USING TELEHEALTH TO OPTIMIZE CARE FOR PEOPLE WITH A MOTOR NEURON DISEASE:

THE DIGITAL ROAD TO PERSONALIZED CARE

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Het gebruik van eHealth om de zorg voor mensen met een zenuwziekte te optimaliseren

De digitale weg naar gepersonaliseerde zorg

(met een samenvatting in het Nederlands)

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Contents

CHAPTER 1

1

General introduction

Motor neuron disease

Motor neuron diseases (MNDs) are fatal diseases that lead to loss of upper and lower motor neurons and can affect all voluntary muscles, and include amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS).[1,2] The presentation of symptoms and the rate of disease progression varies greatly between MND's. ALS is the most prevalent and aggressive MND, affecting both the upper and lower motor neurons, with an average survival of 2 to 4 years from disease onset. However some patients may survive for more than 10 years. In patients with PMA only the lower motor neurons are affected, and the average survival is 5 years from disease onset, while PLS only affects the upper motor neurons and is not fatal in most cases. In a subgroup of patients, PMA and PLS can develop into ALS, generally within the first years after diagnosis.[3–9]

The initial symptoms of MND's may occur in the arms or legs, known as a spinal onset, or show in difficulties with speech and swallowing, known as a bulbar onset. As the disease progresses, patients will experience progressive loss of motor function, which inhibits daily activities, such as walking, writing, getting dressed and eating. Symptoms generally start focal (in one body part), and will spread to other parts of the body.[1,2] Besides physical impairments, cognitive impairments and psychological issues, such as frontotemporal dementia and feelings of hopelessness, are also common in patients with MND.[10,11] Over time, patients with MND will develop respiratory muscle weakness, which will lead to respiratory failure, and consequently, death in most patients.[12,13] Out of all respiratory muscles, weakness of the diaphragm is the main cause of respiratory impairment, as it inhibits adequate inhalation, and leads to shortness of breath (dyspnea). During sleep, diaphragm weakness will lead to nocturnal hypoventilation, resulting in abnormally high carbon dioxide levels in the blood, known as hypercapnia.[14] Patients with prolonged hypercapnia may experience sleep-related complaints (e.g. restless sleep, nightmares, morning headaches) and daytime symptoms (e.g. excessive fatigue, daytime sleepiness), which can cause distress and negatively affect quality of life.[15,16]

Multidisciplinary care

As a result of the complexity and heterogeneity of MND, patients require specialized care at a multidisciplinary ALS clinic, provided by a team consisting of at least a neurologist, (rehabilitation) physician, physical therapist, occupational therapist, speech and language therapist, dietician and psychologist.[17] Due to disease progression, patients are generally monitored every 3 months during a visit to a multidisciplinary clinic.[18] In the Netherlands there are 25 certified multidisciplinary ALS clinics spread across the country, but in most countries the density of specialist centers is lower. In between clinic visits, care at home is

mostly provided by informal caregivers, such as partners or family members, with support from a general physician and home care.

Multidisciplinary MND care mainly includes symptom management, and is aimed at optimizing quality of life.[19] Besides positive effects on quality of life, multidisciplinary MND care also improves survival, when compared to non-specialized care.[20] One of the most effective treatments for improving survival and maintaining quality of life is non-invasive ventilation (NIV), since it reduces hypercapnia and symptoms of hypoventilation through ventilatory support.[21–24] In order to determine the right timing of NIV, national and international guidelines provide recommendations for when to initiate NIV. [25–28]

Patients are generally satisfied with MND care, however, accessing and receiving care at a multidisciplinary clinic can be time-consuming and physically challenging for patients with MND, due to physical disability, long travel distances and long clinic days.[29,30] These issues result in considerable burden of care, and hinder the continuity of care, which may increase distress and negatively affect patients' quality of life and survival. Hence, there is a need to improve the accessibility and continuity of multidisciplinary care, and reduce its burden.

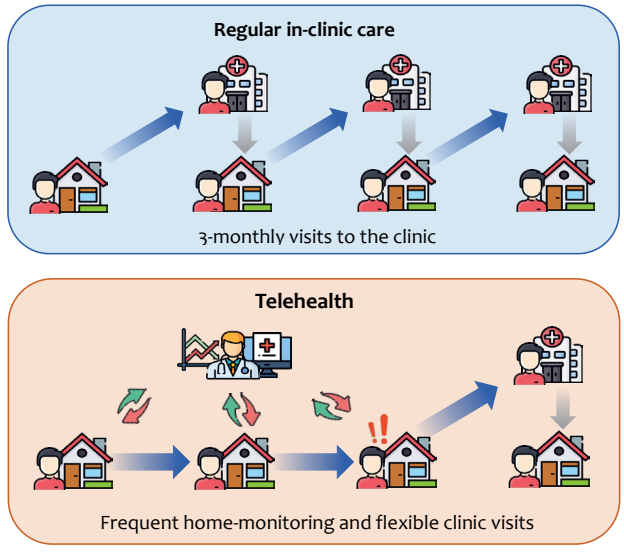

Figure 1 Differences in the monitoring of patients with MND between regular inclinic care and telehealth.

Telehealth and remote monitoring

Telehealth is the remote provision of care through the use of digital technology and holds the potential to improve accessibility and reduce burden of multidisciplinary ALS care, by enabling the monitoring of patients from home (Figure 1). This approach may also enhance the continuity of care, since patients can receive multidisciplinary care, even if they are no longer able to travel to a clinic, e.g. due to the COVID-19 pandemic.[31] In addition, the use of telehealth facilitates monitoring in between clinic visits, which is currently limited in MND care, and allows for more frequent monitoring from home, which can provide healthcare professionals with insight into patients' disease remotely. Furthermore, patients' individual home-based data can be used to tailor care and information to their ever-changing care needs.

Despite the promising benefits of telehealth and the wide availability of digital technologies, the use of telehealth and remote monitoring in care for patients with MND is limited. Correspondingly, there are only a few studies on the use of telehealth in MND care, of which many are pilot studies.[31] These findings suggest that telehealth services are not implemented after the initial pilot phase. It is known from various healthcare settings, that the use and implementation of digital technology has noticeable barriers.[32] For this reason it would be of great benefit to know what factors determine the success of the implementation of telehealth in MND care, and what methods can best be used for remote monitoring of relevant disease-related outcome measures. In particular, the remote monitoring of respiratory function is important, as it can help healthcare professionals to detect respiratory decline earlier and to initiate NIV at the right time. In order to determine appropriate remote respiratory measures, validity and feasibility in a home setting should be investigated.

Aims of this thesis

This thesis aims to expand the knowledge on the use and implementation of telehealth in multidisciplinary MND care, and to identify adequate methods for the remote monitoring of patients with MND.

Sub-aims

- To provide an overview of the current use of digital health technology in ALS care, and factors that may facilitate or hinder implementation of telehealth.
- To evaluate the feasibility of telehealth in multidisciplinary MND care, and the views and experiences of patients with MND on the use of telehealth.
- To determine which respiratory measures can best be used, in terms of validity and feasibility, for the home-monitoring of respiratory function in patients with MND.

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PART I

Telehealth and digital technology

CHAPTER 2

2

The current use of telehealth in ALS care and the barriers to and facilitators of implementation: A Systematic Review

Jochem Helleman, Esther Kruitwagen-van Reenen, Leonard van den Berg, Anne Visser-Meily, Anita Beelen

Amyotropic Lateral Sclerosis and Frontotemporal Degeneration, 2020

Abstract

Objective. We aimed to provide an overview of telehealth used in the care for patients with amyotrophic lateral sclerosis (ALS), and identify the barriers to and facilitators of its implementation.

Methods. We searched Pubmed and Embase to identify relevant articles. Full-text articles with original research reporting on the use of telehealth in ALS care, were included. Data was synthesized using the Consolidation Framework for Implementation Research. Two authors independently screened articles based on the inclusion criteria.

Results. 16 articles were included that investigated three types of telehealth: Videoconferencing, home-based self-monitoring and remote NIV monitoring. Telehealth was mainly used by patients with respiratory impairment and focused on monitoring respiratory function. Facilitators for telehealth implementation were a positive attitude of patients (and caregivers) towards telehealth and the provision of training and ongoing support. Healthcare professionals were more likely to have a negative attitude towards telehealth, due to the lack of personal evaluation/contact and technical issues; this was a known barrier. Other important barriers to telehealth were lack of reimbursement and cost-effectiveness analyses. Barriers and facilitators identified in this review correspond to known determinants found in other healthcare settings.

Conclusions. Our findings show that telehealth in ALS care is well-received by patients and their caregivers. Healthcare professionals, however, show mixed experiences and perceive barriers to telehealth use. Challenges related to finance and legislation may hinder telehealth implementation in ALS care. Future research should report the barriers and facilitators of implementation and determine the cost-effectiveness of telehealth.

Key words: Amyotrophic Lateral Sclerosis, Telehealth, Barriers and facilitators, Implementation

Introduction

Patients with amyotrophic lateral sclerosis (ALS) suffer from progressive disability, which develops at a variable rate, resulting in ever-changing care-needs. Symptomatic management by a multidisciplinary team of specialists is the mainstay of treatment for patients with ALS. This type of care aims to optimize patients' quality of life and survival.[1–5] For this reason, patients should be monitored closely and have continuous access to multidisciplinary care throughout their disease. However, many patients with ALS experience issues with accessing and attending multidisciplinary clinics. These issues are mostly related to long travel distances, difficulty travelling and long days at the clinic.[6,7] In addition, there is a lack of monitoring between clinic visits (in ALS care). The access issues and lack of monitoring limit the continuity of multidisciplinary care, which could negatively affect patients with ALS.

Telehealth has the potential to improve the accessibility and continuity of ALS care by enabling the remote provision of care and facilitating remote monitoring. The use of telehealth allows patients to receive specialist care, regardless of their ability to travel, their level of impairment or the distance to a multidisciplinary clinic. Despite these potential benefits and the availability of digital technology, the use of telehealth in ALS care is currently limited. This view is supported by a recent systematic review that looked into the use of digital technology to improve access to specialist ALS care.[8] The limited number of studies in the review were mostly feasibility or pilot studies and/or included only a small number of patients with ALS. This lack of (robust) literature suggests that telehealth innovations rarely survive beyond the initial pilot phase and are not implemented into usual ALS care.

These findings indicate that there are issues that hinder the implementation of telehealth in ALS care. In order to facilitate telehealth implementation, we describe its current use in ALS care and aim to identify the barriers and facilitators that influence implementation.

Methods

Search strategy

Comprehensive electronic searches were conducted using Pubmed and Embase to look for articles up until 2019. A clinical librarian was consulted regarding the construction of the searches. Search terms used included "amyotrophic lateral sclerosis" or "ALS" or "motor neuron disease" or "MND" or "ALS/MND", combined with "telehealth" or "telemedicine" or "mhealth" or "ehealth" or , "telerehabilitation" or "telemonitoring" or "teleconsultation" or "digital technology" or "mobile technology" or "mobile app". Full search queries for Pubmed are shown in supplementary material 1; we adjusted these for the other databases. Additionally,

reference lists of identified articles were scrutinized and citations of these articles were checked using Google Scholar. Duplicates were removed using Mendeley software.

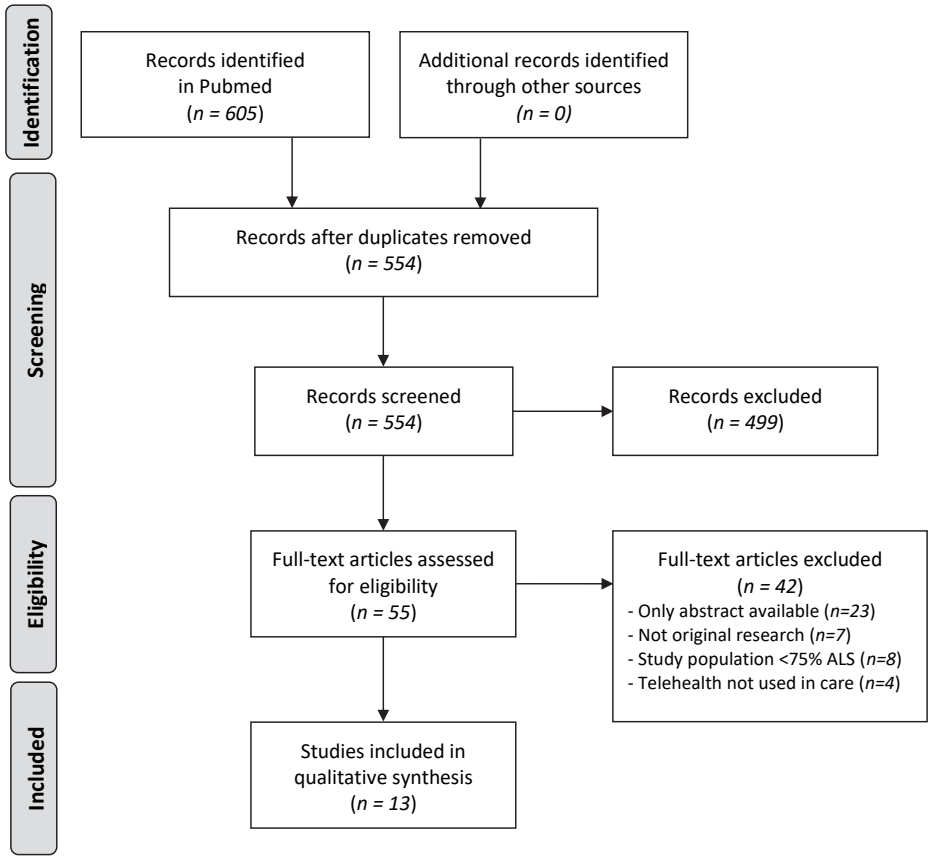

Figure 1. Literature selection flow diagram

Inclusion criteria for review

To be eligible, a study had to meet following criteria: 1) a full-text article with original research, 2) >75% of the study population had to be patients with ALS, 3) report on the use or implementation of telehealth in a healthcare setting, 4) published in English, 5) published in a peer-reviewed journal. Telehealth was defined as the provision of remote healthcare services through the use of digital and telecommunication technologies. The study methodology was assessed (i.e. study design and recruitment strategy), but was not an inclusion criterion for this review. Two reviewers screened titles and abstracts and selected relevant articles. A full-text assessment, also by two reviewers, determined which studies were eligible for inclusion based on the inclusion criteria.

Table 1 Definitions of implementation determinants. Based on the Consolidation Framework for Implementation Research (CFIR).

Domain	Construct	Definition
Innovation characteristics	Core components	The essential and indispensable elements of the innovation.
	Complexity	To what extent the telehealth innovation is difficult to start-up, use or implement.
Patient/caregiver characteristics	User-experiences and benefits	The user-experiences of the patient and caregiver with the telehealth innovation and the perceived benefits or drawbacks.
	Compliance	The ability or willingness of the end-user to use the telehealth innovation
Healthcare professional characteristics	User-experiences and benefits	The user-experiences of the healthcare professional with the telehealth innovation and the perceived benefits or drawbacks.
Inner and outer setting	Available resources	The available software, equipment, support, training, education and time required for operating the telehealth innovation.
	Finance and legislation	The available financial and legislative constructs required for operating the telehealth innovation.

Analysis method

The framework for the qualitative data extraction was based on the Consolidated Framework for Implementation Research (CFIR).[9] This instrument specifies the determinants that affect the implementation of an innovation. The determinants in this review were divided into four domains from the CFIR: Innovation characteristics, patient/caregiver characteristics, healthcare professional characteristics and the inner and outer setting. Innovation characteristics include the core components and complexity of the telehealth innovation that is being used or implemented. Patient/caregiver characteristics include the user-experiences/benefits, and compliance of patient/caregiver end-users. The healthcare professional characteristics include the user-experiences/benefits of healthcare professional end-users. The inner and outer setting includes the available resources, and finance and legislation that the organization has to manage. The definitions of each determinant can be found in table 1.

Results

The final literature search was performed on the 6th of November 2019 and identified a total of 707 articles, 61 of which were reviewed for eligibility. After full-text analysis, 16 articles were included in the review. Reasons for exclusion are shown in Figure 1. At least 429 patients with ALS were included who used telehealth (one study did not report the

number of patients); 65.9% of patients were male and the mean age was 60.5 years. Eight of sixteen studies reported the revised ALS Functional Rating Scale (ALSFRS-R) with a mean total score of 28.0; twelve of sixteen studies reported that 67.5% of patients were ventilated through either non-invasive ventilation (NIV) or tracheostomy invasive ventilation (TIV); and six of sixteen studies reported that 29.2% of patients had a gastrostomy. Details of the included studies can be found in table 2.

Three main types of telehealth were identified: videoconferencing (n=5), home-based self-monitoring (n=7) and remote NIV monitoring (n=4). Videoconferencing is any consultation between a patient/caregiver and a healthcare professional through real-time video. Home-based self-monitoring is the process in which patients (and their caregivers) manually perform measurements at home, and transmit data to the medical team and receive medical support via digital technology. Remote NIV monitoring is the process whereby a patient's digital NIV data are monitored remotely and transmitted to the medical team. One of the studies used the store and forward method in addition to videoconferencing. The store and forward method includes recording a patient assessment at home, after which the recording is stored and forwarded to the medical team for further assessment. The determinants of implementation per study can be found in table 3 and an overview of all identified barriers and facilitators telehealth use/implementation is presented in table 4.

Videoconferencing (n=5)

Innovation characteristics

Core components. Studies reported that videoconferences were attended either by multiple healthcare professionals[10,11] or by one physician.[12,13] In another study, during a home-visit, a nurse set-up a videoconference for the patient and caregiver with the clinical director.[14] A few studies required patients to login on the web server with a personal ID code.[10,12,13]

Complexity. One study reported issues with video and audio, but did not prevent any videoconferences from taking place.[13] Audio issues were solved by using a phone and a pager was used to troubleshoot technical issues. In one study, there were issues with buffering large video files, and an unstable and unreliable internet connection.[14]

Patient/caregiver characteristics

User-experiences and benefits. Three studies reported that patients were satisfied with videoconferencing.[12–14] One study reported that satisfaction with telehealth was not related to disease severity or travel distance.[14] Reported benefits of patients included reduced travel burden, reduced clinical burden and time-saving.[12,13] Remote consultation increased the continuity of care[11,13] and allowed more severely disabled patients to continue receiving specialist care.[13] Caregivers reported a lack of physical evaluation by a healthcare professional.[10]

Table 2. Details of telehealth studies. VC = Videoconference, NIV = Non-invasive ventilation, HCP = Healthcare professional, ALSFRS-R = revised ALS functional rating scale, M = Mean, V = Ventilated patients, G = Patients with gastrostomy, n.r. = not reported.

Publication	Type of telehealth	Study design	Recruitment strategy	Study population	Characteristics of patients
Geronimo et al. (2017)	Videoconferencing	A pilot study investigating feasibility and acceptability.	A convenience sample consisting of patients who were deemed potentially eligible and would likely benefit from VC.	Telehealth (N=20) Caregiver (N=20) HCP (N=15)	Diagnosis (ALS), Age (M=60), Male (64%), ALSFRS-R (M=24)
Nijeweme-d'Hollosy et al. (2006)	Videoconferencing	A pilot study investigating the effect of VC on the quality of care.	A convenience sample consisting of patients who liked working with computers.	Telehealth (N=4)	Diagnosis (ALS), Age (M=42), Male (75%)
van de Rijn (2018)	Videoconferencing	A retrospective chart review investigating the feasibility and utilty of VC.	Patients who had at least one VC were included.	Telehealth (N=97) HCP (N=5)	Diagnosis (ALS), Age (M=58), Male (63%), V (57%), G (23%)
Selkirk et al. (2017)	Videoconferencing	A retrospective cohort study investigating feasibility and effectivity.	Patients who received care for one year at the ALS centre were included. Patients chose telemedicine based on preference, disability level or distance from the clinic.	Telehealth (N=32) Usual care (N=36)	Diagnosis (ALS), Age (M=63), Male (100%), V (72%), G (68%)
Pulley et al. (2019)	Videoconferencing, Store and forward method	A pilot study investigating feasibility and acceptability.	Patients were included regardless of distance from the clinic, mobility or disease severity.	Telehealth (N=18) HCP (N=7)	Diagnosis (ALS), Age (M=64), Male (66%), ALSFRS-R (M=25)
Vitacca et al. (2010)1	Telephone-assisted self-monitoring	A pilot study investigating feasibility and patient/caregiver's satisfaction.	Patients with a caregiver were included.	Telehealth (N=40) Caregiver (N=40)	Diagnosis (ALS), Age (M=63), Male (60%), ALSFRS-R (M=31), V (78%), G (50%)
Vitacca et al. (2010)2	Telephone-assisted self-monitoring	A prospective study investigating feasibility and cost-effectiveness.	Patients who lived <80km from the centre were included.	Telehealth (N=39) Caregiver (N=39) HCP (N=n.r.)	Diagnosis (ALS), Age (M=62), Male (54%), V (69%)
Vitacca et al. (2012)	Telephone-assisted self-monitoring	A prospective study investigating nurse's utilisation and costs.	Patients with an ALSFRS-R <40 were included.	Telehealth (N=73)	Diagnosis (ALS), Age (M=61), Male (60%), ALSFRS-R (M=28), V (49%), G (34%)
Paneron et al.i (2013)	Telephone-assisted self-monitoring	A pilot study evaluating the feasibility of long-term self-monitoring.	Non-bulbar patients with a caregiver and an ALSFRS-R <35 were included.	Telehealth (N=12)	Diagnosis (ALS), Age (M=53), Male (75%), ALSFRS-R (M=20), V (58%)

Ando et al. (2019)1	App-based self-monitoring	A trial investigating the use and feasibility of telemonitoring.	Opportunity sampling was used to recruit patients.	Telehealth (N=13)	Diagnosis (MND), Age (M=66), Male (62%), ALSFRS-R (M=22), V (100%)
Ando et al. (2019)2	App-based self-monitoring	A qualitative study with semi-structured interviews on telehealth use.	Opportunity sampling was used to recruit patients who had completed a trial of telemonitoring.	Telehealth (N=7) Caregiver (N=5)	Diagnosis (MND), Age (M=63), Male (71%), V (100%)
Hobson et al. (2019)	App-based self-monitoring	A randomized controlled pilot and feasibility study investigating the feasibility of an RCT.	Patients with ALS, PMA or PLS who showed a ≥2 point decrease on the ALSFRS-R in the last 18 months were included.	Telehealth (N=20) Usual care (N=20) Caregiver (N=37) HCP (N=1)	Diagnosis (ALS, PMA, PLS), Age (60), Male (70%), V/G (40%)
Almeida et al. (2010)	Remote NIV monitoring	An exploratory trial testing safety, acceptance, and accuracy of remote NIV monitoring.	Volunteering patients were included.	Telehealth (N=n.r.) HCP (N=9)	Diagnosis (ALS), V (100%)
Almeida et al. (2012)	Remote NIV monitoring	A prospective, quasi-randomized controlled trial investigating costs and cost-effectiveness.	Patients who used a 'bi-level' NIV device were screened and assigned into a group according to their residential area.	Telehealth (N=19) Usual care (N=20)	Diagnosis (ALS), Age (M=60), Male (70%), ALSFRS-R (M=33), V (100%), G (0%)
Tura et al. (2007)	Remote NIV monitoring	A preliminary trial investigating feasibility.	n.r.	Telehealth (N=15)	Diagnosis (ALS), V (100%)
Pinto et al. (2010)	Remote NIV monitoring	A prospective, quasi-randomized controlled trial investigating compliance, survival and healthcare utilisation.	Patients who used a 'bi-level' NIV device were assigned to one of two groups according to their residential area.	Telehealth (N=20) Usual care (N=20)	Diagnosis (ALS), Age (M=60), Male (70%), ALSFRS-R (M=33), V (100%), G (0%)

Compliance. Several studies reported that patients felt comfortable and liked working with technology[10,12,14], which determined enthusiasm with telehealth.[14] According to two studies, patients were willing to discuss most practical topics via remote consultation (e.g. medication, equipment, research, symptoms and treatments).[12,13] However, one of these studies indicated reluctance of patients to discuss sensitive topics, such as acceptance/coping and end-of-life, during a remote consultation.[12] These topics would require a face-to-face consultation. Patients were assisted by caregivers in order to use videoconferencing in some studies.[10,12,13]

Healthcare professional characteristics

User-experiences and benefits. One study showed that healthcare professionals were generally satisfied with the communication and provision of care during

videoconferences.[10] In addition, videoconferencing enabled a local therapist to attend the consultations, which normally was not possible with in-clinic care.[12] The healthcare professionals in two studies were able to discuss most, but not all, topics (as reported by patients) through videoconferencing.[12,13] Despite these positive experiences, several studies indicated the lack of a sense of touch perceived by healthcare professionals[10,13,14] and one study reported that healthcare professionals might be uncertain about whether videoconferencing allows for an appropriate medical assessment.[13] Additionally, in one study, healthcare professionals expressed dissatisfaction with the quality of the video and audio, and reported that telehealth was not equal to in-person care.[10] One study reported mixed opinions on time requirement and ease of the process of the store and forward method.[14]

The inner and outer setting

Available resources. Studies showed that the care protocol for videoconferences was the same as for in-clinic care, including equal staff requirement during consultations.[10,11] In a couple of studies, training of healthcare professionals and patients was required for using videoconferencing.[12–14] Technical support for healthcare professionals in two studies was provided by an external information technology organisation[12] or the internal telehealth division.[13]

Finance and legislation. One study reported a lack of reimbursement for telehealth.[13]

Home-based self-monitoring (n=7)

Innovation characteristics

Core components. Studies included the at-home assessment of oximetry[15–20], questions on functional status and symptoms[15,20,21], manually or mechanically assisted coughing, airway suctioning and mechanical in-exsufflation (MI-E)[16], peak cough expiration flow, respiratory discomfort and a clinical diary on changes in clinical condition[19], and body weight and balance.[21] Some studies used a monitoring protocol with daily assessments[17–19], while a number of other studies applied a weekly or bi-weekly monitoring protocol.[15,20,21] Self-monitored data was transmitted either through telephone or a tablet device.[15–21]

Complexity. One study reported that self-monitoring seemed to be too cumbersome due to the large number of daily assessments and complexity of reporting.[19] In contrast, adhering to the self-monitoring protocol in other studies was considered to be easy, due to an appropriate frequency of monitoring and user-friendly technology.[15,21] Specifically oximeters and tablet devices were reported to be user-friendly.[17,20,21] In some cases the self-monitoring protocol was reinforced by home visits[17] or telephone calls.[17,21]

Table 3. Determinants of implementation categorized according to the CFIR domains. M = Mean, V = Ventilated patients, G = Patients with gastrostomy, NIV = Non-invasive ventilation, VC = Videoconference, HCP = Healthcare professional, QoL= Quality of life, ALSFRS = ALS functional rating scale, PCEF = Peak cough expiration flow, MAC = Mechanical assisted coughing, MI-E = Mechanical in-exsufflation, n.a. = Not applicable/ not reported.

