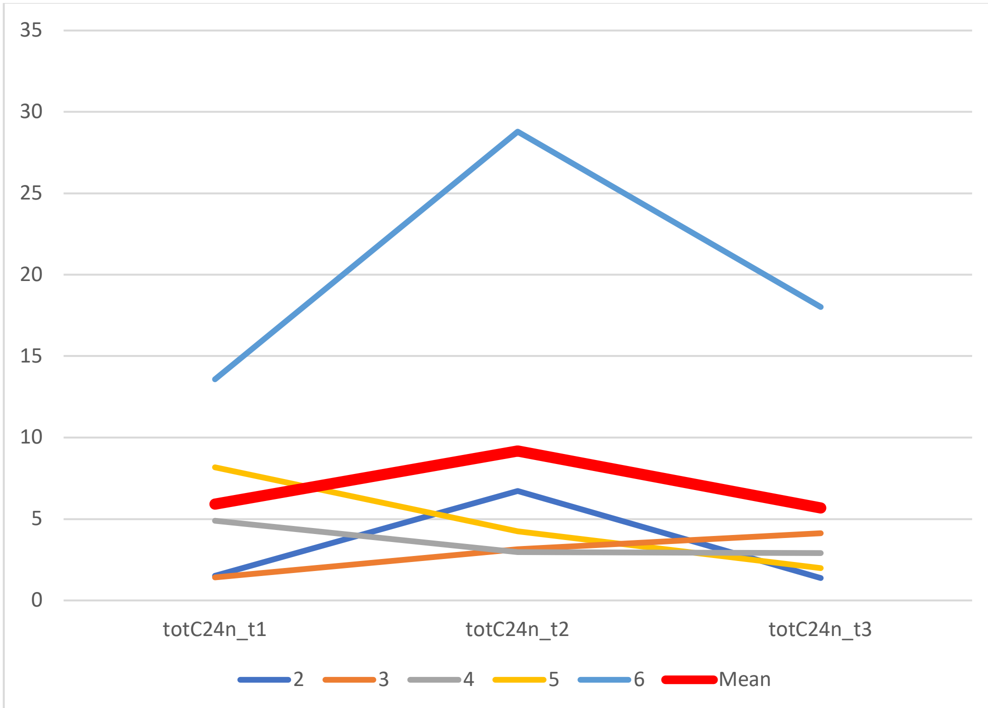
PAS (worst), nectar 10 mL (points) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



PAS (worst), pudding 10 mL (points) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



TotC24, nectar 10 mL (% C2-4) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.



TotC24 (totC24), pudding 10 mL (% C2-4) line graph for the pattern of change over three assessment time points. Lower score corresponds to better functioning.