Videoconferencing				
Publication	**Innovation characteristics**	**Patient/caregiver characteristics**	**Healthcare professional characteristics**	**Inner and outer setting**
Geronimo (2017)	**Core components:** Patients accessed VC through an internet browser using a unique ID code. The VC was attended by the patient, caregiver physician and nurse (other HCP's were optional). Telehealth was found to be feasible. **Complexity:** Future changes to facilitate the use of VC include faster internet connection, compatibility with multiple types of hardware and internet browsers, direct eye contact through video, wider field of view and on-screen identification of HCP's.	**User-experiences and benefits:** Patients experienced reduced travel time and burden. The lack of physical evaluation was disliked by caregivers. **Compliance.** Caregiver needed to assist patient. High comfort and familiarity with technology among patients.	**User-experiences and benefits:** HCP's judged telehealth as not equal to in-person care. HCP's lack the sense of touch. HCP's found communication and making recommendations adequate. A large portion of HCP's were unsatisfied with video and audio quality.	**Available resources:** The care protocol for telehealth was the same for in-clinic care, including similar staff requirement during consultations. **Finance and legislation:** n.r.
Nijeweme-d'Hollosy (2006)	**Core components:** VC between patient, caregiver and physician. A web-application accessible through a virtual private network with a general ALS website and an tele-treatment environment, including planned consultation hours, a chat room and VC. External IT organization provided support. **Complexity:** n.r.	**User-experiences and benefits:** Patients experienced reduced travel time. Patients were satisfied with telehealth and contact during VC. **Compliance:** Patients were willing to discuss most topics through VC, except for acceptance and end-of-life. Patients liked working with computers and caregivers needed to assist when patients were too impaired.	**User-experiences and benefits:** n.r.	**Available resources:** A HCP provided an initial instruction session for patients. **Finance and legislation:** n.r.
van de Rijn (2018)	**Core components:** Patients had to log into a virtual waiting room prior to VC. The VC was attended by the patient, caregiver and physician. HCP's used a pager for troubleshooting technical issues. **Complexity:** All identified technical issues were related to video/ audio, none prevented VC from occurring. Audio issues were solved by using a phone.	**User-experiences and benefits:** It was less necessary to travel for consultations. Patients experienced time saving and a reduction in clinic burden. More continuity of care was seen in patients in a later phase of disease. **Compliance:** Patients were satisfied with VC. Majority of patients were assisted by caregiver. Patients in every phase of the disease preferred VC. Patients were willing to discuss most topics through VC.	**User-experiences and benefits:** HCP's experienced easier communication with local therapist. HCP's are uncertain about proper assessment and lack a physical examination. No time saving for HCP's. Most topics could be discussed via VC.	**Available resources:** A team of coordinators and engineers of the telehealth division provided training and technical support to physicians and patients. **Finance and legislation:** There was a lack of reimbursement for telehealth.

Selkirk (2017)	**Core components:** Prior to a VC patients were evaluated by their local team, a nurse called patient to assess burden, QoL and ALSFRS-R-R, and patients' needs were determined during a bi-weekly meeting of the medical team. The VC was attended by the patient, caregiver, local care team, nurse and neurologist (other HCP's were optional). **Complexity:** n.r.	**User-experiences and benefits:** VC allows for more continuity of care throughout the disease. It was less necessary to travel for consultations. Quality of care was equivalent between regular care and telehealth. **Compliance:** n.r.	**User-experiences and benefits:** n.r.	**Available resources:** The care protocol for telehealth was the same for in-clinic care, including similar staff requirement during consultations. **Finance and legislation:** n.r.
Pulley (2019)	**Core components:** A home visit by a nurse for video recording of clinical assessments. Video of the assessments was cut and assessed by HCP's. Reports by the HCP's were sent to clinical director who created a care plan. The plan was conveyed through VC. The VC was attended by the patient, caregiver, clinical director and at-home nurse. **Complexity:** The lack of availability of patient and nurse delayed VC. Buffering of large video files was a major issue. Internet connection was often unstable and unpredictable.	**User-experiences and benefits:** It was less necessary to travel for consultations. **Compliance:** Patients were satisfied with telehealth, independent of ALS severity and distance from center. Comfort with using technology determines enthusiasm.	**User-experiences and benefits:** Mixed experiences with the ease of the process, lack of physical contact and time requirement. HCP's had limited availability on clinic days. The information obtained from telehealth was sufficient. HCP's assessed the video at their convenience.	**Available resources:** All member of the multidisciplinary team provided extensive training to the nurse in assessment skills. Clinic director conducted videoconferences with nurse at patient's home. Inexpensive commercial devices were used. **Finance and legislation:** There was a lack of reimbursement for telehealth. There was no team conference to discuss a case.

Home-based self-monitoring				
Publication	**Innovation characteristics**	**Patient/caregiver characteristics**	**Healthcare professional characteristics**	**Inner and outer setting**
Vitacca (2010)1	**Core components:** Patients performed daily at-home assessments of pulse oximetry. Weekly scheduled call from a nurse for a clinical interview, consultation planning, updating clinical data (oximetry) and redirecting to a general practitioner or specialist. There was a 24h availability of second-opinion by a respiratory therapist. A call-center facilitated communication. **Complexity:** n.r.	**User-experiences and benefits:** Patients were extremely satisfied with the nurse assistance. Patients had more confidence in handling the disease. 24h availability of second-opinion was valuable. Telehealth provided autonomy and continuity of information and care. **Compliance:** Majority of patients were assisted by caregiver. Caregiver spoke/ assisted when patient lost speech. Devices were simple to use.	**User-experiences and benefits:** n.r.	**Available resources:** Nurse monitored 50 patients with a clinical ALS-card. On demand availability of a nurse during working hours. Providing 24/7 call-center service and second opinion by a general practitioner or specialist. No dedicated therapist needed for second opinion. **Finance and legislation:** System is believed to be sustainable in terms of cost and staff time required (no analysis conducted). Variety of fixed and variable costs.
Vitacca (2010)2	**Core components:** Patients performed at-home assessments of MAC, pulse oximetry and airway suctioning. MI-E was provided for patients in which blood oxygen saturation could not be restored. Weekly scheduled call from respiratory therapist. Calls from patients were redirected by a nurse to one of the specialists for consultation or home-visit. A call-center facilitated communication. **Complexity:** n.r.	**User-experiences and benefits:** Fewer hospital admissions and emergency room visits. Patients experienced an increased feeling of security for home management and considered the intervention effective. **Compliance:** n.r.	**User-experiences and benefits:** HCP's experienced an increased feeling of security for home management.	**Available resources:** On demand telephone access to a triage nurse who directed calls to a specialist. Therapist called patients weekly. Patients were trained to restore blood oxygen saturation through assisted coughing and emergency room visits. **Finance and legislation:** There was a lack of reimbursement for telehealth. Additional costs were home-visits and device rental. Intervention was shown to be cost-effective, due to reduced hospitalization costs.

Vitacca (2012)	**Core components:** Patients performed daily at-home assessments of pulse oximetry. Weekly scheduled calls from a nurse for a clinical interview, updating clinical data (oximetry) and redirecting to a general practitioner or specialist. In addition, patients could request calls 24/7. A call-center facilitated communication. An ALS card-of-risk guided telephone-accessed clinical interviews and facilitated monitoring, care and interoperability. **Complexity:** n.r.	**User-experiences and benefits:** n.r. **Compliance:** Caregiver needed to assist patients.	**User-experiences and benefits:** n.r.	**Available resources:** Providing on demand access to a nurse during working hours and 24/7 call-center service and second opinion by therapist. Providing nures with training to use the ALS-card to monitor disease status and to guide clinical interviews. Clinical ALS-card saved time and expenses on telephone calls. **Finance and legislation:** Health expenditure policy needs optimisation of staff's costs. Large variety of fixed and variable costs. Costs were extrapolated on long-term steady-state telehealth activity, including other chronic diseases.
Paneroni (2013)	**Core components:** Patients performed daily assessments of PCEF, pulse oximetry and respiratory discomfort. Patients also reported changes in respiratory and clinical condition in a diary. Bi-weekly scheduled telephonic support from a physiotherapist. Data was mostly transmitted through email or telephone. **Complexity:** High number of daily assessments and complex of reporting.	**User-experiences and benefits:** n.r. **Compliance:** Caregivers needed to assist when a patient was too impaired. Patients showed low adherence with the monitoring protocol.	**User-experiences and benefits:** n.r.	**Available resources:** Provision of telephonic support by a dedicated therapist. **Finance and legislation:** n.r.
Ando (2019)1	**Core components:** A tablet-style device was used by patients for answering questions and transferring nocturnal pulse oximetry data weekly. Patients could message the clinical team at any time. All patients received education on symptoms related to chest infections and respiratory management **Complexity:** n.r.	**User-experiences and benefits:** **Compliance:** Patients showed high levels of adherence with telemonitoring.	**User-experiences and benefits:** HCP's had the ability to remotely monitor patient's symptoms effectively and offer timely and appropriate support.	**Available resources:** n.r. **Finance and legislation:** n.r.

Ando (2019)2	**Core components:** A tablet-style device that allows clinicians to monitor patient outside of the clinic, regarding their symptom changes, NIV related related issues, nocturnal blood oxygen saturation levels, and patient-ventilator interaction data. The system generated alerts for symptom worsening. **Complexity:** There were some technical issues, but these were often minor and quickly resolved. The message function lead to frustrations due to too small keys and short time allowance for formulating a message.	**User-experiences and benefits:** Patients experienced timely interventions, which resulted in improved physical and psychological well-being. Reduced number of (unnecessary) clinic visits, saving time and costs. Increased self-awareness was experienced by patients. **Compliance:** Patients were supportive of regular monitoring and generally experienced the use of technology as easy. Using the message function was frustrating and challenging for some patients.	**User-experiences and benefits:** n.r.	**Available resources:** n.r. **Finance and legislation:** n.r.
Hobson (2019)	**Core components:** A user-centered telehealth service including weekly assessments of body weight and balance, and using a tablet to complete questions on functional ability, progression, symptoms, well-being. A nurse could view the data on a website; she phoned patients, expedited appointments and lialised the medical team. The system generated alerts for disease worsening. **Complexity:** There were some technical issues, but these were resolved. The connectivity of wifi-enabled scales was unreliable. The software was user-friendly and accessible for patients/caregivers.	**User-experiences and benefits:** Patients/caregivers experienced improved awareness of the disease, reassurance due to increased monitoring and a better connection with the HCP's. Face-to-face technology training was perceived as important. Patients/caregivers would recommend telehealth to others. **Compliance:** Good adherence to self-monitoring was observed. Accordingly, self-monitoring was easy, not tiring or time consuming, and not distressing. Some experienced difficulty using technology due to upper limb disability. Caregivers assisted when patients were too impaired. Low perceived ability to master technology, due to inexperience with technology.	**User-experiences and benefits:** Telehealth use was very easy and cost little time. The nurse could identify early problems, however the information from monitoring was sometimes not detailed enough.Repetitive alerts were frustrating for the nurse and required more time. On most occasions the information from monitoring was sufficient for a HCP to make appropriate decisions.	**Available resources:** Provision of training for technology use and provision of technical support. **Finance and legislation:** n.r.

Remote NIV monitoring				
Publication	**Innovation characteristics**	**Patient/caregiver characteristics**	**Healthcare professional characteristics**	**Inner and outer setting**
Almeida (2010)	**Core components:** An NIV device with flexible use of electronic slots and bi-directional data transmission was used for remote monitoring.A helpline was available for technical issues or worsening of clinical condition. Technician monitored NIV data and flagged physician for immediate change of settings. **Complexity:** The system was suitable and worked well. The connection was found to be robust for transmission of data and setting changes. The speed of data extraction was a limitation. There was need of a fixed telephone line. There were issues with confidentiality.	**User-experiences and benefits:** Reduced need to travel to adjust NIV settings. **Compliance:** Positive comments from patients on easiness of setting arrangements. Automatic monitoring limited the need for manual intervention.	**User-experiences and benefits:** HCP's lacked the sense of touch. The system eased communication with patient. HCP's had the ability to remotely monitor and change NIV settings.	**Available resources:** Helpline support was provided. Testing phase was required to test safety, acceptability and accuracy. Hiring technician for monitoring of NIV data and checking the procedure and mistakes. **Finance and legislation:** Unresolved issues with licensure, reimbursement, telecommunications infrastructure and robust analysis of cost- effectiveness.
Almeida (2012)	**Core components:** An NIV device with bi-directional data transmission was used for remote monitoring. **Complexity:** n.r.	**User-experiences and benefits:** Improved patient enablement and confidence with handling disease. Reduced need to travel to adjust NIV settings. Fewer office visits and hospital admissions. **Compliance:** Automatic monitoring limited the need for manual intervention.	**User-experiences and benefits:** HCP's had the ability to remotely monitor and change NIV settings.	**Available resources:** Higher number of setting changes at start, but lower over the entire period. Fewer office visits and hospital admissions. **Finance and legislation:** Big initial investment needed, but cost effective over time. Device rent was higher in remote monitoring group.
Tura (2007)	**Core components:** An NIV device with flexible use of electronic slots was used for remote monitoring. The wireless connection was found to be robust. A general practitioner or specialist could see data on the web application and send a (voice) message to the patient. **Complexity:** The device was easy to handle, with additional remote control and connection to a smartphone, personal digital assistant or notebook	**User-experiences and benefits:** Reduced need to travel to adjust NIV settings. **Compliance:** Patients reported devices as easy to use, and device settings were easy to adjust. The remote control was appreciated. Automatic monitoring limited the need for manual intervention.	**User-experiences and benefits:** HCP's had the ability to remotely monitor and change NIV settings.	**Available resources:** n.r. **Finance and legislation:** Lack of information on cost-effectiveness.

Pinto (2010)	**Core components:** An NIV device with bi-directional data transmission was used for remote monitoring. A helpline was available for NIV compliance follow-up, setting changes or medical advice. Technician monitored NIV data and flagged physician for immediate change of settings. The NIV device had bi-directional data transmission. **Complexity:** The system was suitable and worked well. The speed of data extraction was limited. There was a need of a fixed telephone line.	**User-experiences and benefits:** Fewer hospital admissions. Reduced need to travel to adjust NIV settings. **Compliance:** Automatic monitoring limited the need for manual intervention.	**User-experiences and benefits:** HCP's had the ability to remotely monitor and change NIV settings.	Available resources: Providing helpline support. Testing phase was required to test safety, acceptability and accuracy. Hiring technician for monitoring of NIV data. Higher number of NIV setting changes at start, but 50% lower over the entire period. Finance and legislation: Reduced hospitalization costs, due to fewer hospital admissions.

Patient characteristics

User-experiences and benefits. Satisfaction with telehealth was reported in three studies.[15,17,21] Patients reported increased awareness of the disease[15,21], more confidence in dealing with the disease[17] and an increased feeling of security for home management of respiratory symptoms.[16] A reduction in hospital admissions was seen in one study[16] and in another study the number of unnecessary clinic visits was reduced, resulting in a saving in time and costs.[15]

Compliance. In several studies, patients were assisted by a caregiver when they were too impaired.[16–18,21] Patients reported in two studies that devices worked well and were easy to use[15,17], but patients in another study had difficulty using a tablet device due to upper limb disability.[21] One study reported that patients showed low compliance with a monitoring protocol with multiple daily measurements.[19] In contrast, two studies reported high adherence with a (bi-)weekly monitoring protocol.[15,21] Accordingly, patients and caregivers in these studies reported that self-monitoring was easy, not time consuming nor tiring.

Healthcare professional characteristics

User-experiences and benefits. It was reported that telehealth allowed healthcare professionals to monitor symptoms effectively, provide timely support[15] and make appropriate decisions in care.[21] One study reported that telephone-assisted self-monitoring increased healthcare professionals' feeling of security for home management of respiratory symptoms.[16] A telehealth nurse reported that telehealth was easy to use and not time-consuming.[21] However, she also reported that information from self-monitoring was often not detailed enough and that repetitive alerts lead to frustration.

The inner and outer setting

Available resources. Studies reported that medical support could be requested through a telephone-call[15–21], a message system[15,20] or email[21], and that support was provided by either a therapist or a nurse. In one study a telehealth nurse remotely monitored patients through a clinical portal, phoned patients, expedited appointments and liaised the medical team.[21] In another study nurses used a standardised ALS card-of-risk to guide telephonic clinical interviews.[18] Nurses in these studies required training for operating the ALS card-of-risk and the clinical portal. Healthcare professionals provided face-to-face training to patients in the process of restoring blood oxygen saturation[16] and in operating a tablet.[21]

Finance and legislation. It was reported that on-demand MI-E rental was cost-effective compared to continuous rental and that fewer hospital admissions reduced hospitalization costs. [16] Telephone-assistance was believed to be sustainable in terms of cost and staff requirement.[17] Reported barriers to the continuation of telehealth use were a lack of

information on cost-effectiveness[18] and a lack of reimbursement.[16] A large variety of fixed and variable costs related to tele-assistance were seen in two studies.[17,18]

Remote NIV monitoring (n=4)

Innovation characteristics

Core components. Studies reported using an NIV device with bi-directional data transmission, which allowed for automatic transmission of NIV data and remote adjustment of NIV settings.[22–25] NIV devices had flexible use of electronic slots, which allowed arrangements to be tailored to patients' needs.[22,24] In two studies, patients had access to a helpline for on-demand medical or technical support; technicians monitored NIV data and flagged the physician to immediately change settings.[22,25]

Complexity. Two studies reported that the NIV devices were easy to use and showed robust wireless connection tests for transmission of data and setting changes.[22,24] In one study, additional functionalities and aids were provided to facilitate NIV use.[24] The speed of data extraction was limited in a two studies.[22,25]

Patient characteristics

User-experiences and benefits. The main benefit for patients was a reduced need to travel to the clinic for adjustment of NIV settings.[22–25] Additionally, fewer hospital admissions were reported.[23,25] In one study, patients experienced improved enablement and more confidence in managing the disease.[23]

Compliance. The bi-directional and automatic functionality limited the need for manual intervention by patients and caregivers for monitoring. Patients reported that the NIV devices were easy to use, and that settings were easy to change/arrange.[22,24] In one study, patients appreciated the extra aids that were provided to facilitate NIV use.[24]

Healthcare professional characteristics

User-experiences and benefits. One study reported that remote monitoring facilitated communication with the patient, but that healthcare professionals missed the sense of touch.(10) In all studies, healthcare professionals had the ability to remotely monitor NIV and adjust settings, which would not be possible with usual in-clinic care.[22–25].

The inner and outer setting

Available resources. In some studies, on-demand support was provided through a helpline.[22,25] A testing phase was required in two studies and (cardio-pulmonology) technicians were hired to monitor NIV data[22,25] and check procedures and mistakes.[22] Two

studies reported that the number of NIV setting changes was 50% lower over the entire period of NIV use, compared to usual care, hence saving time.[22,25]

Finance and legislation. One study reported that a large initial investment is required to set up telehealth and that remote NIV monitoring in ALS care is cost-effective.[23] Another study reported that the number of hospital admissions was reduced, which resulted in lower hospitalization costs.[25] Reported barriers to telehealth implementation were a lack of robust cost-effectiveness-analysis[22,24] and issues with reimbursement.[22]

Discussion

This review identified three different types of telehealth used in ALS care and showed that telehealth was mainly targeted at patients with respiratory impairment. Furthermore, we found that the barriers and facilitators of telehealth implementation in ALS care were consistent with the determinants identified in other healthcare settings. The main barriers hindering implementation of telehealth in ALS care were related to issues with finance and legislation, and lack of personal contact perceived by healthcare professionals.

Table 4. The barriers to and facilitators of telehealth use/ implementation in ALS care.

Facilitators	
Innovation characteristics	Complexity
	- Robust wireless connection
	- User-friendly devices
	- Additional aids for devices
Patient/caregiver characteristics	User-experiences and benefits
	- Reduced travel time and burden
	- Reduced clinic burden
	- Fewer hospital admissions/ emergency room visits
	- Increased feeling of enablement/ self-confidence
	- Increased feeling of security
	Compliance
	- Easy to use devices
	- Comfort and familiarity with using technology
	- Caregiver assistance
	- Automatic monitoring
	- High adherence to self-monitoring
Healthcare professional characteristics	User-experiences and benefits
	- Increased feeling of security
	- Insight into remote monitoring of data
	- Better communication

Inner and outer setting	Available resources
	- Ongoing support for end-users
	- Training of end-users
	- Standardized clinical assessment (card-of-risk)
	Finance and legislation
	- Sustainable in costs and time requirement
	- Cost-effective MI-E rental/ NIV use
	- Inexpensive commercial devices
	- Reduced hospitalization costs
Barriers	
Innovation characteristics	Complexity
	- Cumbersome monitoring protocol
	- Technical issues
	- Slow internet connection
	- Slow data extraction/ buffering
Patient/caregiver characteristics	User-experiences and drawbacks
	- Lack of physical evaluation/contact
	Compliance
	- Low adherence to self-monitoring
	- Unwilling to discuss sensitive topics through telehealth
Healthcare professional characteristics	User-experiences and benefits
	- Lack of physical evaluation/ contact
	- Uncertainty about comprehensive medical assessment
	- No time saving/ costing extra time
Inner and outer setting	Finance and legislation
	- Big initial investment
	- Large variety of fixed and variable costs
	- Lack of reimbursement
	- Lack of cost-effectiveness analyses

It was noticeable in this review that the proportion of patients who were ventilated through NIV or TIV (68%) was much higher compared to the general ALS population (18-36%).[26,27] In addition, 10 of 11 remote monitoring studies focused primarily on respiratory function, such as oximetry, (assisted) coughing, respiratory symptoms and NIV. These findings demonstrate that patients in the included studies are not representative of a general ALS population and that telehealth is focused on respiratory function up until now.

Determinants of implementation

Our results indicate that patients with ALS (and their caregivers) have a positive attitude to the use of telehealth. This may be attributed to patients' perceived benefits of telehealth (e.g. an increased feeling of enablement, reduced travel and clinical burden) and good compliance to telehealth use (i.e. easy to use devices, comfort with using technology

and caregiver assistance). A positive attitude of patients/caregivers is a facilitator for implementation as it increases acceptance of telehealth and positively influences the attitude of healthcare professionals.[28,29] It should be noted that several studies recruited a convenience sample of patients, who were likely to benefit from telehealth, or liked working with technology. This may have affected patients' experiences. Results suggest that healthcare professionals in ALS care have a more negative attitude towards telehealth. Despite being positive about communication through telehealth, healthcare professionals mostly reported barriers, such as technical issues, a lack of physical evaluation/contact and issues with a comprehensive medical assessment. A negative attitude among healthcare professionals creates resistance to telehealth and is a known barrier to implementation.[28,29] Regrettably, more than half of the studies did not evaluate user-experiences of healthcare professionals and therefore lack this information. Two important facilitators in this review that positively influenced the attitude of end-users were the provision of training and ongoing support. Despite requiring more staff time, the provision of training and ongoing support ensures that end-users are able to apply technology properly, which is essential for a successful implementation.[28,29] One of the main barriers to implementation of telehealth in ALS care were issues related to finance and legislation. Studies mostly reported a lack of robust cost-effectiveness analyses and a lack of reimbursement for telehealth. These are important issues that are also known in other healthcare settings, and hinder the implementation and integration of telehealth in ALS care. There was, however, evidence to support that on-demand MI-E rental and remote NIV monitoring were cost-effective, primarily due to a lower number of emergency room visits and hospital admissions. This financial benefit of telehealth is a facilitator for implementation and should be investigated in future research.

Clinical implications

Current telehealth innovations are mainly targeted at a subgroup of patients with ALS, which means that a substantial portion of the ALS population does not benefit from them. Ideally, all patients with ALS should be able to benefit from the use of telehealth, irrespective of the disease stage or type of impairments. Recent evidence has shown that this is feasible and of benefit for patients with motor neuron disease.[21] For this reason, future innovations should remotely monitor all relevant domains of functioning from early on in the disease. This will help healthcare professionals with 1) detecting early signs and symptoms, 2) informing patients about changes in all aspects of the disease and 3) providing timely care and information. Additionally, if started in an early disease stage, patients will be able to receive training and become familiar with technology and remote monitoring before becoming severely impaired.

To make sure a telehealth innovation truly meets the needs of end-users, both patients and healthcare professionals should be involved throughout the development process.[21,30] The

involvement of end-users will promote a positive attitude towards telehealth and increase acceptance, thus facilitating implementation.[28,29] Furthermore, telehealth innovations should be personalised, as the rate of disease progression is highly variable and the care needs of patients with ALS are ever-changing. The personalisation of telehealth promotes patient engagement[31] and involves the tailoring of monitoring frequency, clinic visit scheduling and the provision of care and information. To further increase patient engagement with remote monitoring, notifications and personal feedback could be provided.[31]

To improve remote monitoring and the usability of monitoring-data for research purposes, standardised outcome measures should be established and patients should be involved in determining which measures are relevant. Ideally, outcome measures should be associated with disease progression and survival, as this will help with the timely provision of interventions, assistive devices and information. Examples of such outcome measures are the ALSFRS-R, weight loss and vital capacity.[32–34] Also assessments on cognition, quality of life and caregiver burden could be included to facilitate psychological support.

Future research

In order to improve the implementation of telehealth in ALS care, future studies should be aimed at identifying the determinants of implementation and investigating how they affect the success of telehealth. Improved reporting (on determinants) will help to create a more detailed overview of relevant determinants, which is essential to guide healthcare professionals in the implementation of future telehealth innovations in ALS care. Furthermore, future research should focus on investigating the cost-effectiveness. Robust analyses will specifically facilitate the use of telehealth beyond the initial pilot phase.

Limitations

The main limitation of this review is that there were no studies primarily aimed at identifying the determinants of implementation. As a result, positive and negative aspects of telehealth might not have been reported or were not specifically reported as barriers or facilitators of telehealth implementation. For this reason, we may have missed a number of potential barriers, such as issues with (national) policy and incompatibility with the current infrastructure. Another limitation is that a number of studies included a convenience sample, which may have resulted in biased patients' experiences.

Conclusion

Our findings show that telehealth in ALS care is well-received by patients and their caregivers, as a result of user-friendly technology and experienced benefits. The provision of training and ongoing support to end-users has shown to be key for a successful telehealth implementation. Issues with reimbursement of telehealth and lacking information on cost-effectiveness were the main challenges. Future research should specifically focus on reporting barriers and facilitators to guide future telehealth implementation and help design new implementation strategies.

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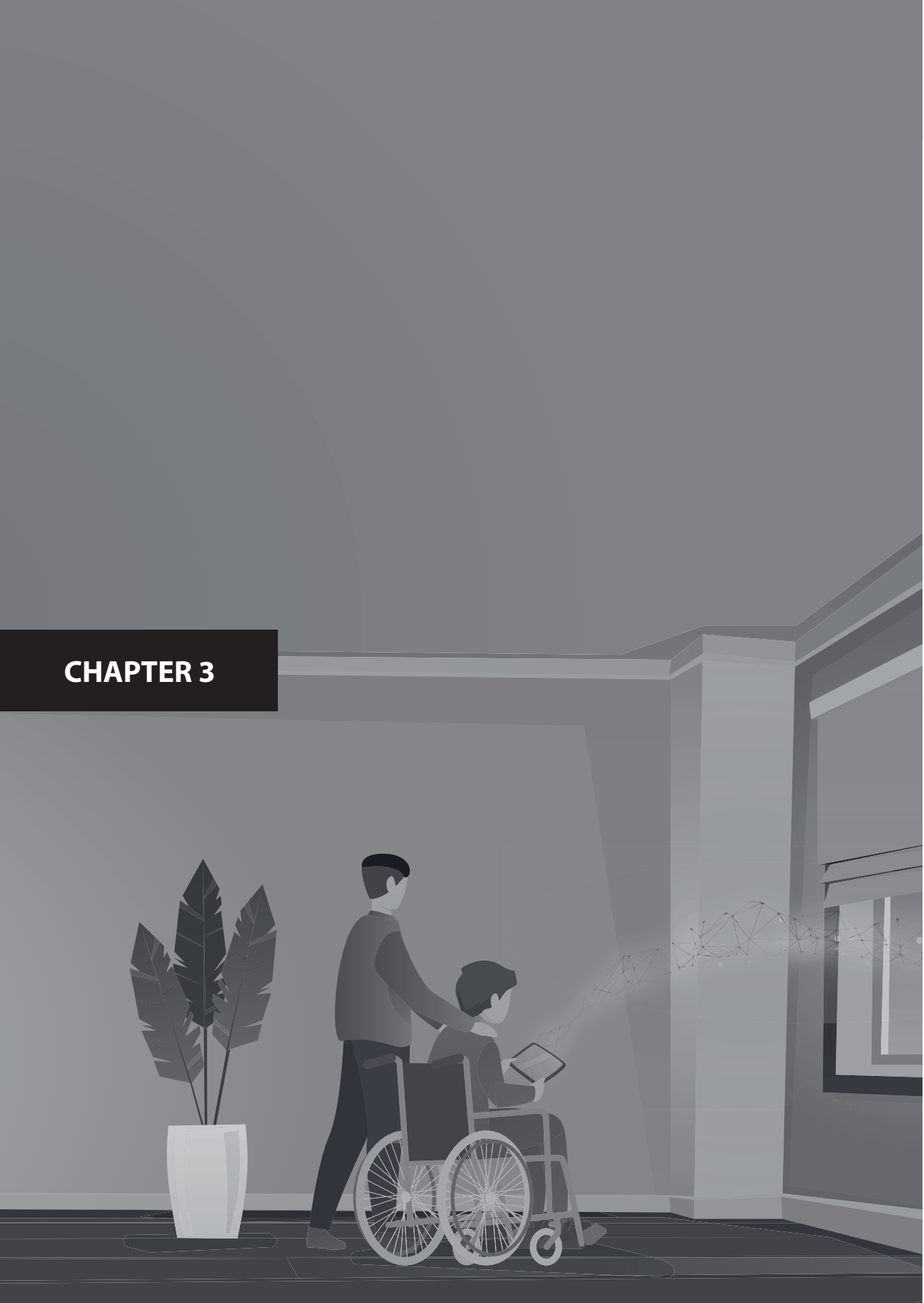
Supplementary material 1

PubMed search (6 November 2019):

#	Searches
1	"Amyotrophic Lateral Sclerosis"[Mesh] OR
2	"Motor Neuron Disease"[Mesh] OR
3	Amyotrophic Lateral Sclerosis[tiab] OR ALS[tiab] OR ALS/MND[tiab] OR
4	Motor Neuron Disease*[tiab] OR Motor Neuron Disorder*[tiab] OR MND[tiab] OR
5	AND
6	"Telemedicine"[Mesh] OR
7	"Telenursing"[Mesh] OR
8	"Cell phones"[Mesh] OR
9	"Medical informatics"[Mesh] OR
10	"Computers, handheld"[Mesh] OR
11	"Mobile applications"[Mesh] OR
12	mobile health*[tiab] OR mhealth*[tiab] OR m-health*[tiab] OR
13	ehealth*[tiab] OR e-health*[tiab] OR
14	telehealth*[tiab] OR tele-health*[tiab] OR
15	telemedic*[tiab] OR tele-medic*[tiab] OR
16	econsult*[tiab] OR e-consult*[tiab] OR remote consult*[tiab] OR teleconsult*[tiab] OR tele-consult*[tiab] OR distant consult*[tiab] OR distance consult*[tiab] OR
17	ecounsel*[tiab] OR e-counsel*[tiab] OR remote counsel*[tiab] OR telecounsel*[tiab] OR tele-counsel*[tiab] OR distant counsel*[tiab] OR distance counsel*[tiab] OR
18	ediagnos*[tiab] OR e-diagnos[tiab] OR
19	telenursing[tiab] OR tele-nursing[tiab] OR
20	telerehabilitation[tiab] OR tele-rehabilitation[tiab] OR
21	telecare*[tiab] OR tele-care*[tiab] OR
22	telemonitor*[tiab] OR tele-monitor*[tiab] OR remote monitor*[tiab] OR
23	app[tiab] OR apps[tiab] OR mobile app*[tiab] OR phone app*[tiab] OR telephone app*[tiab] OR health app*[tiab] OR
24	mobile technolog*[tiab] OR digital technolog*[tiab] OR health technolog*[tiab] OR
25	webportal*[tiab] OR digital portal*[tiab] OR online portal*[tiab] OR patient portal*[tiab]
26	digital platform*[tiab] OR online platform*[tiab] OR patient platform*[tiab] OR
27	digital system*[tiab] OR online system*[tiab] OR
28	e-coach*[tiab] OR
29	wearable*[tiab]

CHAPTER 3



3

Telehealth as part of specialized ALS care: feasibility and user-experiences with "ALS home-monitoring and coaching"

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Abstract

Objective. To evaluate the use of telehealth as part of specialized care for patients with amyotrophic lateral sclerosis (ALS) and the user experiences of patients and healthcare professionals.

Methods. 50 patients with ALS were recruited from a single specialist centre and used telehealth, consisting of an ALS-app for self-monitoring and messaging, alerts for symptom-worsening, and nurse practitioner follow-up. Patients self-monitored their well-being (daily-report), body weight (weekly) and functional status (monthly). The use of the telehealth service was evaluated through adoption rate, dropout rate and adherence to self-monitoring. User-experiences were collected through online surveys among 23 patients and 9 healthcare professionals, and interviews with 12 patients.

Results. The adoption rate was 80%, dropout rate 4% and median follow-up was 11 months. Good adherence was seen in 49% of patients for well-being, 83% for body weight and 87% for functional assessment. For patients who discontinued using telehealth due to the end-of-life phase, median time between last measurement and death was 19 days. The majority of patients experienced using telehealth as easy, helpful, not burdensome , and reported satisfaction with flexible clinic visits and the continuity of care. Healthcare professionals reported that telehealth was of added value in ALS-care.

Conclusions. ALS-care supplemented by home-monitoring and nurse practitioner follow-up was shown to be suitable and widely accepted by patients and healthcare professionals in our ALS clinic. Success factors were low self-monitoring burden, a user-friendly platform and the provision of personalised feedback. Further research is needed to replicate these findings in other ALS clinics.

Key words: amyotrophic lateral sclerosis, telehealth, self-monitoring, app, user-experiences

Introduction

A multidisciplinary specialist team approach in the management of Amyotrophic Lateral Sclerosis (ALS) is the gold standard of care, aimed at improving quality of life and survival through symptom management[1]. Currently, however, patients experience considerable barriers and burden related to multidisciplinary clinic (MDC) attendance, every three to four months. Travel barriers, such as long distances and limited mobility, and long exhausting clinic days due to seeing multiple healthcare professionals, have been reported as disadvantages of MDC attendance[2,3].

A possible solution for these issues is the use of telehealth. Telehealth has the potential to supplement in-person specialist care by allowing patients with ALS to be monitored and receive personalised advice and information in the comfort of their own home through telecommunication technologies. In contrast to in-person specialist care, access to telehealth is independent of patients' ability to travel or distance from a MDC. In addition, telehealth facilitates remote monitoring of patients between clinic visits, which is currently lacking in ALS care. The remote monitoring of disease progression could help the multidisciplinary care team to tailor care and information to the ever-changing needs of patients with ALS.

In co-creation with patients, caregivers, healthcare professionals, managers and information technologists, we developed the telehealth service *ALS Home-monitoring and Coaching*. A pilot study (*N*=10) in 2016 confirmed its feasibility[4]. On 1st May 2017, the telehealth service was implemented in specialist care at the ALS clinic of the University Medical Centre Utrecht, the Netherlands, where patients with motor neuron disease receive multidisciplinary care. The telehealth service has been used for over 18 months and patients with ALS were invited to use it as part of their care.

The aim of this study is to evaluate the use of *ALS Home-monitoring and Coaching* in specialist ALS care, and the user experiences from the perspectives of patients and healthcare professionals.

Materials and methods

Study Design, Setting and Population

This prospective single centre cohort study was performed at the specialized ALS clinic in Utrecht. The catchment area was the province of Utrecht, with a maximum travel distance of 50km. All patients with ALS who received multidisciplinary care at the ALS clinic between May 2017 and November 2018 were eligible for inclusion. During a regular visit

to the multidisciplinary clinic, a rehabilitation physician invited patients to use telehealth. Patients who participated were followed-up until 28th November 2018.

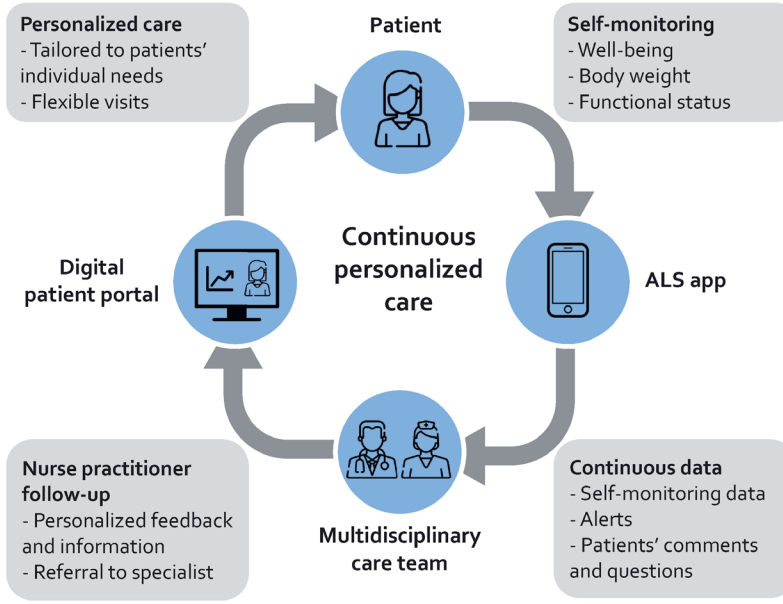

Figure 1. The continuos personalized care design of ALS Home- monitoring and Coaching

The telehealth service

The design process of *ALS Home-monitoring and Coaching* was inspired by the user-centered design approach which aims to truly meet the needs of end-users (patients and healthcare professionals)[5]. Involving patients in the development process resulted in the design of an appropriate self-monitoring protocol and a user-friendly telehealth service. In order to standardise remote monitoring, a protocol was developed based on ALS guidelines and expert opinion from members of the multidisciplinary care team. The protocol specified what information and feedback should be provided to the patient in response to changes in functioning. It also specified the timing of referral to the multidisciplinary care team and what topics the nurse practitioner should discuss with members of the team. The key features of *ALS Home-monitoring and Coaching* were: 1) App-based self-monitoring, 2) a message function, 3) alerts and 4) follow-up by a nurse practitioner. An overview of the key features can be found in Figure 1.

App-based self-monitoring

The ALS app (by Focuscura, The Netherlands) was operational on a smartphone, tablet and personal computer. Patients were offered a tablet when they had no electronic device compatible with the ALS app. When patients had upper limb impairment, (informal)

caregivers assisted with operating the smartphone/tablet and self-monitoring. Patients were able to use eye-control when using a computer for self-monitoring. During an introductory interview, the nurse practitioner created an account for patients and helped them install the ALS app. Patients used the ALS app to self-monitor their health status, through the assessment of well-being, body weight and functional status. Well-being was assessed by answering the question 'How are you today?' with a score from 1 to 10. Additionally, patients were invited to comment on their score and well-being in the ALS app through a free-text entry. Body weight was assessed with a regular or Bluetooth body weight scale. All patients were offered a Bluetooth scale, but patients were allowed to use their own scale. The Bluetooth scale transmitted the body weight data automatically to the ALS app, while patients with a regular scale had to enter the data manually. Functional status was assessed with a self-administration version of the revised ALS functional rating scale (ALSFRS-R).[6] The default self-monitoring frequencies were daily for well-being, weekly for body weight and monthly for functional status. At the start of monitoring, frequencies were set at default, but could be adjusted to patients' preference. To remind patients about self-monitoring, a notification was automatically sent by email at an agreed-upon time and day of the week. Patients had open access to their own data, which was accessible in the ALS app. Once a measurement had been completed, the data were transmitted automatically to a central server, also accessible to healthcare professionals. Additionally, the ALS app was integrated in the electronic health records, which facilitated data accessibility for the multidisciplinary care team.

Message function

The ALS app included a free-text message function, which allowed for patients to comment on or ask questions about any topic including: symptoms, treatments, aids, personal issues, technical issues or consultation planning. Depending on the question or comment, the nurse practitioner answered the questions and gave advice within three days, and if needed referred patients to the multidisciplinary care team. Patients were informed about a possible delay in the reply and in case of urgency they were told to contact their general practitioner

Alerts

Alerts signalled the nurse practitioner when a significant change in health status occurred involving a drop to (or below) a pre-determined threshold. Alerts were generated when 1) body weight had decreased by 5% and 10% of premorbid weight, 2) the well-being question was answered with a score of two or lower and 3) any item score of the ALSFRS-R dropped one point or more relative to the last measurement. The nurse practitioner monitored the individual alerts and trends of all patients and discussed the changes in health status weekly with the multidisciplinary care team.

Monthly follow-up by nurse practitioner

In addition to the follow-up on patient's messages, the nurse practitioner, who was engaged with all patients, evaluated their individual health status data and provided monthly personalised feedback and information via an e-consult or telephone consultation. Patients could access the e-consult in their electronic medical record, through a web portal login with two factor authentication (digital identification: the online ID allowing access to services and government websites in the Netherlands, with username, password and short message service (SMS) verification). The nurse practitioner was supervised by a rehabilitation physician and used the standardised monitoring protocol to ensure adequate personalised feedback and information for all patients. If necessary, patients were referred by the nurse practitioner to members of the multidisciplinary care team for a face-to-face consultation.

Outcome measures for the use of the ALS app

The use of the ALS app was evaluated through the adoption rate, adherence, and dropout. Adoption rate was calculated as the proportion of patients who chose to adopt telehealth. Adherence was defined as the percentage of completed self-monitoring assessments agreed upon. Adherence was calculated for patients who had activated their account for ≥1 month for well-being and body weight, and for ≥2 months for functional status. The dropout was defined as the number of patients who discontinued telehealth due to reasons unrelated to the end-of-life phase or death.

User-experience assessment

Surveys

Patients. Patients whose account was activated for over four months were invited to fill in a one-time online survey designed for the purpose of the study. Patients received an email with a link to the survey that was accessible on a secure survey website (Collector 2015.Q2). Data were stored on the web-server of the website. The survey evaluated user experiences, such as ease of use, perceived burden, and perceived benefits. Patients were asked to respond to a number of statements and questions on a 5-point Likert scale. Scores of 4 or higher were coded as being in agreement.

Healthcare professionals. A one-time online survey was administered to all members of the multidisciplinary care team at the UMCU. Healthcare professionals received an email with a link to the survey that was accessible on a secure survey website (Collector 2015. Q2). The survey evaluated the extent to which the self-monitoring data were used by the healthcare professionals and whether the use of telehealth led to changes in care.

Semi-structured interviews

Semi-structured interviews were conducted by two of the investigators (JH, RvE) to further explore opinions and experiences of patients regarding the use of telehealth. Consecutive patients who completed the survey were selected. The interviews were discontinued when data saturation was reached.

Analysis

Two groups of patients were distinguished: prevalent and incident patients. Prevalent patients included those who were diagnosed and received multidisciplinary care at the ALS clinic before the implementation of telehealth on 1st May 2017 (including patients who participated in the pilot). The prevalent group was a convenience sample, as these patients were selected by the rehabilitation physician based on health status, disease progression and potential benefits of telehealth use. Incident patients included all consecutive patients who were diagnosed and started to receive multidisciplinary care at the ALS clinic after the implementation of telehealth. In order to avoid selection bias, the adoption rate was only calculated for the sub-group of incident patients.

Table 1 Patient characteristics [a]Level of education was classified as low (none, grade school, high school and technical or trade school) and high (University degree or Graduate school). ALSFRS-R = ALS Functional Rating Scale Revised. SD = Standard deviation. IQR = interquartile range.

Characteristic	All patients (N=50)	N	Prevalent patients (N=18)	N	Incident patients (N=32)	N
Gender, male *n(%)*	32 (64,0)	50	11 (61.1)	18	21 (65.6)	32
Age (years), *mean(SD)*	61.4 (13.0)	50	56.3 (15.1)	18	64.2 (11.0)	32
Level of education[a], *n(%)*		34		16		18
- Low	16 (47.1)		9 (56.3)		7 (38.9)	
- High	18 (52.9)		7 (43.8)		11 (61.1)	
Diagnosis, *n(%)*		50		18		32
- ALS	38 (76.0)		11 (61.1)		27 (84.4)	
- PMA	12 (24.0)		7 (38.9)		5 (15.6)	
Site of onset, *n(%)*		46		17		29
- Bulbar	13 (28.3)		3 (17.6)		10 (34.5)	
- Spinal	33 (71.7)		14 (82.4)		19 (65.5)	
ALSFRS-R at diagnosis, *mean(SD)*	42.0 (3.7)	43	42.9 (2.6)	14	41.6 (4.1)	29
ALSFRS-R at start monitoring, *mean(SD)*	38.3 (8.1)	48	33.8 (9.1)	18	41.0 (6.1)	30
Time between diagnosis and start monitoring (months), *median(IQR)*	2.4 (1.4-14.3)	48	19.7 (10.6-44.5)	18	1.6 (1.3-2.4)	30

Self-monitoring adherence was calculated for all patients and reported as the percentage of patients that showed good adherence. The adherence of an assessment was judged as good when patients completed ≥50% of agreed-upon measurements for well-being and body weight and ≥75% for functional status. A minimal adherence of 50% was considered to be sufficient for patients to reflect on their well-being and for healthcare professionals to observe a trend in body weight between clinic visits. Body weight adherence was calculated until patients were unable to weigh themselves due to the inability to stand (ALSFRS-R item 8 score=0). A minimal adherence of 75% for the assessment of functional status was required, as the ALSFRS-R was only measured once per month and the provision of tailored feedback and information was mainly based on ALSFRS-R scores.

The survey results were reported as the number and percentage of subjects who (totally) agreed to a statement. Data from the structured interviews were digitally recorded and transcribed verbatim. The interviews were coded by two independent researchers. Thematic analysis was performed until data saturation was reached and no more themes emerged.[7]

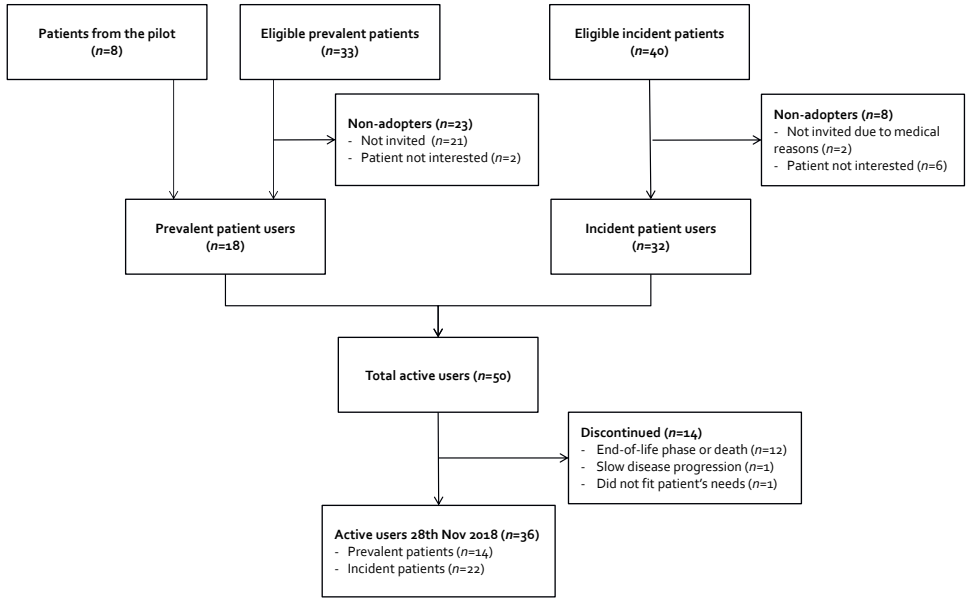

Figure 2. Flowchart of users of ALS Home-monitoring and Coaching

Results

In the period 1st May 2017 to 28th November 2018, a total of 50 patients used *ALS Home-monitoring and Coaching*, consisting of 18 prevalent and 32 incident patients. The inclusion flowchart can be found in figure 2. A total of 41 prevalent patients received care before the

implementation of the telehealth service, 8 of which were already enrolled in the pilot, 21 of which were not invited (reasons not documented), 12 were invited of which 10 adopted telehealth. 40 newly diagnosed incident patients were referred to the multidisciplinary care team and were invited to use telehealth between May 2017 and November 2018; of these 32 (80%) adopted telehealth. A total of 14 patients discontinued using telehealth in the follow-up period. The most frequently reported reason for discontinuing telehealth was no added benefit from telehealth due to the end-of-life phase or death (*n*=12). For patients who discontinued telehealth in the end-of-life phase, median time between the final measurement and death was 19.0 days (IQR=7.8-49.0). There were two dropouts in this study. Reasons for dropping out were no perceived use due to slow disease progression (*n*=1) and telehealth did not fit patient's needs (*n*=1).

Patients were, on average, 61 years old at diagnosis, mostly male (64%), diagnosed with ALS (76%), and had spinal onset (72%). See table 1 for an overview of all patient characteristics. 4 patients had an electronic device that was not compatible with the ALS app and therefore received a tablet for self-monitoring, all other patients had compatible devices. 6 patients received a Bluetooth scale, all other patients preferred using their own scale. Patients were followed-up for a median of 10.8 months (IQR=5.9-13.2)(Figure 3).

Adherence and user-data

Good adherence was seen in 49% of patients for the assessment of well-being, in 83% for the assessment of body weight and in 87% for the assessment of functional status.

Table 2 Patient survey results

Survey item	n (%)	Total (N=23)
I experience the use of telehealth as easy.	19 (83)	23
I experience the use of telehealth as burdensome.	3 (13)	23
I experience the use of telehealth as time consuming.	2 (9)	23
I experience the use of telehealth as helpful in care.	19 (83)	23
I succeeded in logging onto my electronic patient record and reading the personal feedback and information in the e-consult.	20 (87)	23
I experience logging onto the electronic patient record as easy.	11 (55)	20
I experience receiving information through the electronic patient record as positive.	18 (90)	20
I experience receiving personalized feedback as positive.	19 (95)	20
Inserting and seeing data about how I am functioning was a positive experience.	17 (74)	23
I experience more control over care.	20 (87)	23
Telehealth helps me to make decisions about care.	13 (59)	22
I believe that care with telehealth is better than care without it.	18 (82)	22
I intend to keep using telehealth.	22 (96)	23
I would recommend telehealth to other patients.	22 (96)	23

A total of 2003 messages were sent to the nurse practitioner via the ALS app by 47 patients (M=42.6, range=3-268). Most of the messages were comments explaining the given well-being score. 241 well-being alerts were generated in

17 patients (M=14.2, range=1-44), 395 body weight alerts were generated in 31 patients (M=12.7, range=1-39) and 263 functional status alerts were generated in 47 patients (M=5.6, range=1-14).

Table 3 Healthcare professional survey results.

Survey question	Responses		
	Regularly	Sometimes	(Almost) never
How often do you use the well-being data to prepare for consultations?	4/9	3/9	2/9
How often do you use the body weight data to prepare for consultations?	6/9	0/9	3/9
How often do you use the functional status data to prepare for consultations?	6/9	1/9	2/9
How often do you have a consultation due to a referral by the nurse practitioner?	7/9	2/9	0/9

Survey statement	Responses		
	(Totally) agree	Neutral	(Totally) disagree
The use of telehealth reduces the workload of healthcare professionals.	2/9	5/9	2/9
Telehealth is of added value to usual ALS care.	9/9	0/9	0/9
I would recommend the use of telehealth to other healthcare professionals.	9/9	0/9	0/9

User-experiences

Patient survey

In total 23 out of 34 patients who were invited, completed the survey (response rate 68%); 17 of whom were men and with an average age of 63.2 years. Patients completed the survey after using telehealth for a median duration of 5.8 months (IQR=4.7-10.9). The majority of patients were positive about receiving personalised feedback and information, and perceived the use of telehealth as helpful, easy and not burdensome. All but one patient would recommend the use of *ALS Home-monitoring and Coaching* to others. Patients had mixed opinions on the ease of logging onto their electronic medical record with their

digital ID to access the monthly feedback through the e-consult. All patient survey results can be found in Table 2.

Healthcare professional survey

The healthcare professional survey was administered 18 months after the implementation of telehealth and was completed by 9 of 11 (82%) healthcare professionals of the multidisciplinary care team (two rehabilitation physicians, two occupational therapists, two physical therapists, a speech therapist, a dietician and a social worker). The survey showed that the majority of healthcare professionals used the monitored data to prepare for consultations (Table 3). Healthcare professionals reported that they had consultations as a result of referral by the nurse practitioner.

Workload was similar compared to care without telehealth for most healthcare professionals, but in-person consultations were used more effectively, as the available monitoring data helped them in preparing the consultation . Furthermore, all healthcare professionals reported that the use of telehealth was of added value in ALS care and that they would recommend it to other healthcare professionals.

Structured patient interviews

The interviews showed negative as well as positive experiences. Themes related to negative experiences were log on issues and being confronted by decreasing ALSFRS-R scores. Themes related to positive experiences were the user-friendliness of the ALS app, the low burden of the self-monitoring protocol, better understanding of the disease, increased perceived control over care, greater continuity of care and reassurance, more flexible consultations and moments for self-reflection. Identified themes are presented in Table 4.

Table 4 Overview of themes regarding patients' experiences with telehealth, supported by quotes.

Topic	Theme	Description	Quotes
Negative experiences	Log-in issues	Some of the patients experienced logging into the electronic patient record with their digital ID as a barrier for reading the feedback in their e-consultations. Most patients, however, did not perceive this as a barrier.	*"A hassle with the digital ID, it takes four steps before you find out what it's about."* Patient 2 *"Logging in is difficult with the digital ID."* Patient 10
	Confronting experiences	Self-monitoring of health status and specifically the functional status assessment, was experienced as confronting by some of the patients in the early disease stages. This was due to the answer options of the ALSFRS-R showing the worsening of the disease yet to come. However, over time patients got used to the idea and no longer experienced it as confronting. Furthermore, patients generally had no interest in the graphs and the decline their data showed.	*"At the start it was a bit confrontational. You see things and think: 'is that what is going to happen?'. On the other hand, you get used to it the more often you do it."* Patient 1 *"It is like a falling stock market, you are simply not happy about it. I understand that it is great for science, but it is useless for the patient."* Patient 6
Positive experiences	User-friendliness	In general patients were very satisfied with the ALS app, because it was easy to use and worked well. Some patients did have some minor technical complaints (notifications did not repeat, app-screen did not rotate with phone).	*"Very user-friendly. Nothing to comment on. Graphs look clean, well laid out."* Patient 1
	Low burden	The majority of patients reported that self-monitoring cost very little time and was not burdensome. Patients felt that they got much more in return compared to the amount of time and effort that was required.	*"It is so easy… a daily routine. More of a burden, but you get more in return. On balance, the end result is always positive; despite requiring something from me, I have the feeling that I get a lot more out of it than if I did not do it."* Patient 1
	Self-reflection	A benefit of self-monitoring reported by patients was that it helped them reflect on their mood and feelings.	*"The greatest advantage is that you become aware of how you are doing, and that's good. When I am aware that I am feeling really good or even slightly worse, those are the moments I use the app."* Patient 2 *"Actually choosing a fixed moment of the day to reflect on that day. How am I feeling and why? Because you don't always know what the cause is and this makes you think about it. A moment of reflection."* Patient 12

	Increased perceived control	Patients experienced more control over their healthcare due to telehealth. Patients reported that the use of telehealth facilitated communication with the ALS care team, which helped them to better indicate which topics they wanted to discuss or focus on.	*"I think that by monitoring myself, I am able to give others more information to make decisions about me. I am in control and can enable others to observe me better."* Patient 1 *"It is an easy way for me to pass things on to the physician. I tell them what the problem is and the hospital indicates what is useful. So I am in control without having to possess the knowledge. I just want advice. This makes it more problem-driven and up-to-date. And I like that."* Patient 10
	Continuity of care/ reassurance	At home, patients experienced the feeling of being monitored continuously by the ALS care team in between visits, which felt personal and reassuring. Patients also found it a comforting thought to know that the ALS care team would intervene when the disease would worsen.	*"You really have the feeling that there is continuous interaction, that someone is keeping an eye on you. You are no longer counting the days from one consultation to another."* Patient 2 *"That's what I find ideal. We will not be going again in three months' time, because if the app shows in a month that I am not doing well, the hospital takes the initiative. I have experienced this and I like it. This means I do not have to wonder 'should I call the physician?', because if the physician is worried they will call me. Now that's what I call service."* Patient 10 *"I notice that the measurements are being read and that the care team knows how I am doing from day to day."* Patient 11
	Flexible consultations	Continuous monitoring allowed for more flexible consultations, which patients were highly satisfied about. Patients liked that it reduced the amount of unnecessary visits and travel burden.	*"My last appointment was 6 months ago, i.e. the routine visit. I find that smart, because if it is not necessary, then it is not necessary."* Patient 1 *"For now we have agreed with the physician not to plan a new appointment but to do that on the basis of the app. If no tests are necessary, there is no point, it is only an extra burden."* Patient 7 *"You don't feel you are going for no good reason. You have some control over that."* Patient 12

Discussion

This study showed that the use of home-monitoring and nurse practitioner follow-up was suitable for the provision of multidisciplinary ALS care, with a high adoption rate, good adherence, few dropouts and positive experiences from patients and healthcare professionals. This is the first study to report on the use of an implemented app-based telehealth service with self-monitoring in specialized ALS care.

The majority of newly diagnosed patients in the current study adopted telehealth, showing that patients with ALS were willing to use technology in their care. Previous research has shown that patients with ALS are generally familiar with using technology.[8–11] Patients who did not adopt telehealth were, on average, older and the majority were female.

Patients showed good overall adherence to the self-monitoring protocol. Facilitators of self-monitoring adherence in the current study were a user-friendly app, low burden of self-monitoring and use of notifications. These factors have also been identified as facilitators of self-monitoring in previous literature.[12] Another facilitator of adherence was the provision of monthly personalised feedback on the self-monitoring data.[12] This likely motivated patients to adhere to the self-monitoring protocol. Furthermore, most healthcare professionals used the monitored data during regular in-clinic consultations. Other factors that motivated patients were a feeling of control they gained through self-monitoring, as well as more flexible clinic visits tailored to their needs. A barrier to telehealth use was difficulty accessing the e-consult. Providing personalised feedback in the ALS app could facilitate accessibility in the future.

In contrast to the current study, Paneroni et al. [13] reported low adherence to a self-monitoring protocol. This was likely a result of the complexity of reporting and the high number of daily assessments in this study. In two other studies good adherence with (bi-) weekly home-based self-monitoring was observed.[14,15] Accordingly, patients reported that technology was user-friendly and self-monitoring was easy.[15,16]

Although we found good overall adherence in the current study, it was noticeable that adherence to the well-being assessment was low compared to the adherence to the bodyweight and functional status assessments. Low adherence was likely due to the fact that the default frequency with daily assessments was too high for some of the patients. For this reason, self-monitoring frequencies were lowered at individual patients' request. The requested changes in frequency were, however, not taken into account in the calculation of adherence as these were not documented in the ALS app. The missing information resulted in an underestimation of adherence. Despite the lower adherence of the well-being assessment, 85% of patients completed the well-being assessment at least

once per week. This was found to be sufficient for the provision of psychological support and for patients to self-reflect on their well-being.

A remarkable finding was that patients continued to use the ALS app to contact the ALS clinic and read the personal feedback from the nurse practitioner until shortly before their death. These findings suggest that patients valued communication with the nurse practitioner in the end-of-life phase, despite the fact that care in the end-of-life phase is on the whole provided by a general practitioner. Accordingly, the interviews showed that patients experienced more continuity of care and a feeling of reassurance as a result of remote monitoring by the nurse practitioner.

An important aspect of remote monitoring was alerts for disease worsening, which were found to be appropriate for the provision of feedback and information in most cases. However, for the well-being assessment repetitive alerts were seen in two patients who gave low scores consecutively. These patients were called by the nurse practitioner and received psychological support. Repetitive alerts were also generated in some patients for the body weight assessment, as these patients remained stable in body weight below the cut-off value. The nurse practitioner did not perceive these repetitive alerts as a burden. The alerts that were generated for every drop of the ALSFRS-R score were found to be abundant, as the nurse practitioner would provide monthly feedback three days after patients completed the ALSFRS-R, regardless of any changes in score. For this reason, we have removed all alerts for the functional status assessment.

So far, previous research on the use of telehealth in ALS has reported on home-based self-monitoring, videoconferencing, the store and forward method, and remote monitoring of non-invasive ventilation.[17] A parallel publication reported on the use of a telehealth system similar to *ALS Home-monitoring and Coaching,* which also included a patient app for self-monitoring, a clinical portal, alerts and a telehealth nurse.[15,18] In this trial patients and caregivers reported that telehealth was easy to use, self-monitoring did not cost a lot of time and they would recommend telehealth to others. These findings are similar to the results of the current study, and support that app-based self-monitoring is a suitable method for providing remote care to patients with ALS.

Currently, the platform costs associated with the telehealth service are funded by the University Medical Centre Utrecht as there is no reimbursement for this type of telehealth. The lack of reimbursement is the main barrier to widespread implementation and use of telehealth. In order to facilitate the future implementation and use of telehealth, healthcare insurance companies should include telehealth in their reimbursement options.

Limitations

The current study was conducted in a single specialized centre, which limits the generalizability of the results and the transferability to other settings. We are, however, working on the nationwide implementation of *ALS Home-monitoring and Coaching,* which will allow us to evaluate its feasibility in other healthcare settings and generalize future findings. The results obtained from the prevalent patients may suffer from selection bias, as this was a convenience sample. Furthermore the response rate of the patient survey was relatively low, which could mean the results of the survey may have a risk-of-bias. A methodological and technical limitation was that requested changes in self-monitoring frequency were not documented in the ALS app software. As a result, the missing data lead to an underestimation of adherence. In the current study we chose to exclude the assessment of caregiver user-experiences. However, caregivers play an important role in assisting patients with the use of telehealth, for this reason this is an interesting topic for future research. Future studies should also investigate the cost-effectiveness of *ALS Home-monitoring and Coaching,* its feasibility in other healthcare settings, and the effect of personalised care on the timing of therapies and assistive devices.

Conclusion

In conclusion, we have shown that ALS care supplemented by app-based self-monitoring and nurse practitioner follow-up was suitable and widely accepted by patients and healthcare professionals. Success factors of the telehealth service were low self-monitoring burden, a user-friendly platform and the provision of personalised feedback. A potential barrier for widespread implementation of this telehealth service, is the lack of reimbursement. Future research should investigate the cost-effectiveness and the feasibility of this telehealth service in other healthcare settings.

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CHAPTER 4

4

Patient perspectives on digital healthcare technology in care and clinical trials for motor neuron disease: An international survey

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Abstract

Objectives. To capture the patient's attitude toward remote monitoring of motor neuron disease (MND) in care and clinical trials, and their concerns and preferences regarding the use of digital technology.

Methods. We performed an international multi-centre survey study in three MND clinics in The Netherlands, the United Kingdom and Australia. The survey was co-developed by investigators and eight patients with MND. The main topics included: patients' attitude towards receiving remote care, frequency of monitoring and use of devices, participating in decentralized clinical trials, and their preferences for and concerns with digital technology. Patients were invited either by e-mail or postal mail to participate in the study.

Results. In total, 332 patients with MND participated, of which 200 from The Netherlands, 91 from the United Kingdom and 41 from Australia. A majority of patients indicated they would be happy to self-monitor their health from home (69%), be remotely monitored by a multidisciplinary care team (75%), and would be willing to participate in clinical trials from home (65%). Patients considered respiratory function and muscle strength to be most valuable for home-monitoring. The majority of patients considered the use of at least 3 devices/apps (75%) and a at least a weekly frequency (61%) to be acceptable for home-monitoring. In contrast, 15% of patients indicated they would not wish to perform home-measurements; this subgroup was more concerned about the burden of conducting the measurements, distress due to self-monitoring of disease progression, privacy and data security.

Conclusion. Most patients with MND surveyed exhibited a positive attitude towards the use of digital technology in both care and clinical trial settings. A subgroup of patients described a number of concerns that unless addressed risk being barriers to universal adoption. Addressing these barriers early in the design and implementation of remote digital technology with a user centred design approach will reduce the risk of technology exclusion.

Keywords: motor neuron disease, amyotrophic lateral sclerosis, digital technology, survey, patient perspective

Introduction

Patients suffering from motor neuron disease (MND) experience progressive muscle weakness due to the deterioration of motor neurons, limiting their ability to communicate and perform daily tasks (1,2). Besides physical impairments, about half of patients may also develop cognitive impairment, such as frontotemporal dementia (3). Eventually the disease leads to death on average in 2 to 4 years as a result of respiratory failure(1,2). The rate of disease progression, and the occurrence and severity of symptoms, varies greatly among patients. Therefore, a flexible approach towards management is required such that the patient's clinical condition is monitored at intervals that best reflect both the needs of the patient, and the trajectory of their disease. Moreover, despite the added value of attending, visits to a multidisciplinary clinic may be perceived by patients as excessively time-consuming, and can be challenging for caregivers, especially when patients experience severe physical disabilities (4,5).

Remote digital technologies have the potential to reduce the burden, and improve the accessibility and personalization of care and clinical trials, by enabling tailored collection of disease-related outcomes from home, and facilitating communication between patients and healthcare professionals (6,7). In addition, remote digital technologies can accelerate the search to find effective treatment (8–13). Despite these clear benefits, the real-world use of remote digital technology in MND has been limited, for a large part due to financial barriers (6,14). However, since the COVID-19 pandemic, there has been an increase in the adoption of policies that allow for billing and reimbursement for telehealth, together with an increase in the use of telehealth in MND care (15–23).

To further facilitate the wide-scale adoption and utilization of digital healthcare technologies in MND care and clinical trials, a road map has been recently published(24). One of the main objectives of the road map is to find a set of reliable digital outcome measures that can be captured by patients with MND from home, through a user-centered co-design approach. This approach includes the involvement of end-users (e.g. patients), throughout the process, so that an innovation fits the needs of end-users (25). To date, there is limited information available regarding patient preferences for digital technology. Understanding the user perspective is essential to achieve long-term adherence and adoption in the community. In this international multi-centre study, therefore, we aim to capture patients' attitudes toward remote MND care and monitoring from home, together with their preferences and concerns about digital technology, and evaluate differences in patients' perspectives between countries.

Methods

Study design, population and setting

This cross-sectional, multi-center survey study aimed to include patients aged 18 and over with a diagnosis within the spectrum of motor neuron disease including Amyotrophic Lateral Sclerosis (ALS), Primary Lateral Sclerosis (PLS) and Progressive Muscular Atrophy (PMA), at all stages of disease and irrespective of cognitive impairment. There were no exclusion criteria. Ethics approval was obtained from the local ethics committee prior to the start of the study, and patients provided either written or digital informed consent before participating. All survey data was collected between November 2020 and November 2021. The present study was conducted by multidisciplinary MND clinics in Utrecht, The Netherlands; Sheffield United, Kingdom (UK); and Brisbane, Australia.

The survey

The survey was developed in English and Dutch by investigators from the participating clinics, in collaboration with eight patients with MND. The main topics included: patients' preferences for and concerns with performing measurements at home, and patients' attitude towards receiving care remotely and participating in decentralized clinical trials. Additional topics included the current use of digital technology in daily life and healthcare. Patients answered options on a 5-point Likert scale ranging from 'Totally disagree' to 'Totally agree', and from 'Not valuable at all' to 'Very valuable'. For questions regarding the technology used in care, multiple answers could be selected from a list of technologies, or patients could report a technology that was not on the list by selecting 'other'. One question provided a list of seven outcome measures for home-monitoring, of which patients had to rank a top three of the most valuable outcome measures. Furthermore, patients could indicate their preferred maximal number (from '0' to '7') and frequency (from 'Daily' to 'Quarterly or less') of home assessments. The complete survey is provided in Appendix 1.

Patient recruitment and procedures

For the Netherlands, the national ALS registry was used. A subset of 375 patients who had given prior informed consent to be approached for future research were invited to participate. Patients received an invitation to participate either via e-mail or post, depending on whether an email address was available in the database. The e-mail included a link to an online platform (EDC Castor) with access to the patient information sheet, consent form, and survey. The same documents on paper, together with a postage paid envelope were sent by post to those who did not have an email address available. A reminder was sent by e-mail four weeks later to those who had not replied. Those who had not opened the email within four weeks, received the survey by post. In the UK, 221 patients who attended the Sheffield MND clinic were invited to participate, which included both patients living in Sheffield and the surrounding counties, as well as out of area patients who attended the Sheffield

MND clinic for a second opinion or participation in clinical trials. Patients were invited to participate by postal mail and received a patient information sheet, consent form, a postage paid envelope and the survey. A reminder was sent after one month to those who had not replied. In Australia, a subset of 151 patients from Queensland, Victoria or Western Australia, who were listed in a national MND registry and previously consented to be contacted for future research were invited to participate. National calls for research participation were also distributed by social media by the Motor Neurone Disease Research Australia and FightMND foundations. Patients were sent an e-mail outlining the project; information included a patient information sheet and consent form, and instructions on how to contact study personnel. Upon completion of the consent form, patients were e-mailed a unique survey token, which provided access to the survey using an online platform (LimeSurvey). Reminder emails were sent to all consenting participants one months after consent, for patients that did not complete the survey.

Statistical analysis

For statistical analysis, all 5-point Likert scales were converted to a 3-point scale (Disagree (1-2), Neutral (3) and Agree (4-5); Not valuable (1-2), Neutral (3) and Valuable (4-5)), and reported as the percentage of patients that selected the response. A chi-square test was used to assess differences in item responses and other nominal variables between the three countries, and the one-way ANOVA was used to assess differences in continuous variables. Multinomial regression was used to assess whether survey items were related to covariates, i.e., age (younger adults <65 years; older adults ≥65 years), sex (male; female) and site of disease onset (spinal; bulbar). One item required respondents to rank three of the seven proposed home measures for home-monitoring from most valuable to least valuable. Rank 1 received a score of 3, rank 2 a score of 2 and rank 3 a score of 1; measures not listed in the top 3 received a score of 0. The total rank score of each home measure was subsequently calculated by taking the sum of the rank scores, and were divided by the maximal possible score (all patients ranked a measure as 1st), resulting in a score between 0 and 1. For the comparisons between countries, the total rank scores of each home measure per country were normalized by dividing them by the highest possible score of that country.

Table 1. Patient characteristics at enrolment. Data are given in mean (SD) or n (%). [a] Data are median (25th – 75th percentile), *† Significantly different (p<0.05), ** p-value tests whether the three countries are similar of different from each other.

Characteristic	The Netherlands *(N = 200)*	United Kingdom *(N = 91)*	Australia *(N = 41)*	*p*-value **
Sex, *male (%)*	135 (68.2)	55 (61.1)	29 (70.7)	0.42
Age at enrolment, *years*	63.4 (10.2)*	66.8 (10.2)*	64.8 (7.8)	0.029
Diagnosis, *n (%)*				
- ALS	142 (72.1)*	57 (64.8)†	15 (36.6)*†	<0.001

- PMA	35 (17.8)*	13 (14.8)	0 (0)*	0.031
- PLS	20 (10.2)	16 (18.2)	5 (12.2)	0.122
- MND	0 (0)*	2 (2.3)†	21 (51.2)*†	<0.001
Symptom onset, *bulbar (%)*	34 (17.2)	19 (21.3)	4 (12.1)	0.44
Symptom duration,[a] *months*	42.1 (21.7-68.5)*	64.1 (27.1-148.3)*†	44.0 (24.6-77.7)†	<0.001
Diagnostic delay,[a] *months*	13.7 (6.9-29)	17.5 (8.4–29.5)	16.0 (5.3-25.5)	0.51
Method of completing questionnaire, *digitally*	171 (85.5)*	0 (0)*	100 (0)*	<0.001
Current digital technology use, (>1 times per week) *n (%)*				
- Smartphone	169 (85.8)*	67 (79.3)*†	38 (92.7)†	0.017
- Computer/laptop	123 (62.4)*	42 (50.6)*†	32 (78.0)†	0.003
- Tablet	102 (51.8)*	53 (63.2)	31 (75.6)*	0.016
- At least one of the above	188 (95.4)	83 (90.1)	39 (95.1)	0.46
Participated in research including at least one clinic visit, *n (%)*	90 (45.7)*	47 (52.2)†	29 (70.7)*†	0.024

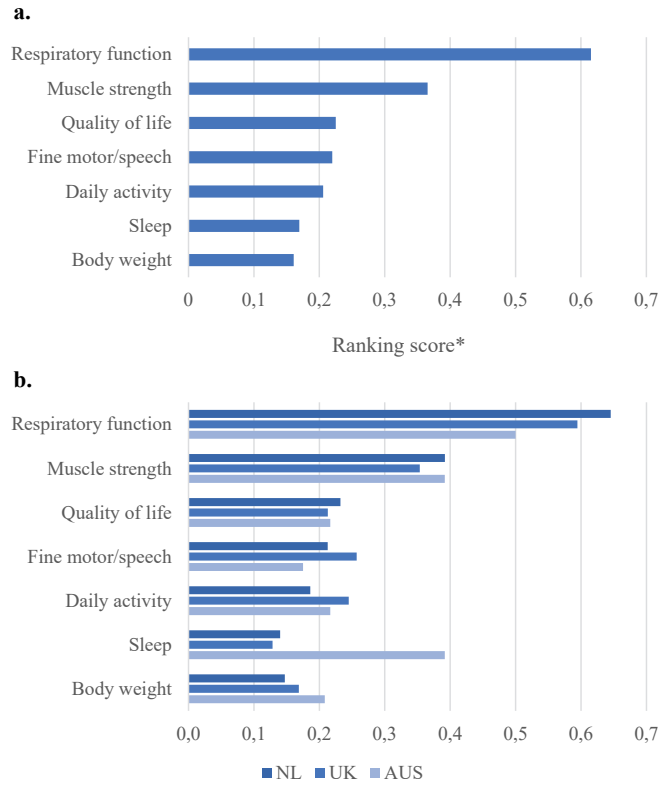

Figure 1 Most valuable outcome measure for home-monitoring according to patients.

NL = The Netherlands, UK = United Kingdom, AUS = Australia. Patients ranked a top 3 out of 7 proposed outcome measures from most valuable to less valuable. 1st place received a score of 3, 2nd place a score of 2, and 3rd a score of 1. *The ranking score is the sum of scores per outcome measure. (a) Ranking scores were normalized by dividing a ranking score by the highest possible ranking score, (b) Ranking scores were normalized per country by dividing a ranking score by the maximal possible ranking score per country.

Results

In total, 332 patients with MND participated in the study; 200 in The Netherlands, 91 in the UK and 41 in Australia. The response rate for those directly contacted was 53.4% for The Netherlands, 41.6% for the UK, 27.1% for Australia; patient characteristics per country are presented in **Table 1**. The overall majority of patients had access to internet (95.6%) and used a digital device (smartphone, computer or tablet) several times per week (93.1%); this was similar across countries (p = 0.46, **Table 1**). Also in healthcare most patients (85.9%) had experience with the use digital technology, such as electronic health records, mobile health apps, wearables, video consultations, email or mobile text messaging. An increase of use of technology in healthcare due to the COVID-19 pandemic was reported by 48.6% of patients. In this subgroup of patients, 75.1% started using video consultations, 30.6% e-mail, 19.1% text messaging and 12.7% a mobile health app to receive care remotely.

Attitude and preferences regarding home-monitoring

The majority of patients liked the idea of monitoring their own health at home (68.9%), although there were differences across the countries (UK=58.8%, The Netherlands=74.0%, Australia=70.7% ; *p*=0.022). Of all patients, 14.6% indicated that they would not wish to perform measurements at home, which was similar across countries (*p*=0.82). Women were more likely to dislike the idea of performing measurements at home, compared to men (20.0% vs 11.6%, *p*=0.021). There were no significant differences in attitude between age groups or patients with a spinal or bulbar disease onset.

The two outcome measures that were considered most valuable for home-monitoring were respiratory function and muscle strength; the ranking of the other measures is presented in Figure 1. Across all countries 74.9% of patients were willing to use 3 or more devices for home-monitoring, and 60.7% of patients were willing to perform home-measurements at least weekly, and 86.1% of patient at least monthly(Figure 2). Men were more likely to choose 3 or more devices for home-monitoring compared to women (80.3 vs 63.5%, *p*=0.044); there were no significant differences in the number of devices or monitoring frequency preferences between genders, age groups or patients with a spinal and bulbar disease onset.

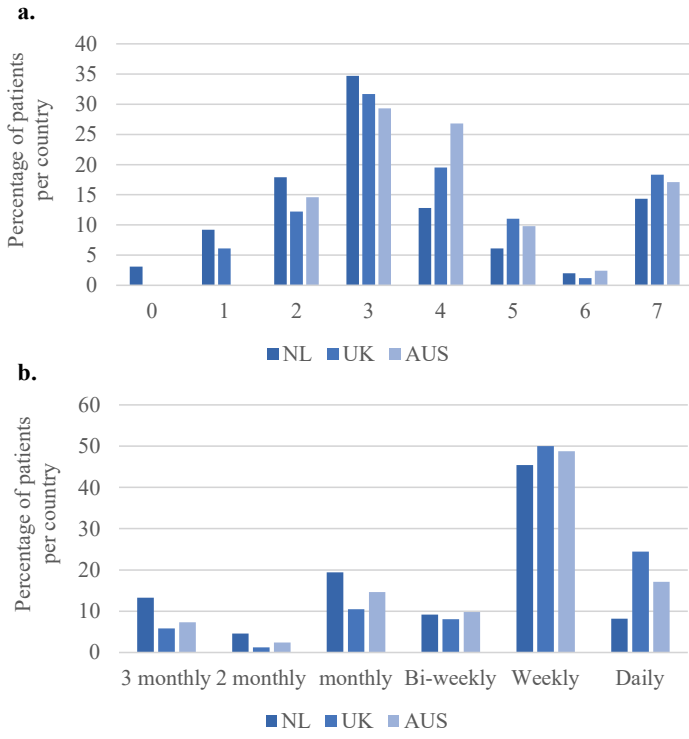

Figure 2 Preferred (a) maximum number of apps/devices and (b) frequency for home-monitoring according to patients. NL = The Netherlands, UK = United Kingdom, AUS = Australia. Figures show the percentage of patients per country who chose (a) a number of apps/devices and (b) frequency for home-monitoring.

Concerns with home-monitoring

Some patients considered that home-monitoring would be too distressing (22.2%), or too burdensome (10.5%), and lead to problems with data security (16.8%), data being sold to third parties (11.0%), and privacy (3.3%)(Figure 3). Differences in concerns between countries were found in 'home-monitoring being too burdensome' between The Netherlands (13%) and Australia (0%, p=0.001), in 'data security' between The Netherlands (6.2%) and the UK (34.1%, p<0.001) and Australia (34.2%, p<0.001), and in 'data being sold to third parties' between the UK (22.2%, p=0.002) and The Netherlands (8%) and Australia (0%)(Figure 3). Patients who would not like home-monitoring reported more concerns, compared to those who were neutral about or would like home-monitoring (Figure 4). Furthermore, older adults (≥65 years) were more likely to think that home-monitoring would be too burdensome compared to younger adults (14.3 vs 6.7%, p=0.012); there were no significant differences in concerns between genders, or between patients with a spinal and bulbar disease onset.

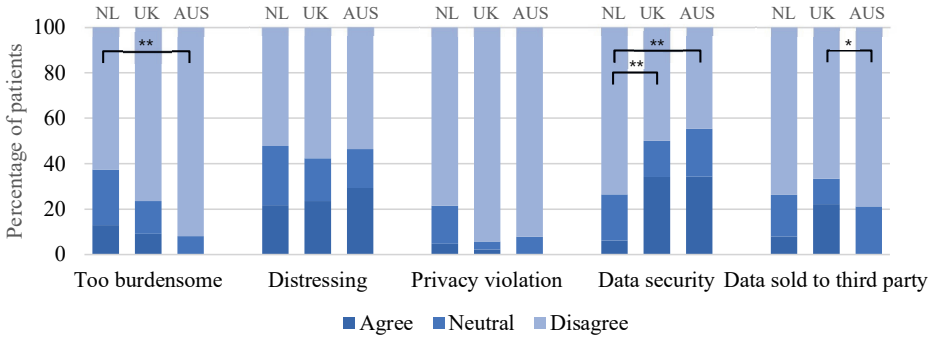

Figure 3 Concerns with home-monitoring per country. NL = The Netherlands, UK = United Kingdom, AUS = Australia, *p<0.05, **p<0.001. Distressing = Feelings of distress due to selfmonitoring of disease progression.

Remote MND healthcare

Most patients (74.5%) would like to be remotely monitored by their multidisciplinary care team; this was similar across countries (p=0.60). 10.1% of patients did not feel the need for remote care, with significantly more patients in The Netherlands (12.3%, p=0.019) and Australia (14.6%, p=0.001) reporting that they do not feel the need for remote care, compared to the UK (5.8%). Older adults were more likely to be reluctant towards remote care, compared to younger adults (13.5 vs 6.7%, p=0.021); there was no difference in reluctance towards remote care between genders or between patients with spinal and bulbar disease onset. The potential benefits of digital healthcare technology use that were valued most by patients were improved communication with the multidisciplinary care team (75.9%) and better insight into their disease course (83.0%).

Remote participation in clinical research and trials

Approximately half of patients (50.6%) had participated in clinical research that required an in-clinic visit. In the other half of patients, the most common reasons for not participating were: (1) not having received an invitation to participate (44.0%), (2) thinking participation would be too burdensome (21.0%) and (3) too long travel distances (19.0%). Out of all respondents, 65.2% liked the idea of participating in clinical trials without visits to the clinic, and 46.2% would participate in clinical trials more often/easily if this could be done remotely (Figure 5). However, 41.0% of patients disliked the idea of participating in a clinical trial without personal contact with a healthcare professional. Respondents mostly valued the potential of digital healthcare technology to make clinical trials shorter (73.2%), and more accessible to a broader group of patients (82.7%).

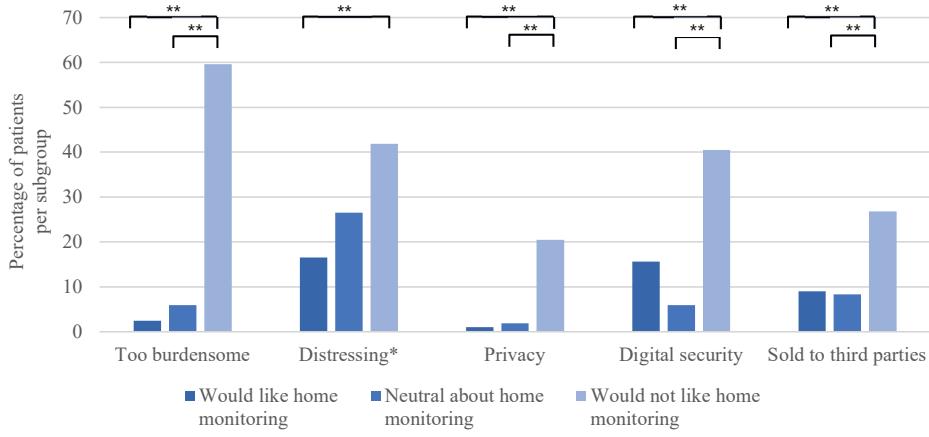

Figure 4 Concerns with home-monitoring based on patients' attitude towards home-monitoring. We distinguished three subgroups: patients who would like home-monitoring (n=221), patients who would not like home-monitoring (n=47), and patients who are neutral about home-monitoring (n=54). *p<0.05, **p<0.001. Distressing = Feelings of distress due to self-monitoring of disease progression.

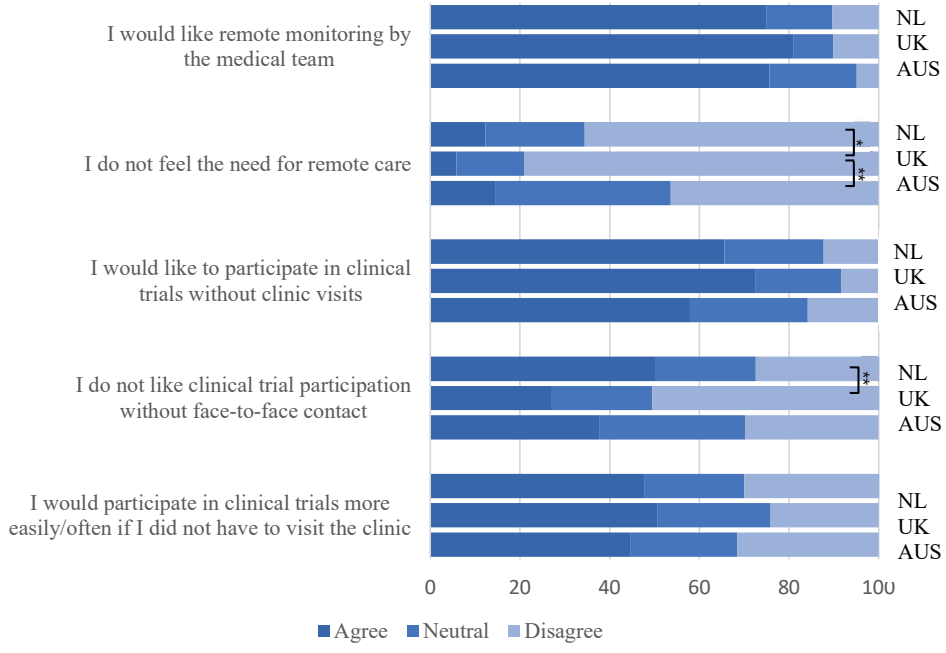

Figure 5 Patients' attitude towards remote healthcare and clinical trials. NL = The Netherlands, UK = United Kingdom, AUS = Australia, *p<0.05, **p<0.001.

Discussion

We have shown that that the majority of patients with MND in The Netherlands, UK and Australia have a positive attitude toward performing MND-related measurements at home, remote monitoring by the multidisciplinary care team, and remote participation in clinical trials. Respiratory function and muscle strength were considered to be the most valuable measures for home-monitoring, and using three to four apps/devices at a weekly frequency was considered acceptable for home-monitoring. Our findings highlight that a subgroup of patients have concerns with the use of digital technology at home. Important concerns that need to be considered are patient burden and distress of being confronted with physical deterioration, and data security or use of data by third-party collaborators.

Previous studies on the use of remote digital technology in MND care have shown that self-monitoring of health-related outcomes and frequent communication with a multidisciplinary care team may improve the patients' understanding of, and control over, the disease, and enhance the continuity of care throughout the course of the disease (7,8,26–28). Moreover, the implementation of remote digital technology in clinical care may facilitate the decentralization of clinical trials and new digital efficacy endpoints may increase a trial's ability to detect treatment benefit and help to accelerate clinical development (10,29,30). Furthermore, our findings indicate that the use of remote digital technology may increase clinical trial enrolment, since a considerable portion of patients is more willing to participate in clinical trials if clinic visits are not, or less frequently, required. Considering the fact that often only a selected subset of patients can participate in clinical trials (31), the use of remote digital technology may also help to include a broader group of patients, such as those who are rapidly progressing or more severely disabled, by reducing the burden of clinical trial participation. In turn, the diversification of trial populations can potentially improve the generalizability of clinical trial results. However, we should be aware of the risk that patients who are compliant with using digital technology at home may be similar to the subset of patients who are already participating in clinical trials (e.g. male, slow disease progression, younger)(32).

Interestingly, the majority of patients had little to no concerns regarding the use of remote digital technology at home, which may be due to the fact that most patients in our cohort were familiar with digital technology use. Feelings of distress due to self-monitoring of disease progression was the biggest concern for patients across countries, together with data security in the UK and Australia. There were some differences between countries in patients' attitude towards the remote provision of care and clinical trial participation without face-to-face contact, which may suggest that a tailored approach is needed when implementing remote digital health technology. A reason for the limited differences between countries could be that the majority of patients in all three cohorts had access

to internet and had experience with digital technology use in daily life and healthcare. A small subgroup of patients, however, was reluctant towards home-monitoring and the remote provision of care, of which the majority expected home-monitoring to be too burdensome. Albeit a minority, women and older adults were more likely to be reluctant towards home-monitoring or the remote provision of care, which corresponds to previous research which found that women and older adults were less positive towards health technology and experienced more barriers with technology use, due to, among others, inexperience and lower self-efficacy with technology (33,34). These findings suggest that it is important to involve patients from various demographics when determining how to measure remote digital health outcomes in care or clinical trials, especially those who are less experienced with digital technology. By doing so, it will enhance familiarity with digital technology among people with lower digital literacy, help to select patient-friendly devices and assessments, and ensure that home monitoring is compliant for a broad group of patients.

Out of all remote digital health outcomes that were proposed in the present study, patients considered respiratory function and muscle strength to be the most valuable. These two outcome measures can provide patients with more insight into their disease (progression), and in turn, help patients to make a decision on when to initiate non-invasive ventilation or start using assistive devices (35). In addition, respiratory function and muscle strength are known to be related to disease progression, functional ability and quality of life in patients with MND (36–40), and are, therefore, important outcomes in both care and clinical trials. So far, direct assessments of muscle strength (e.g. grip strength and leg extension strength), and indirect assessments (e.g. plasma creatinine) have the potential to be used for home monitoring of muscle strength (9,41–43). For the home-monitoring of respiratory function, the assessment of vital capacity, maximal inspiratory pressure and patient-reported symptoms of dyspnea have been proposed in previous studies (44–48). Future studies could focus on how respiratory function, muscle strength and other relevant digital health outcomes can best be utilized at home, with the involvement of patients with MND.

Limitations

Strengths of the present study are the multi-centre design and inclusion of a cohort of patients with MND from different national backgrounds. A limitation is the potential of recruitment bias, since the average response rate was relatively low. In addition, a large portion of patients were recruited digitally, which increases the likelihood of a positive attitude towards digital technology use, or familiarity with technology in daily life. As such, it is likely that we missed patients with lower digital literacy or social economic

status, since these populations experience more difficulties with gaining access to digital health technology, and participation in research [49,51]. Despite this, there were only minor differences between digitally recruited patients and those recruited by postal mail. Nevertheless, it remains important to evaluate strategies to better involve MND populations with lower digital literacy and social economic status, and facilitate their engagement in research.

Conclusion

Patients across three countries report a willingness to use several digital healthcare technologies for frequent home-monitoring, and have a positive attitude towards receiving multidisciplinary care remotely and participating in decentralized clinical trials. Future studies could investigate how remote digital outcomes can be best utilized at home and implemented in MND healthcare and clinical trials, as a collaborative effort between patients and their informal caregivers, healthcare professionals and researchers.

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Appendix 1

The use of digital technology in ALS/MND care and clinical trials

The purpose of this questionnaire is to investigate what people with ALS/MND think of 1) the use of digital technology in care and clinical trials, 2) receiving care remotely, 3) participating in clinical trials remotely and 4) performing health assessments at home.

1. The use of digital technology and internet

The use of digital technology includes the use of e-mail, texting, smartphones, tablets, computers/laptops, mobile apps, wearables and other electronic devices that can measure variables, such as a Fitbit, smartwatch, Bluetooth scale or respiratory function test.

1.1. I have internet access at home.

O Yes O No

1.2. I use a tablet.

O Daily	O Multiple times per week	O Once per week	O Twice per month	O Once per month or less	O Never

1.3. I use a computer/laptop.

O Daily	O Multiple times per week	O Once per week	O Twice per month	O Once per month or less	O Never

1.4. I use a smartphone.

O Daily	O Multiple times per week	O Once per week	O Twice per month	O Once per month or less	O Never

1.5. I use internet (websites).

O Daily	O Multiple times per week	O Once per week	O Twice per month	O Once per month or less	O Never

1.6. I use e-mail.

O Daily	O Multiple times per week	O Once per week	O Twice per month	O Once per month or less	O Never

1.7. Irrespective of your current impairments, do you experience difficulties understanding how to operate any of the above-mentioned technologies? (You may give multiple answers)

☐ Yes, a computer/laptop

☐ Yes, a smartphone

☐ Yes, a tablet
☐ Yes, internet/websites
☐ Yes, e-Mail
☐ Yes, Texting/Whatsapp/iMessage
☐ No/ none

1.8. Which digital technologies have you used in care for communication with a healthcare professional or for assessing your health? (You may give multiple answers)

☐ e-Mail
☐ Text messaging/Whatsapp/iMessage
☐ Wearable (e.g. Smartwatch, Fitbit)
☐ Mobile health app
☐ Electronic health record/ digital patient environment
☐ Video call/ videoconference (e.g. Skype, Zoom)
☐ Other digital technology: _____
☐ None

1.9. Has the use of digital technology in care changed since the start of the COVID-19 pandemic?

O Yes, I use more digital technology
O Yes, I use less digital technology
O No, nothing changed

1.10. Since the start of the COVID-19 pandemic, what digital technology that you did not yet use in care have you started using? (You may give multiple answers)

☐ e-Mail
☐ Text messaging/Whatsapp/iMessage
☐ Wearable (e.g. Smartwatch, Fitbit)
☐ Mobile health app
☐ Electronic health record/ digital patient environment
☐ Video call/ videoconference (e.g. Skype, Zoom)
☐ Other digital technology: _____
☐ None

2. The remote provision of care

2.1. I would like to stay in contact with the medical team from home (in between clinic visits).

O Totally disagree	O Disagree	O Neutral	O Agree	O Totally agree	O No opinion

2.2. I like the idea of the medical team remotely monitoring my health.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

2.3. I like the idea of monitoring my own health.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

2.4. I do not feel the need for receiving care remotely.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

2.5. I find it off-putting to monitor my own health.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

3. Remote participation in clinical trials

3.1. I have participated in a clinical trial for which I had to visit the clinic.

O Yes
O No
O I don't know

3.1.1. If not, what was the reason? (You may give multiple answers)

☐ Too burdensome
☐ No time
☐ No interest
☐ Not invited
☐ Not eligible
☐ No way of transportation
☐ No caregiver
☐ Travel-related costs
☐ Too far
☐ Other

3.2. I like the idea of participating in clinical trials or clinical research from home without clinic visits.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

3.3. I do not like participating in clinical trials or clinical research without face-to-face contact with a healthcare professional.

O Totally disagree	O Disagree	O Neutral	O Agree	O Totally agree	O No opinion

3.4. I would participate in clinical trials or clinical research more easily/often if I did not have to visit the clinic.

O Totally disagree	O Disagree	O Neutral	O Agree	O Totally agree	O No opinion

4. Potential benefits

The use of digital technology for self-monitoring at home can lead to number of changes in care and clinical trials. Please indicate how much you value each change.

4.1. Fewer visits to the clinic.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

4.2. Improved communication with medical team/ investigator.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

Care

4.3. Reduced burden from clinic visits/ long clinic days.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

4.4. Better timing of clinic/ hospital visits.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

4.5. Better timing of interventions and information in care.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

4.6. Better timing of the provision of assistive devices in care.

Do not value	1 O	2 O	3 O	4 O	5 O	Value a lot

4.7. Better insight in my disease course (better preparation for future).

Do not value	1	2	3	4	5	Value a lot
	O	O	O	O	O	

4.8. Better insight in current health status/ functional status.

Do not value	1	2	3	4	5	Value a lot
	O	O	O	O	O	

Clinical trials

4.9. Reduced burden of clinical trial participation.

Do not value	1	2	3	4	5	Value a lot
	O	O	O	O	O	

4.10. Clinical trials become cheaper and faster.

Do not value	1	2	3	4	5	Value a lot
	O	O	O	O	O	

4.11. Clinical trials become accessible for a broader group of patients.

Do not value	1	2	3	4	5	Value a lot
	O	O	O	O	O	

5. What to measure?

There are a number of proposed assessments that patients with ALS/MND could perform at home. Please indicate to what extent you believe the following assessments are valuable. If you are unable to perform one of the following assessments, please indicate how much you would have valued the assessment if you had been able to.

5.1. Respiratory function testing. This measure consists of performing three maximal efforts of in- and expiration using a portable pulmonary device.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.2. Body weight. This measure consists of using a body weight scale.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.3. Daily physical activity. This measure consists of wearing a small wearable on your hip.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.4. Muscle strength. This measure consists of performing three maximal efforts of a strength test for the thigh muscles.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.5. Quality of life and symptoms. This measure consists of filling out a digital questionnaire on an electronic device on quality of life and symptoms.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.6. Motor skills and speech function. This measure consists of performing tasks on a smartphone/tablet for fine motor skills and speech function.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

5.7. Sleep. This measure consists of a device that is placed under your mattress, that measures movement at night during sleep.

Not valuable	1	2	3	4	5	Very valuable
	O	O	O	O	O	

6. Ranking

6.1. Which of the before-mentioned assessments do you find most valuable?

Give your top 3. From 1 (most valuable) to 3 (less valuable).

Fill in the number of the assessment (e.g. 5.3, 5.6, 5.1).

1. _____
2. _____
3. _____

7. How much to measure.

7.1. The maximal number of devices or assessments that I find acceptable to use at home is:

1	2	3	4	5	6	7
O	O	O	O	O	O	O

7.2. The highest frequency that I find acceptable for performing assessments at home is:

Daily	Weekly	Bi-weekly	Monthly	Bi-monthly	Quarterly or less
O	O	O	O	O	O

8. Preferences and concerns

8.1. I would like to see and access my own data.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.2. I would like to have insight into my current rate of disease progression.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.3. I would like to have insight into my predicted disease course and/or prognosis.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.4. I believe that the use of telehealth at home will be too burdensome.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.5. I would not like to perform measurements at home.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.6. I believe that the use of telehealth violates my privacy.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.7. I believe that data safety is an issue for telehealth.

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

8.8. I am afraid that my data will be used by or sold to third-parties

O Totally disagree O Disagree O Neutral O Agree O Totally agree O No opinion

PART II

11

Remote monitoring of respiratory function

CHAPTER 5

5

Using patient-reported symptoms of dyspnea for screening reduced respiratory function in patients with motor neuron diseases

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Abstract

Background. Poor monitoring of respiratory function may lead to late initiation of non-invasive ventilation (NIV) in patients with motor neuron diseases (MND). Monitoring could be improved by remotely assessing hypoventilation symptoms between clinic visits. We aimed to determine which patient-reported hypoventilation symptoms are best for screening reduced respiratory function in patients with MND, and compared them to the respiratory domain of the amyotrophic lateral sclerosis functional rating scale (ALSFRS-R).

Methods. This prospective multicenter study included 100 patients with MND, who were able to perform a supine vital capacity test. Reduced respiratory function was defined as a predicted supine vital capacity ≤80%. We developed a 14-item hypoventilation symptom questionnaire (HYSQ) based on guidelines, expert opinion and think-aloud interviews with patients. Symptoms of the HYSQ were related to dyspnea, sleep-quality, sleepiness/fatigue and pneumonia. The diagnostic performances of these symptoms and the ALSFRS-R respiratory domain were determined from the receiver operating characteristic (ROC) curves, area under the curve (AUC), sensitivity, specificity, predictive values and accuracy.

Results. Dyspnea-related symptoms (dyspnea while eating/talking, while lying flat and during light activity) were combined into the MND Dyspnea Scale (MND-DS). ROC-curves showed that the MND-DS had the best diagnostic performance, with the highest AUC=0.72, sensitivity=75% and accuracy=71%. Sleep-quality symptoms, sleepiness/fatigue-related symptoms and the ALSFRS-R respiratory domain showed weak diagnostic performance.

Conclusion. The diagnostic performance of the MND-DS was better than the respiratory domain of the ALSFRS-R for screening reduced respiratory function in patients with MND, and is, therefore, the preferred method for (remotely) monitoring respiratory function.

Keywords: motor neuron disease, amyotrophic lateral sclerosis, dyspnea, vital capacity, respiratory function, patient-reported outcome measure

Introduction

Motor neuron diseases (MND) are rapidly progressive neurodegenerative diseases, which include amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS). The main cause of death is respiratory failure due to diaphragm weakness.[1] One of the first signs of diaphragm weakness is nocturnal hypoventilation. Prolonged hypoventilation leads to hypercapnia, which causes clinical symptoms, such as sleep disturbances and daytime fatigue.[2] These symptoms may negatively affect patients' quality of life.

Non-invasive ventilation (NIV) is the most effective intervention for improving quality of life and relieving symptoms in patients with MND[2]. The effect of NIV on the rate of respiratory decline and survival has been shown to be associated with the timing of NIV initiation.[3,4] The guidelines for MND specify a number of criteria for the timing of NIV initiation, based on pulmonary function tests, blood gas analysis and respiratory symptoms.[5–7] Despite these guidelines, NIV is often initiated late[8], which could lead to reduced compliance and worse survival. Literature suggests that poor monitoring of respiratory function as a result of lacking pulmonary function tests, may be one of the causes of late NIV inititation.[8–13]

One way to improve the monitoring of respiratory function is by remotely monitoring respiratory symptoms that are indicative of a reduced pulmonary function test score. This approach enables more frequent assessments of respiratory function compared to usual care, may facilitate early detection of respiratory dysfunction and allows patients to stay at home, saving travel time and costs. Unlike performing pulmonary function tests, the remote assessment of respiratory symptoms is simple, not requiring a medical device or skill to complete.

Currently, the respiratory domain of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) is commonly used for assessing respiratory symptoms in patients with MND. However, there has been some criticism about the screening value of this domain.[14,15] For this reason, it would be valuable to know which symptoms are better than the respiratory domain of the ALSFRS-R for screening a reduced pulmonary function test score. In clinical care, the vital capacity (VC) test is the most used pulmonary function test for assessing respiratory function in patients with MND. Knowing which symptoms are best for screening a reduced VC will help healthcare professionals to remotely identify those who may need to be referred to a pulmonologist for comprehensive assessment.

We, therefore, developed a hypoventilation symptom questionnaire (HYSQ), based on guidelines, expert opinion and think-aloud interviews with patients, and compared the diagnostic performance of the HYSQ with the respiratory domain of the ALSFRS-R.

Methods

Hypoventilation symptom questionnaire

The patient-reported hypoventilation symptom questionnaire (HYSQ) was developed in order to standardize the assessment of hypoventilation symptoms. Recent literature has provided evidence that patient-reported outcome measures are feasible and of added value in routine ALS care.[16] A preliminary questionnaire of 19 items was created based on literature, expert opinion and guidelines for management of MND.[5,6] It assessed the extent to which patients experienced the symptoms of hypoventilation. Items could be scored from 0 (not at all) to 4 (to a great extent). Think-aloud interviews were conducted, in which patients verbalize their thoughts as they read and complete the questionnaire, to investigate whether they were able to understand the items and whether they used correct reasoning when answering the items. A total of 10 think-aloud interviews were conducted with ALS patients. After completing these interviews, items were adjusted linguistically or removed when patients did not fully understand them. The final version of the HYSQ consisted of 14 items: Disturbed sleep, difficulty returning to sleep, nightmares, night sweats, waking up tired, morning headache, daytime sleepiness, fatigue, concentration problems, pneumonia, dyspnea while seated, dyspnea while eating/talking, dyspnea while supine and dyspnea during light activity (table 1). The full questionnaire can be found in Online Resource 1.

Table 1 The hypoventilation symptom questionnaire and the diagnostic performance of individual items. [a]Indicates whether the AUC is significantly higher than 0.5 (=chance). [b]Also known as orthopnea. ROC=Receiver operating characteristic, AUC= Area under the curve.

Hypoventilation Symptom Questionnaire	Diagnostic performance (ROC analysis)	
	AUC	p-value[a]
1. At night I wake up often.	.58	.18
2. When I wake up at night, it takes a long time before I fall asleep again.	.50	.99
3. At night I have nightmares.	.54	.46
4. I wake up at night/in the morning drenched in sweat.	.46	.54
5. I feel tired when I wake up in the morning.	.50	.99
6. I experience headaches after I wake up in the morning.	.57	.27
7. I find it difficult to stay awake during the day (e.g. while watching TV or reading a book).	.59	.15
8. I experience fatigue during the day.	.50	.99
9. I have difficulties concentrating (e.g. when watching TV or reading a book).	.49	.83
10. I suffer from pneumonia (i.e. excessive coughing and mucus in my throat).	.65	<.05
11. I feel short of breath when sitting still.	.62	<.05
12. I feel short of breath when talking or eating.	.66	<.01
13. I feel short of breath when I lie flat on my back.[b]	.66	<.01
14. I feel short of breath during light activities (e.g. walking, washing or getting dressed).	.72	<.01

Study design and population

This prospective multi-center study aimed to include 100 consecutive patients with ALS, PMA or PLS, aged 18 and over. Patients were excluded from the study if they were receiving NIV or tracheostomy ventilation, unable to understand the questionnaire due to cognitive dysfunction or when a correct performance of the pulmonary function test was not possible due to bulbar impairment. Ethics approval was obtained prior to the start of the study and patients gave informed consent before participating.

Setting and procedure

A total of six multidisciplinary ALS clinics in the Netherlands participated in the current study, three of which were rehabilitation centers and three university medical centers. During a regular visit to a multidisciplinary clinic, between August 2018 and November 2019, patients were invited by a rehabilitation physician or physical therapist to take part in the study. Patients were asked to perform a pulmonary function test three times and fill in the HYSQ and the ALSFRS-R. The ALSFRS-R is a validated questionnaire that indicates the level of functional impairment in four domains of functioning: bulbar function, fine and gross motor skills, and respiratory function.[17] Each domain consists of 3 items that are scored from 0 (fully impaired) to 4 (not impaired), resulting in a total score between 0 (worst) and 48 (best).

Pulmonary function test

The pulmonary function test used in the current study was the forced vital capacity (FVC) test in supine position. It has been shown that this test can predict diaphragm weakness and survival better than an upright FVC or the difference between the upright and supine FVC.[18–20] In addition, the supine FVC has been highly correlated to the trans-diaphragmatic pressure, which is the 'gold standard' for assessing diaphragmatic weakness.[21] Patients who were not able to perform the supine FVC correctly (e.g. due to air leakage or orthopnea), were allowed to perform a slow vital capacity (SVC) test in supine position. Literature has shown that the results of the SVC and FVC are very similar and interchangeable.[22,23] We, therefore, report the supine VC.

Test-retest HYSQ

We aimed to include 50 patients in the test-retest analysis. One week after the baseline assessment, the patients were sent an e-mail with a digital link to an online version of the HYSQ on a secure survey website. Patients had one week to fill in the online questionnaire; if they exceeded this time period, the retest was invalid and not used in the reliability analysis.

Analyses

The highest value of three supine VC test attempts was converted to a percentage of the predicted VC, using age, height and ethnicity, according to the reference values from the Global Lung Function Initiative 2012.[24] The threshold for a reduced respiratory function was ≤80% of the predicted supine VC.[6]

In current clinical practice, items 10 (dyspnea), 11 (orthopnea) and 12 (respiratory insufficiency) of the ALSFRS-R are used to assess respiratory function in patients with MND. In the present study, we excluded item 12 from the analysis as it assesses whether patients use NIV, which was an exclusion criterion. We report the ALSFRS-$R_{10,11}$.

Relative operating characteristics (ROC) curves and the area under the curve (AUC) were obtained for all individual HYSQ items. Items with an AUC ≥0.6 and asymptotic significance ($p<0.05$) were combined into an HYSQ sum score. An exploratory factor analysis was performed with a varimax rotation in order to determine the factor structure and constructs of the HYSQ. Items were considered to contribute to a factor with a factor loading ≥0.5.

ROC curves and the AUC were obtained for the HYSQ sum score, HYSQ factors and ALSFRS-$R_{10,11}$. The ROC curves were assessed to determine the optimal cut-off score for correct identifications of reduced respiratory function (as a dichotomous outcome). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (true positive rate + true negative rate) were calculated. A finding was considered a true-positive, when a patient experienced symptoms based on the optimal cut-off score, with a supine VC ≤ 80%, and a finding was considered a true negative, when a patient did not experience symptoms based on the cut-off score, with a supine VC > 80%. A correlation analysis was performed to determine the strength of the relationship between the symptoms (HYSQ and ALSFRS-$R_{10,11}$) and respiratory function.

The test-retest reliability of the HYSQ sum score and HYSQ factors were determined using the Intraclass Correlation Coefficient (ICC) and the absolute reliability was determined using the minimal detectable change (MDC). The MDC with a confidence interval of 95% was calculated with the standard error of the mean (SEM) using the formula: MDC = SEM * $\sqrt{2}$ * 1.96. All analyses were performed with SPSS 25 software.

Results

A total of 100 patients were included in the current study. Their average age was 64, 63% were male, 63% were diagnosed with ALS, 81% had spinal onset and the mean ALSFRS-R

score was 36. One patient did not perform a supine VC and was, therefore, excluded from the analysis. Nine patients had missing ALSFRS-R data. All patient characteristics are presented in Table 2.

Table 2 Patient characteristics. ALS = amyotrophic lateral sclerosis, PMA = progressive muscular atrophy, PLS = primary lateral sclerosis, COPD = chronic obstructive pulmonary disease, VC = vital capacity, SD = Standard deviation, IQR = Interquartile range, ALSFRS-R = revised ALS functional rating scale, ALSFRS-$R_{10,11}$ = ALSFRS-R items 10 and 11.

Characteristic	**Patients** (N=100)	**N**
Gender (male), *n(%)*	63 (63.0)	100
Age (years), *mean(SD)*	63.8 (10.4)	100
Ethnicity, *n(%)*		100
- Caucasian	96 (96.0)	
- Asian	2 (2.0)	
- Other/ mixed	2 (2.0)	
Current smoker, *n(%)*	20 (20.2)	99
Diagnosis, *n(%)*		99
- ALS	62 (62.6)	
- PMA	23 (23.2)	
- PLS	14 (14.1)	
Site of onset, *n(%)*		99
- Bulbar	19 (19.2)	
- Spinal	80 (80.8)	
Comorbidities, *n(%)*		100
- COPD	6 (6.0)	
- Apnea	1 (1.0)	
- None	93 (93.0)	
Respiratory function (% of predicted supine VC), *mean (SD)*	72.4 (22.7)	99
Reduced respiratory function (≤80% predicted supine VC), *n(%)*	56 (56.6)	99
Disease duration from diagnosis (months), *median (IQR)*	14.3 (6.2-29.2)	97
Diagnostic delay (months), *median (IQR)*	12.5 (6.5-26.0)	97
ALSFRS-R, *mean(SD)*	36.0 (7.0)	91
ALSFRS-R (respiratory domain), *mean (SD)*	11.2 (1.5)	91
ALSFRS-$R_{10,11}$, *mean (SD)*	7.2 (1.3)	91

The AUC of all individual HYSQ items are presented in Table 1. Items 10 to 14 proved to have the best individual diagnostic performance with an AUC >0.6 and asymptotic significance ($p<0.05$); they were combined into an HYSQ sum score. An exploratory factor analysis identified three factors: factor 1 was related to dyspnea , factor 2 to sleep quality, and factor 3 to sleepiness/fatigue. Pneumonia was the only symptom that did not correlate well with any of these three factors (Table 3). The ROC curve and AUC of the HYSQ sum score, HYSQ factors and the ALSFRS-$R_{10,11}$ are presented in Figure 1. The largest AUCs, were observed in the HYSQ sum score (0.75) and factor 1 (0.72), followed by the ALSFRS-$R_{10,11}$ (0.62). The optimal cut-off score for correct identification of a reduced respiratory function was ≥2 for factor 1, factor 2 and the HYSQ sum score, ≥3 for factor 3, and ≤7 for the ALSFRS-$R_{10,11.}$

The sensitivity, specificity, PPV, NPV and accuracy are shown in Table 4. The HYSQ sum score and factor 1 showed the best diagnostic performance, with an accuracy of 71% (true positive rate=42%) and 72% (true positive rate=43%), respectively. The HYSQ sum score and factor 1 misclassified 17% and 14% of patients as having a reduced respiratory function (false positives), and misclassified 12% and 14% of patients as having normal respiratory function (false negatives), respectively.

Further analysis of the HYSQ sum score and factor 1 showed that item 11 (dyspnea while seated) was only present when other types of dyspnea were already more severe. For this reason we assumed that *dyspnea while seated* was not of added value for the early screening of respiratory function. Accordingly, we obtained the ROC curve of the revised HYSQ sum score and revised factor 1-a (item 11 removed), and observed equal AUCs, and no changes in sensitivity, specificity, PPV, NPV or accuracy. When we looked further into revised factor 1-a, items 3 (nightmares) and 6 (morning headache) did not seem to fit the construct of dyspnea well, and in addition, they had the lowest AUCs. For this reason, we evaluated their contribution to the diagnostic performance of the revised factor 1-a. We found that the removal of *nightmares* did not lead to any changes in any of the diagnostic performance parameters. The removal of *morning headache* resulted in one true positive changing to a false negative, therefore slightly reducing the accuracy from 72% to 71%. However, due to the lack of contribution of items 3 and 6 to the diagnostic performance, we removed these items from the revised factor 1-a. The diagnostic performance parameters of the revised factor 1-b (items 3, 6 and 11 removed) and revised HYSQ sum score are presented in Table 4 with the optimal cut-off score of ≥2. With higher cut-off scores (3 to 6), the sensitivity of the revised factor 1-b showed the largest increase compared to the revised HYSQ sum score and (unrevised) factor 1 (Table 5).

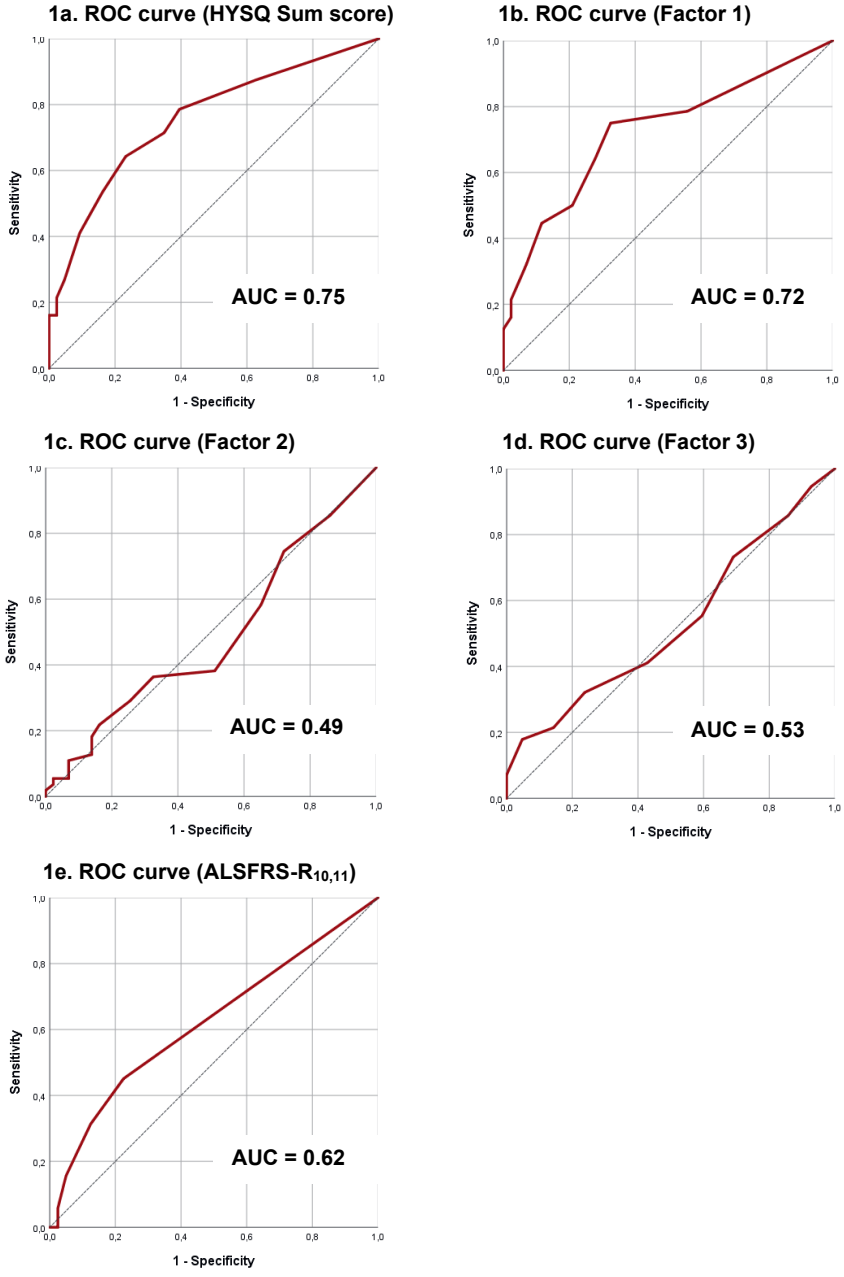

Figure 1 The ROC curves for predicting reduced respiratory function as a dichotomous outcome. HYSQ sum score= items 10 to 14, Factor 1= items 3, 6, 11 to 14, Factor 2= items 1, 2, 4 and 5, Factor 3= items 7 to 9, ALSFRS R 10,11 = items 10 and 11 of the revised amyotrophic lateral sclerosis functional rating scale, ROC = receiver operating characteri stic, AUC = Area under the curve.

Table 3 Factor analysis results. Three factors were identified with an eigenvalue greater than 1. The factor loading indicates the strength of the relationship between the HYSQ symptom and the identified factors. [a]Also known as orthopnea.

	HYSQ Symptom	Factor loading
Factor 1	3. Nightmares	.66
	6. Morning headache	.75
	11. Dyspnea while seated	.81
	12. Dyspnea while talking/eating	.66
	13. Dyspnea while lying flat[a]	.90
	14. Dyspnea during light activity	.65
Factor 2	1. Restless sleep	.81
	2. Difficulty returning to sleep	.89
	4. Nightsweats	.54
	5. Waking up unrefreshed	.74
Factor 3	7. Daytime sleepiness	.77
	8. Fatigue	.61
	9. Concentration problems	.77
None	10. Pneumonia	-

Table 4 Diagnostic performance and reliability. *p<0.05, HYSQ = hypoventilation symptom questionnaire, HYSQ sum score= items 10 to 14, Factor 1= items 3,6, 11 to 14, Factor 2= items 1, 2, 4 and 5, Factor 3= items 7 to 9, Revised HYSQ sum score = items 10, 12 to 14, Revised factor 1-a= items 3, 6, 12 to 14, Revised factor 1-b= items 12 to 14. MND-DS= Motor Neuron Disease Dyspnea Scale, PPV = positive predictive value, NPV = negative predictive value, Accuracy = true positive rate + true negative rate, ICC = Intraclass Correlation Coefficient, MDC = Minimal detectable change, n.a. = not applicable.

Statistic	HYSQ sum score	Factor 1	Factor 2	Factor 3	ALSFRS-$R_{10,11}$	Revised HYSQ sum score	Revised factor 1-a	Revised factor 1-b (MND-DS)
Sensitivity *(%)*	72.1	75.0	56.9	58.6	71.9	72.1	75.0	74.5
Specificity *(%)*	68.4	67.4	46.2	46.4	52.5	68.4	67.4	65.9
PPV *(%)*	78.6	75.0	74.5	73.2	45.1	78.6	75.0	73.2
NPV *(%)*	60.5	67.4	27.9	31.0	77.5	60.5	67.4	67.4
Accuracy *(%)*	70.7	71.7	53.5	54.5	54.5	70.7	71.7	70.7
Correlation *(r)*	-0.51*	-0.50*	-0.12	-0.08	0.30*	-0.50*	-0.50*	-0.50*
ICC	0.85	0.89	0.88	0.85	n.a.	0.85	0.89	0.88
MDC	1.23	1.32	1.04	0.75	n.a.	1.00	1.08	0.81

The revised HYSQ sum score (r=-.50, p<0.001), revised factor 1-b (r=-.50, p<0.001), and the ALSFRS-$R_{10,11}$ (r= .30, p=0.004) were significantly correlated to respiratory function, but factor 2 (r= -.12, p= 0.26) and factor 3 (r= -0.08, p= 0.42) were not. The retest was completed by 48 patients, on average 9 days after the baseline assessment. The test-retest reliability and absolute reliability were shown to be good in all variables, with high ICC values and low MDC values (table 3). The MDC values of the HYSQ sum score and factor 1 improved after they were revised.

Based on our results, we concluded that revised factor 1-b had the best overall diagnostic performance and reliability. For this reason the symptoms of revised factor 1-b (dyspnea while eating/talking, dyspnea while lying flat and dyspnea during light activity) were combined into the Motor Neuron Disease Dyspnea Scale (MND-DS)(see Online Resource 2). Each item of this scale can be scored from 0 to 4, resulting in a possible total score between 0 (no dyspnea) and 12 (severe dyspnea), with an optimal cut-off-score of ≥2 and 75% sensitivity.

Table 5 Sensitivity with higher symptom cut-off scores. *The cut-off score for an optimal area under the curve. HYSQ = Hypoventilation Symptom Questionnaire, MND-DS = Motor Neuron Disease Dyspnea Scale.

Variables	Cut-off scores				
	≥2*	≥3	≥4	≥5	≥6
HYSQ sum score	72.1	72.7	78.3	81.1	85.2
Factor 1	75.0	75.0	75.7	83.3	85.7
Revised HYSQ sum score	72.1	71.7	79.5	83.3	88.0
Revised factor 1-b (MND-DS)	74.5	75.6	81.3	90.0	93.8

Discussion:

We have developed a patient-reported scale (MND-DS) that, in the majority of cases, is able to identify whether or not patients with MND have reduced respiratory function. The MND-DS proved to have a better diagnostic performance than the respiratory domain of the ALSFRS-R. This suggests that it is preferable to use the new scale for monitoring respiratory function and for referring patients to a pulmonologist for comprehensive assessment. Furthermore, sleep quality-related symptoms and sleepiness/fatigue-related symptoms were weak in identifying reduced respiratory function and had a weak relationship with supine VC. This demonstrates that in the present study these symptoms were less suitable for monitoring respiratory function.

Our findings suggest that of all hypoventilation symptoms, dyspnea (and orthopnea) could best be used for remote monitoring to screen for reduced respiratory function in patients with MND. Another reason for monitoring these symptoms regularly is that they are well-correlated with, and good predictors of, NIV use .[25–27] Correspondingly, studies have shown that most healthcare professionals in Europe and the United States consider the symptoms of dyspnea and orthopnea to be (one of) the most important parameters for prescribing NIV to patients with MND.[8,11,28,29] In these studies, sleep-related symptoms were often also considered important when deciding on prescribing NIV, and in the Netherlands they were used more often than dyspnea and orthopnea when deciding on NIV.[29] Interestingly, our study showed that sleep-related symptoms had low diagnostic performance and a weak relationship with supine VC. A reason for this finding could be that the supine VC is not an appropriate measure for assessing sleep disordered breathing. Future research, could evaluate the diagnostic performance of sleep-related symptoms with an overnight polysomnography, which is the gold standard for assessing sleep disordered breathing. Another possible reason for the weak relationship is that sleep disturbances may be caused by non-respiratory factors such as muscle cramps, pain, reduced mobility, choking or anxiety.[25,30] Accordingly, a study has shown that sleep-related symptoms did not correlate with nocturnal abnormalities of blood carbon dioxide and oxygen levels.[25,31] These findings suggest that it may be better for healthcare professionals to assess dyspnea and orthopnea when trying to identify patients with a reduced respiratory function, and that sleep-related symptoms should be assessed for the detecting sleep disturbances and possibly sleep disordered breathing.

When we look at previous studies that have investigated the relationship between hypoventilation symptoms and respiratory function, we find contrasting results. Jackson and colleagues[20] investigated the relationship between a hypoventilation symptom scale (similar to the HYSQ) and various pulmonary function tests (including supine VC) in a small sample of 13 patients with ALS. They found no significant correlations between any of the pulmonary function tests and the total score of the symptom scale. A possible reason is that they combined all symptoms into one score, which means that weakly correlated items also contributed to the total score. Another study also found no correlation between a validated dyspnea questionnaire and three respiratory measures (including supine VC) in patients with ALS.[32] This 15-item questionnaire covered different aspects of dyspnea, including the emotional burden/distress caused by dyspnea. Several items asked whether dyspnea leads to feelings of isolation, depression and fear. These aspects may vary in individuals with similar levels of respiratory dysfunction, and may, therefore, have a weaker relationship with respiratory function. Furthermore, patients who were on NIV were included in the study, which could have affected the results, since NIV is known to relieve dyspnea-related symptoms.

When using the MND-DS for monitoring, a subgroup of patients will be misclassified as having normal respiratory function (false negative) or as having reduced respiratory function (false positives). Despite the misclassification of false positive patients, these patients were symptomatic with dyspnea and/or orthopnea, which is an important indication for NIV initiation and therefore a valid reason for referral to the multidisciplinary care team or a pulmonologist.[27,28] The group of false negative patients, however, was identified as asymptomatic, meaning they would not be referred whilst having reduced respiratory function. This shows that a lack of symptoms in patients with MND does not exclude a reduced respiratory function. For this reason, the MND-DS should be used for monitoring between clinic visits, in combination with regular in-clinic pulmonary function testing. In order to identify all patients with reduced respiratory function through remote monitoring, the assessment of symptoms should be combined with home-based VC testing. A recent study has demonstrated that patients and their caregivers are able to perform a VC test reliably when following live-video instructions in a clinical setting.[33] It is not known, however, whether patients with MND are able to validly and reliably perform VC tests independently at home. For this reason, future studies could compare home-based VC tests performed by patients with MND (and their caregiver) with those performed in-clinic by a healthcare professional.

Strengths and limitations

The strengths of the present study are the multicenter design and the relatively large cohort of patients with MND. We chose not to use the gold standard (i.e. trans-diaphragmatic pressure) for assessing respiratory function in the present study, as this method is invasive and labor intensive. Instead we used the supine VC, which is highly correlated to trans-diaphragmatic pressure, widely available and feasible in clinical practice. The assessment of the supine VC was performed with validated spirometers by experienced physical therapists or rehabilitation physicians. The assessments were not, however, standardized across centers, which may have caused slight measurement differences. We do not believe that these potential differences could have changed the outcome of the present study.

Conclusion

The newly developed MND-DS may be a valuable tool for remotely monitoring respiratory function between clinic visits, as of all symptoms, it is the most accurate in identifying whether patients with MND have reduced respiratory function. The MND-DS showed better diagnostic performance than the ALSFRS-R respiratory domain, suggesting that the use of the MND-DS is preferred in the attempt to identify patients with a reduced respiratory function. Symptoms related to sleep quality or sleepiness/fatigue did not appear to be useful for screening reduced respiratory function. To further improve remote monitoring of respiratory function, the assessment of the MND-DS could be combined with home-based VC testing. Future research should evaluate the feasibility of home-

based VC testing in patients with MND and re-address the respiratory domain of the ALSFRS-R.

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Supplementary material 1

Hypoventilation Symptom Questionnaire (HYSQ)

Please indicate the extent to which you experienced the following symptoms in the last 2 weeks:

1. At night I wake up often.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

2. When I wake up at night, it takes a long time before I fall asleep again.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

3. At night I have nightmares.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

4. I wake up at night/in the morning drenched in sweat.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

5. I feel tired when I wake up in the morning.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

6. I experience headaches after I wake up in the morning.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

7. I find it difficult to stay awake during the day (e.g. while watching TV or reading a book).

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

8. I experience fatigue during the day.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

9. I have difficulties concentrating (e.g. when watching TV or reading a book).

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

10. I suffer from pneumonia (i.e. excessive coughing and mucus in my throat).

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

11. I feel short of breath when sitting still.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

12. I feel short of breath when talking or eating.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

13. I feel short of breath when I lie flat on my back.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

14. I feel short of breath during light activities (e.g. walking, washing or getting dressed).

Not at all	**0**	**1**	**2**	**3**	**4**	To a great extent
	O	O	O	O	O	

Supplementary material 2

Motor Neuron Disease – Dyspnea Scale (MND-DS)

Please indicate the extent to which you experienced the following symptoms in the last 2 weeks:

1. I feel short of breath when talking or eating.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

2. I feel short of breath when I lie flat on my back.

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

3. I feel short of breath during light activities (e.g. walking, washing or getting dressed).

Not at all	0	1	2	3	4	To a great extent
	O	O	O	O	O	

CHAPTER 6

6

Home-monitoring of vital capacity in patients with motor neuron disease

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Abstract

Background. Home-monitoring of spirometry has the potential to improve care for patients with a motor neuron disease (MND) by enabling early detection of respiratory dysfunction and reducing travel burden. Our aim was to evaluate the validity and feasibility of home-monitoring vital capacity (VC) in patients with MND.

Methods. We included 33 patients with amyotrophic lateral sclerosis, progressive muscular atrophy or primary lateral sclerosis who completed a 12-week home-monitoring protocol, consisting of 4-weekly unsupervised home assessments of VC and a functional rating scale. At baseline, during a home visit, patients/caregivers were trained in performing a VC test, and the investigator performed a supervised VC test, which was repeated at final follow-up during a second home visit. Validity of the unsupervised VC tests was evaluated by the differences between supervised and unsupervised VC tests, and through Bland-Altman 95% limits-of-agreement. Feasibility was assessed by means of a survey of user-experiences.

Results: The 95% limits-of-agreement were [−14.3; 11.7] %predicted VC, and 88% of unsupervised VC tests fell within 10 %predicted of supervised VC. 88% of patients experienced VC testing as easy and not burdensome, however, 15% patients did not think their VC test was performed as well as in the clinic. 94% of patients would like home-monitoring of VC in MND care.

Discussion: Unsupervised VC testing at home, with prior face-to-face training, is a valid and time-efficient method for the remote monitoring of respiratory function, and well-accepted by patients with MND and their caregivers.

Key words: motor neuron disease, amyotrophic lateral sclerosis, respiratory function, vital capacity, remote monitoring, validity

Introduction

In patients with a motor neuron disease (MND), respiratory failure is the main cause of death [1,2]. When patients show signs or symptoms of respiratory dysfunction, as described in clinical guidelines, non-invasive ventilation (NIV) is recommended [3–5]. Studies have shown that the use of NIV prolongs survival and improves quality of life [6–8]. Regular monitoring of respiratory function is essential to ensure timely detection of respiratory dysfunction so that NIV can be initiated [3–5]. In current MND healthcare, respiratory function is monitored during regular visits to a multidisciplinary clinic. Two drawbacks of this type of monitoring are that clinic visits can be time consuming and burdensome for patients with MND, and that patients have to visit the clinic irrespective of whether there is a decrease in respiratory function [9,10]. This suggests that current respiratory monitoring may be insufficiently tailored to the needs of patients.

A potential solution is the home-monitoring of respiratory function through the use of telehealth. This approach allows for more frequent assessments, higher continuity of monitoring, especially when patients are not able to visit the clinic, and easy communication between patients and the multidisciplinary care team [11–16]. The use of telehealth may help to detect respiratory function decline early, and schedule clinic visits and initiate clinical interventions on time. One method of home-monitoring is the assessment of patient-reported symptoms of dyspnea, which was found to be useful for screening whether patients with MND had reduced vital capacity (VC)[17]. However, a drawback of dependence on self-reported dyspnea/orthopnea is that patients with low VC but without symptoms will not be identified (false negative rate = 14%). For this reason, combining patient-reported symptoms of dyspnea with home-based VC testing may reduce false negative findings and improve the home-monitoring of respiratory function.

The VC test has prognostic value in patients with MND [18,19], and is easy to perform with a handheld spirometer, which is affordable and widely available. For these reasons, the VC test is suitable and relevant for home-monitoring; however, in MND care, its application for home-monitoring is still lacking [20]. Recently, a study showed that during COVID-19, it was feasible to perform home-based VC testing with supervision via video and that it was well-received by patients with MND in a healthcare setting [21]. However, one trial showed that when patients performed VC tests at home without supervision, the remote VC measurement was significantly higher than the usual in-clinic VC measurement and compliance was suboptimal [22]. These findings show the potential of home-monitoring of VC, but also indicate that more evidence is needed to support its implementation.

The aim of the present study is, therefore, to evaluate the validity and feasibility of unsupervised home-monitoring of VC in patients with MND.

Methods

Study design and population

This prospective cohort study aimed to include patients with MND, who were 18 years old or over and had access to a smartphone or tablet. Different diagnoses of MND were involved: amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS). The exclusion criteria were the use of non-invasive ventilation during the daytime, tracheostomy, or the inability to perform a VC test with or without caregiver assistance. Ethics approval from the Medical Ethics Committee of the University Medical Center Utrecht was obtained prior to the start of the study and patients gave their informed consent before participating.

Setting and procedure

This study was conducted by the University Medical Center in Utrecht, the Netherlands, in collaboration with the Revant Center for Rehabilitation in Breda. Both centers have a multidisciplinary care team, coordinated by a physician. All study activities were performed at the patients' homes, meaning that patients could participate in the present study without having to visit a multidisciplinary clinic. Patients who, between August 2020 and February 2021, received MND care from the multidisciplinary care teams were invited by the treating physician to participate. Most patients had access to the telehealth service *ALS Home-monitoring and Coaching* as part of their usual care. This telehealth service included the mobile ALS app for self-monitoring and messaging, which facilitated remote monitoring and communication between the patient and the multidisciplinary care team. A full description of *ALS Home-monitoring and Coaching* is available in a previous publication [12].

Figure 1 Performing a vital capacity test with a full face mask . Left: A hammer grip around the tube. Right: Holding the mask with the tube placed between the fingers.

Study assessments

Respiratory function was assessed by making three attempts to perform the vital capacity (VC) test in upright position, using a low-cost (ca. €100,-) handheld spirometer with Bluetooth connection to a mobile app (Spirobank Smart®, Medical International Research, Italy). The VC tests were performed with a full-face mask (Figure 1) to enable testing in patients with bulbar impairment [23]. Patients recorded the time, date and VC test scores on a paper form, and also sent the VC test scores digitally to their multidisciplinary care team via the ALS app or by email, which allowed members of the multidisciplinary ALS care team to monitor respiratory function. The revised ALS functional rating scale (ALSFRS-R) was used to assess functional impairment [17,24], and was self-monitored monthly as part of *ALS Home-monitoring and Coaching.* Patients who did not use telehealth completed the ALSFRS-R on paper at every follow-up. We created a survey to evaluate user-experiences of patients and caregivers who assisted with VC testing; see tables 2 and 3 for the items of the survey. Items were scored on a 5-point Likert scale: the extent to which patients/caregivers considered aspects of VC testing to be difficult (answer options: Very easy – Very difficult), or the extent to which they agreed with a statement on VC testing (answer options: Totally agree – Totally disagree).

Baseline protocol

At baseline (T0), the supervised VC test and ALSFRS-R were completed during a home visit. The investigator helped patients to install the mobile app on their smartphone, after which the supervised VC was performed. VC tests were either performed forcefully (FVC) or slowly (SVC), depending on which method was most effective/suitable for the patient [19]. Patients (and their caregivers) were instructed on how to perform the VC test independently, and practiced VC testing. If required, the investigator gave tips on how to improve the way the VC test was performed. When proper technique was observed (e.g. correct placement of mask, maximal in and exhalation, upright body position), the investigator left the room, and the patient performed an unsupervised VC test, to ensure that patients were able to do this without supervision. Unsupervised VC tests that were performed during the baseline home visit, were not included in the analysis.

Follow-up protocol

The total follow-up period was 12 weeks, with 4-weekly unsupervised assessments. One day after the home visit (T1), patients completed their baseline unsupervised VC tests. At 4 weeks (T2), 8 weeks (T3) and 12 weeks (T4) after baseline, patients completed unsupervised VC tests and the ALSFRS-R. The investigator sent a reminder on the days of follow-up either via text-message or e-mail, depending on patient preference. At T4 the investigator visited the patient's home at least 1 hour after patients had completed their unsupervised VC tests. During this final home visit, a supervised VC test was performed

and patients (and their caregivers) were asked to fill in the survey on user-experiences and to indicate the average duration of their VC testing sessions.

Analyses

The highest VC test score, out of three attempts, at each time-point was converted to a percentage of the predicted (%predicted) VC, using height, age, and ethnicity (reference values used from Global Lung Function Initiative 2012)[25,26]. We used the unsupervised test at T1 as baseline, since the unsupervised VC tests performed at T0 may have been affected by the prior supervised VC tests. Validity of unsupervised VC testing was assessed through the Bland-Altman 95% limits of agreement and Lin's concordance correlation coefficient (CCC) between the supervised VC at T0 and the unsupervised VC at T1, and between the supervised and unsupervised VC at T4. Based on clinical experience, we considered a maximal difference of 10 % predicted between supervised and unsupervised VC as an acceptable limit of agreement, since this will allow healthcare professionals to determine a trend of VC over time when the VC is monitored at 4-weekly intervals. Additionally, the coefficient of variation of supervised VC testing in patients with MND was already 6.3 %predicted in a previous study [27]. A paired t-test was conducted to assess the change in supervised and unsupervised VC between T0 and T4, and whether there was a systematic difference between supervised and unsupervised VC. Furthermore, we evaluated whether the agreement between supervised and unsupervised VC was different after 12 weeks of home-monitoring compared to baseline. In order to obtain insight into the variation in unsupervised VC testing over time, we used linear regression to determine the average slope over the 12 week period for each individual patient, and we calculated the standard error (SE) which indicates to what extent the VC values deviate from the linear regression line. We then ranked patients from lowest to highest SE and created a subgroup for each quartile (25%) of patients. These subgroups were used to create 4 separate plots for the longitudinal unsupervised VC data of individual patients to facilitate interpretation of the data. Furthermore, in the Bland-Altman plots, the subgroups are indicated for each data point (i.e. patient), in order indicate whether greater variability showed larger differences between unsupervised and supervised VC. An alpha of <0.05 was considered to be statistically significant. Feasibility of unsupervised home-based VC testing was determined through the adherence to the 4-weekly VC protocol, time cost of VC testing and user-experiences. Unsupervised VC testing was considered feasible when ≥75% of all unsupervised VC tests had been carried out, and each testing session completed within 20 minutes. An item of the user-experience survey was considered feasible when ≥75% of patients answered '(totally) agree' on positive statements, '(totally) disagree' on negative statements, and '(very) easy' on difficulty statements.

Table 1 Baseline patient characteristics. ALS = amyotrophic lateral sclerosis, PMA = progressive muscular atrophy, PLS = primary lateral sclerosis, NIV = Non-invasive ventilation, VC = vital capacity, SD = Standard deviation, IQR = Interquartile range, MND = Motor neuron disease, ALSFRS-R = revised ALS functional rating scale.

Characteristic	**Patients** (N=33)
Gender (male), *n(%)*	26 (78.8)
Age (years), *mean(SD)*	60.5 (13.2)
Diagnosis, *n(%)*	
- ALS	25 (75.8)
- PMA	5 (15.2)
- PLS	3 (9.1)
Site of onset, *n(%)*	
- Bulbar	7 (21.2)
- Spinal	26 (78.8)
Nightly NIV, *n(%)*	3 (12.1)
Gastrostomy, *n(%)*	2 (6.1)
Telehealth use, *n(%)*	29 (87.8)
Respiratory function (% of predicted VC), *mean (SD)*	78.4 (25.6)
Disease duration from first symptoms (months), *median (IQR)*	35.6 (17.2-52.2)
ALSFRS-R, *mean (SD)*	35.9 (7.3)
ALSFRS-R (respiratory domain), *mean (SD)*	11.0 (1.3)

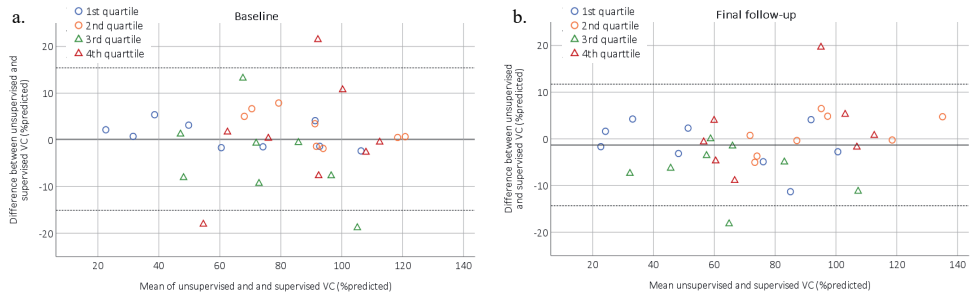

Figure 2 Bland-Altman plots. VC = vital capacity, Dashed line = 95% limits of agreement. The 4 quartile groups are based on the variability of the unsupervised VC scores over time, where 1st quartile = lowest variability and 4th quartile = highest variability.

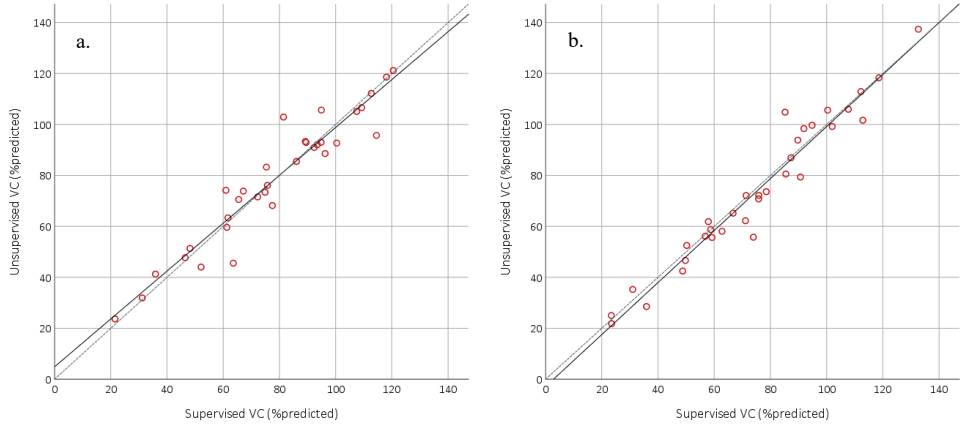

Figure 3 Scatterplot of un supervised vs supervised vital capacity. VC = vital capacity. D ashed line = line of identity. a) at baseline, Lin s CCC =0.9 53 , b) at final follow up, Lin s CCC =0.9 71

Results

We included 33 patients with MND, with an average age of 60.5 years, 79% of whom were male. 76% were diagnosed with ALS, 15% with PMA and 9% with PLS, and 78.8% had spinal onset. At baseline, 3 patients were on nightly NIV, and one patient started with nightly NIV during the study period. Most patients (88%) used telehealth as part of their usual care. All baseline patient characteristics are presented in Table 1. Nine patients were assisted with VC testing by a partner (N=4), family member (N=3) or a home nurse (N=2). The mean change over the 12-week period for the ALSFRS-R total score was −2.1 points.

Validity of unsupervised VC testing

The 95% limits of agreement and the mean difference were [−15.1; 15.4] and 0.12 %predicted (p=0.928) at baseline, respectively, and [−14.3; 11.7] and −1.33 %predicted (p=0.259) at final follow-up, respectively (Figure 2). The difference between unsupervised and supervised VC was smaller than 10 % predicted in 28 of 33 (85%) patients at baseline and in 29 of 33 (88%) patients at final follow-up. The median absolute difference between supervised and unsupervised VC at baseline and final follow-up were 2.6 (IQR=1.3-7.8) and 4.1 (IQR=1.6-5.8) %predicted, respectively. Lin's CCC was excellent at baseline (0.953), as well as at final follow-up (0.971)(Figure 3).

Table 2 User-experiences of patients. *Missing data is due to patients answering "not applicable/ no opinion", VC = vital capacity.

Item	(Very) easy *n(%)*	Neutral *n(%)*	(Very) Difficult *n(%)*	N*
Placing the mask on my face was	23 (82.1)	4 (14.3)	1 (3.6)	28
Handling the spirometer was	26 (92.8)	1 (3.6)	1 (3.6)	28
Starting a VC test in the app was	30 (96.8)	1 (3.2)	0 (0)	31
Performing a VC test was	29 (87.9)	3 (9.1)	1 (3)	33
Judging whether the test was performed correctly was	26 (78.8)	3 (9.7)	3 (9.7)	32
Item	**(Totally) agree** *n(%)*	**Neutral** *n(%)*	**(Totally) disagree** *n(%)*	**N***
The spirometer is user friendly	31 (93.9)	1 (3)	1 (3)	33
The spirometry app was user-friendly	30 (90.9)	3 (9.1)	0 (0)	33
The spirometer is appropriate for home-monitoring of respiratory function	30 (90.9)	3 (9.1)	0 (0)	33
I would like to monitor my respiratory function from home for care purposes	30 (93.8)	2 (6.3)	0 (0)	32
I know how to perform a VC test	33 (100)	0 (0)	0 (0)	33
I believe that my VC test at home is performed just as well as a usual VC test in the clinic	24 (72.8)	4 (12.1)	5 (15.1)	33
I am unsure about performing the VC test correctly in the absence of a healthcare professional	2 (6.5)	4 (12.9)	25 (80.6)	31
Performing VC tests at home is burdensome	2 (6.3)	2 (6.3)	28 (87.5)	32

Between baseline and final follow-up both the supervised VC (Mean = -3.31, p=0.045) and unsupervised VC (-4.77, p=0.036) decreased significantly. We also compared the change in supervised and unsupervised VC between baseline and final follow-up, which showed a good correlation (ρ=0.74, p<0.001). The plots of individual unsupervised VC data can be found in Figure 4,where the range of SE was 0.36-0.96 %predicted for the first quartile of patients, 1.02-2.16 %predicted for the second quartile of patients, 2.28-3.98 %predicted for the third quartile of patients, and 4.56-10.47 %predicted for the fourth quartile of patients .

Table 3 User-experiences of caregivers. Missing data is due to caregivers answering "not applicable/ no opinion", VC = vital capacity.

Item	(Very) easy	Neutral	(Very) Difficult
Placing the mask on his/her face was	8/9	1/9	1/9
Handling the spirometer was	8/9	0/9	1/9
Starting a VC test in the app was	8/8	0/8	0/8
Performing a VC test was	7/8	1/8	0/8
Judging whether the test was performed correctly was	7/9	2/9	0/9
Item	**(Totally) agree**	**Neutral**	**(Totally) disagree**
The spirometer is user friendly	8/9	1/9	0/9
The spirometry app is user-friendly	7/8	1/8	0/8
The spirometer is appropriate for home-monitoring of respiratory function	8/9	1/9	0/9
I would like to monitor my respiratory function from home for care purposes	8/9	0/9	1/9
I know how to (help) perform a VC test	8/9	1/9	0/9
I believe that my VC test at home is performed just as well as a usual VC test in the clinic	5/9	1/9	3/9
I am unsure about performing the VC test correctly in the absence of a healthcare professional	1/9	1/9	7/9
Helping to perform VC tests at home is burdensome	0/9	2/9	7/9

Feasibility of home-monitoring

All 33 participants completed 100% of their VC assessments, 32 (97%) within 20 min, and 29 (88%) within 15 min. Patients reported that the spirometer and spirometry app were user-friendly, and that unsupervised VC testing was considered to be easy and not burdensome (Table 2). Most patients (30, 93.8%) would like their respiratory function from home for care purposes. Even patients with limited hand function were able to handle the spirometer and independently perform a VC test, as 29% (7/24) of patients who were not assisted by a caregiver had an ALSFRS-R fine motor score of ≤6. This was due to the fact that the face mask, that was attached to the mouthpiece of the spirometer, made it easier to hold the spirometer. 3 patients experienced difficulties with determining whether a VC test was performed correctly and 2 patients felt insecure about their VC test performance in absence of a healthcare professional. Furthermore, 5 patients did not think that the unsupervised VC tests were performed as well as supervised tests in the clinic.

Based on the comments reported by patients during unsupervised VC testing, there were some difficulties that affected VC test performance: excessive mucus in throat (patient 4, Figure 4c at T2), physical fatigue (patient 17, Figure 4d at T1), pain in stomach caused by a gastrostomy tube (patient 24, Figure 4d at T4), not being able to concentrate during

testing (patient 26, Figure 4b at T3), or physical discomfort due to an uncomfortable body position in wheelchair (patient 33, Figure 4c at T4).

Most caregivers who assisted with VC testing reported that the spirometer (n=7) and mobile app (n=8) were user-friendly, and that helping with VC testing was easy (n=7) and not burdensome (n=7)(Table 3). The majority of caregivers believed they were able to (help) perform a VC test correctly (n=8), and judge whether a VC test had been performed correctly (n=7). Some of the caregivers (n=3) did not think that they performed the unsupervised VC as well as a healthcare professional in a clinic.

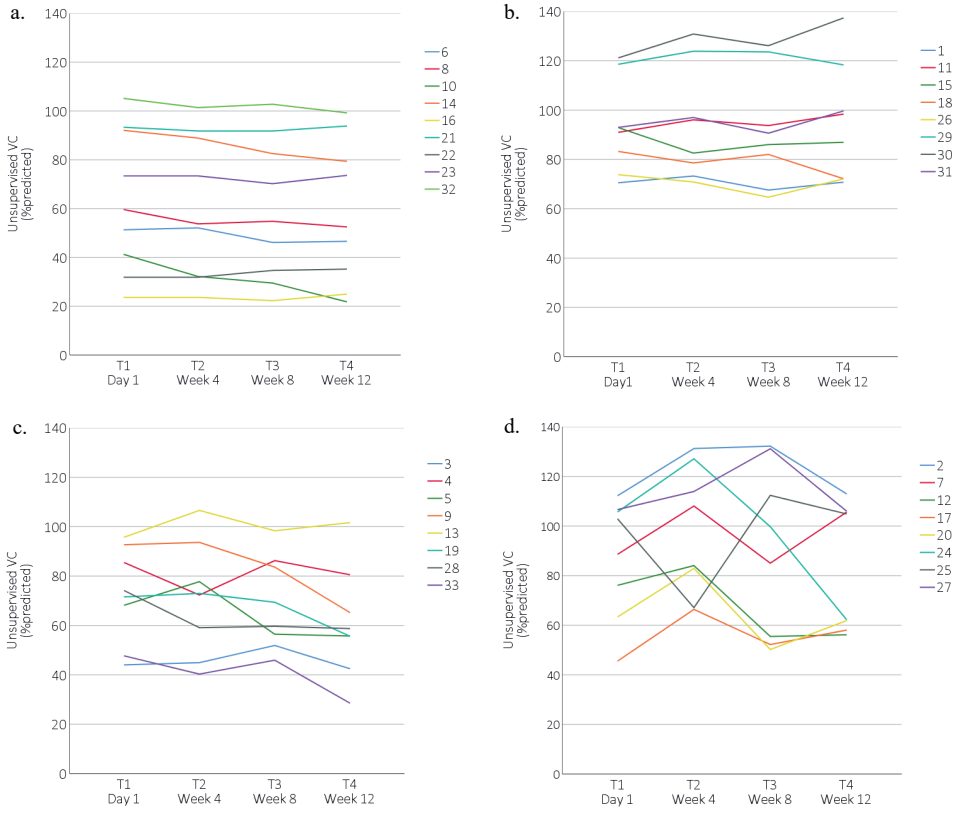

Figure 4 Unsupervised vital capacity over time per individual patient. VC = vital capacity. Patients were ranked from low to high variability, based on the standard error (SE) of the unsupervised VC scores over time and split into four quartiles (i.e. 25% of patients in each group). a) patients in the first quartile (SE range = 0.36-0.96 %predicted), b) patients in the second quartile (SE range = 1.02-2.16 %predicted), c) patients in the third quartile (SE range = 2.28-3.98 %predicted), and d) patients in the fourth quartile (SE range = 4.56-10.47 %predicted).

Discussion

The present study showed that unsupervised home-monitoring of VC, after one face-to-face training, was a valid method for the remote monitoring of respiratory function in patients with MND. Furthermore, the 4-weekly home-monitoring of VC without supervision was feasible, since adherence was excellent, and most patients and caregivers experienced VC testing as easy and not burdensome. Lastly, patients and caregivers were motivated to continue with home-monitoring of VC in MND healthcare.

Our results on the validity and feasibility of unsupervised VC testing at home are promising and show that this can be a time-efficient method in MND care for both patients and healthcare professionals for remotely monitoring respiratory function. We provided insight into the variation in unsupervised VC testing over time, which showed that most patients had a stable trend of VC during the 12-week period. However, the course of the unsupervised VC of some patients were highly variable over time, and generally showed larger differences with the supervised VC, indicating that these patients may require additional supervision during home-monitoring, e.g. through video.

We found that there was no systematic difference between unsupervised and supervised VC, but at final follow-up we observed that supervised VC test scores were more likely to be higher than the unsupervised VC test scores, when compared to baseline. This may indicate that the performance of the unsupervised VC test decreases over time in some patients. This finding is in contrast to previous studies, which reported that remote VC assessments were systematically higher than usual in-clinic VC assessments [22,28]. An explanation for this finding, is that in the present study all VC tests were performed at patients' homes, including the supervised tests. This limited the factors that may have negatively affected VC test performance, such as the burden of travelling and visiting a clinic.

We found that all patients adhered to the 4-weekly monitoring protocol, and that this frequency was acceptable. This corresponds to findings of a recent study, in which most patients reported that the highest acceptable frequency for remote respiratory assessments was monthly [21]. In the present study, facilitating factors for adherence to VC testing at home were that the spirometer and app were user-friendly, and VC testing was easy, not burdensome and not time consuming. A previous study reported suboptimal adherence with a weekly VC protocol, mainly due to connection problems and patients forgetting to complete measurements [22]. During our study we were fortunate that the spirometer and app only rarely malfunctioned, which resulted in re-doing a VC test, but never prevented patients from testing. Furthermore, the problem of forgetting a VC test was tackled by sending a reminder at each follow-up. Another facilitator for adherence

was the fact that home-monitoring of VC was part of an existing telehealth service and that VC test results were monitored by the multidisciplinary care team. Patients are likely to be more motivated to complete assessments at home, when they know healthcare professionals are monitoring their data closely and will provide feedback when necessary [29].

During unsupervised home-monitoring there were several factors, unrelated to respiratory muscle weakness, that hindered optimal VC test performance, such as pain, physical fatigue or loss of concentration. This suggests that it is important that patients provide comments on their physical and psychological well-being at time of VC testing, in order to help healthcare professionals interpret VC scores remotely. Moreover, some patients and caregivers experienced difficulties with determining whether a VC test was performed correctly, and felt insecure about proper VC test performance without supervision. These patients may prefer access to online instruction-videos [30] or require video-supervision during home-monitoring, which has been shown to be well-accepted by patients with MND [21,28]. A disadvantage of video-supervised monitoring, is that it takes healthcare professionals considerably more time, compared to unsupervised monitoring. Interestingly, one study reported that only a few patients felt they were able to perform a VC test at home without video supervision, which contrasts with our study sample, where the majority believed they were able to perform a VC test at home without supervision. A reason for this discrepancy may be that patients in the present study were trained in unsupervised VC, and that most patients already had experience with telehealth and remote monitoring.

Clinical implications

Our findings indicate that a single face-to-face training session prior to VC testing at home was sufficient for most patients to learn how to perform a VC test independently. In clinical practice, patients could be trained in VC testing during a visit to a multidisciplinary clinic or at home. Starting home-monitoring of VC shortly after diagnosis is most beneficial, as insight into the rate of disease progression can guide the timing of clinical interventions. When patients show noticeable or unexpected changes in their unsupervised VC during home-monitoring, a face-to-face or video consultation may be scheduled in order to determine whether a change in VC was caused by respiratory muscle weakness, or other factors, such as pain/discomfort, illness, fatigue or performing the VC test incorrectly. Support during VC testing at home could be improved by including MND-specific prompts, and written and visual feedback (e.g. flow-volume curve) in the mobile spirometry app.

Home-monitoring of VC could be combined with patient-reported symptoms of dyspnea, in order to provide healthcare professionals with more insight into the patient's respiratory function and reduce false negative findings. When home-monitoring data indicates the

presence of respiratory dysfunction, based on VC, symptoms or both, patients should be referred to a multidisciplinary clinic for further examination. An advantage of this approach is that the frequency and timing of clinic visits will be tailored to the rate of disease progression and needs of individual patients. In turn, this may result in earlier detection of a respiratory function decline, and more timely referral to a pulmonologist or initiation of NIV, compared to the usual 3 monthly in-clinic care. This study contributes to the recently published Road Map, that was created to facilitate the wide-scale adoption of digital technology and remote monitoring in MND, as it provides evidence on how to measure respiratory function in patients with MND [31].

Strengths and limitations

A strength of the present study is that home-monitoring of VC was part of an existing telehealth service, which facilitated home-monitoring and communication, and optimized adherence. A limitation is the fact that the majority of patients in our cohort were male and relatively young, which reduces the generalizability of our results. Future studies could assess long-term home-monitoring of VC, and determine to what extent the course of unsupervised VC over time corresponds to disease progression, and how it relates to decision-making in MND care. We assessed the upright VC in the present study, despite studies showing that in some patients the upright FVC may remain stable even when respiratory insufficiency is already present [32–35]. Based on existing literature, the maximal inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP) or supine VC may be more sensitive in detecting respiratory muscle weakness [18,27,36–38]. However, due to the lack of low-cost respiratory pressure meters, home-monitoring of MIP and SNIP will be much more costly. Furthermore, the supine VC test can be challenging and burdensome to perform for patients with gross motor disability, as it requires transfer to a flat surface. As a result, more patients may require assistance from a caregiver, which increases caregiver burden and may reduce adherence. However, future studies could evaluate whether other pulmonary function tests, besides the upright VC, are valid and feasible for home-monitoring in patients with MND.

Conclusion

Unsupervised VC testing at home, with prior face-to-face training and reminders during follow-up, is a valid and feasible method for the remote monitoring of respiratory function in MND care, and well-received by patients and their caregivers.

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CHAPTER 7

7

General discussion

The main aims of this thesis were to expand the knowledge on the use and implementation of telehealth in multidisciplinary MND care, and to identify adequate methods for the remote monitoring of patients with MND.

The use of telehealth in MND healthcare

It is well-documented that telehealth can have positive effects on clinical outcomes related to physical and mental health in various populations, and that it promotes self-management and improves disease control, especially in severe diseases.[1–3] In turn, telehealth in care for patients with MND may improve the continuity of care, and allow for personalized care, which helps to tailor care and information to the ever-changing care needs of patients (Figure 1). Despite the wide availability of digital health technologies and the increasing interest in telehealth in recent years, the use of telehealth in MND remains limited.[4,5] When looking at the use of telehealth for patients with MND prior to the COVID-19 pandemic, we found that existing telehealth services (with exception of telemedicine) were mostly used for a select subgroup of patients with respiratory insufficiency, who were in an advanced stage of the disease (**Chapter 2**). The use of telehealth is beneficial for this subgroup, as they may experience more difficulties travelling to a clinic due to their physical impairments. However the use of telehealth is also valuable in earlier stages of the disease, e.g. to help determine when to initiate clinical interventions. For this reason, it is of importance that telehealth becomes available for a broader group of patients with MND. This can be achieved by including a range of disease-related outcome measures, such as functional ability and psychological well-being, that are relevant for home-monitoring throughout the course of the disease.

Continuity of care

As described in **Chapter 3,** the telehealth service *ALS Home-monitoring and Coaching* was available for all patients with MND and designed to remotely monitor patients from early in the course of their disease. Findings in this chapter show that patients with MND were willing to start using telehealth from shortly after diagnosis, and also continued using telehealth until shortly before death. Especially remote contact with the multidisciplinary care team was appreciated by the patients. Existing research has shown that the use of telemedicine (i.e. video consultations) also improves the continuity of MND care in the final disease stages, as well as during the COVID-19 pandemic.[6–9] These findings indicate that patients in all disease stages were willing and able to use telehealth/telemedicine, and that these remote approaches allow for accessible specialist care in times when travelling to a multidisciplinary clinic is very challenging or not possible. The improved continuity of care as a result of telehealth is for a large part dependent on the availability of (informal) caregivers, since a subgroup of patients with physical or cognitive impairments is not able

to perform home-assessments independently, and requires assistance from a caregiver (**Chapters 2 & 3**). As a result, the use of telehealth may increase burden on caregivers, which is already high in MND.[10] It is, therefore, important to consult with both the patient and caregiver when deciding on whether to start with telehealth and the contents of the remote monitoring protocol. So far, caregivers have reported satisfaction with the use of telehealth, which may suggest that burden of telehealth is not too high.[11,12]

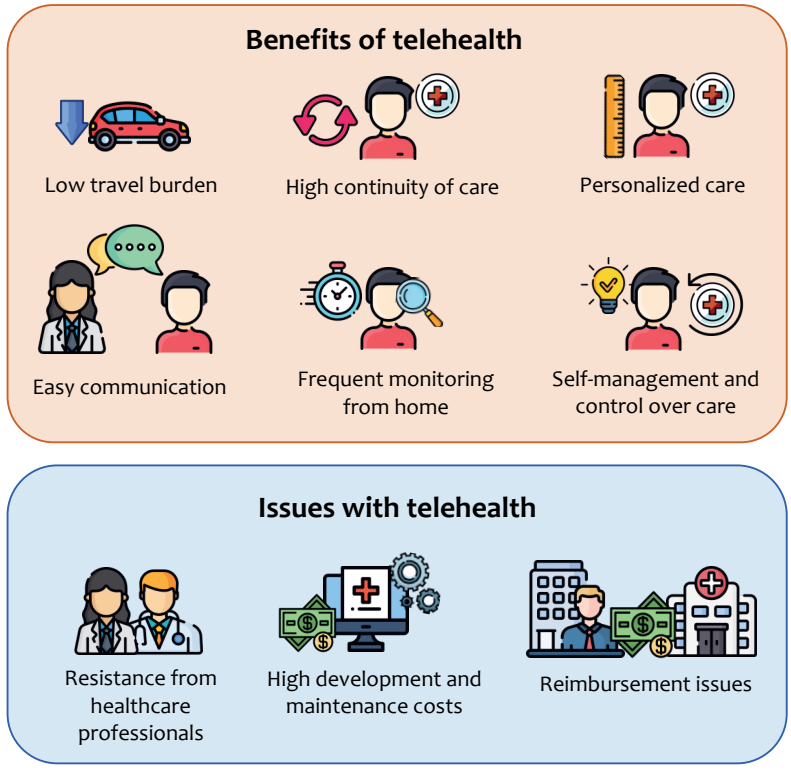

Figure 1 The benefits of and issues with telehealth based on data from this thesis and previous scientific studies.

Personalized care

Not only the continuity of care, but also the personalization of care can be improved by telehealth. Personalized care is important for patients with MND due to the clinical heterogeneity of the disease, which shows through differences in site of disease onset, rate of disease progression, occurrence of symptoms and the level of cognitive impairment. In **Chapter 3** the personalization of care was achieved by adjusting the timing, frequency and contents of information, feedback and clinic visits, based on data from the home assessments and the needs of patients. As a result, patients reported they had more insight into their disease, which helped with making informed decisions about

care and increased their feeling of control over the disease. Similarly, in other chronic diseases, such as heart failure, hypertension, idiophatic pulmonary fibrosis, and diabetes, self-monitoring at home made patients more aware, and more confident in handling the disease and making care-decisions.[13–18] Importantly, the increased perceived control as a result of personalized care has shown to improve psychological well-being in patients.[1913,20] These findings indicate that the use of telehealth makes the care process as a whole more accessible and patient-friendly, and puts more emphasis on giving patients the control over their own care process.

Determinants of telehealth implementation in MND care

An important step to enhance the use and implementation of MND-specific telehealth services, is identifying why previous endeavors have failed to be implemented in MND care, and how these issues can be resolved.

Costs

One of the main barriers to the implementation of telehealth in MND care is the lack of reimbursement of relatively high, initial starting costs, while eventually telehealth may save substantial costs by more efficient care (**Chapter 2**). One of the reasons for the high initial costs is that medical centers each develop their own telehealth service, and try to 'reinvent the wheel', which is time-consuming. Instead, it would be more efficient and cost-effective to develop one central telehealth platform that can be used by multiple medical centers. This approach allows centers to combine their financial resources, and share costs related to the development, design and maintenance of telehealth, making it more affordable and transparent for insurance companies and other payers. In addition, multiple centers can combine their knowledge and collaborate to design the optimal telehealth service. Moreover, by increasing the number of telehealth users, the cost of telehealth per patient will be reduced. Accordingly, the costs of *ALS Home-monitoring and Coaching* per patient were relatively high, due to the fact that only 50 to 70 patients used telehealth in one medical center. In The Netherlands the first part of a nation-wide implementation project, has been completed, where the first 10 (out of 25) multidisciplinary clinics of the ALS care network were introduced to 'ALS Home-monitoring and Coaching'.[21] Benefits of this care network are that it facilitates communication between clinics and speeds up the diffusion of telehealth. The final aim is to provide telehealth to 500 patients with MND in the Netherlands to make telehealth cost-effective and MND healthcare more efficient and accessible for patients.

Reimbursement

Another important barrier to telehealth implementation is the lack of reimbursement for telehealth. This issue was also identified in various diseases and healthcare settings.[22–24] Showing that insurance companies that do not, or barely, include telehealth in their reimbursement options was a widespread problem that limited the use of telehealth.[25] However, due to the COVID-19 pandemic, in which patients with MND in most countries were not allowed to visit a clinic, MND care was forced to adapt, and started to provide care remotely. As a result, countries quickly adopted new policies and legislation, that would allow billing and reimbursement of telehealth and telemedicine.[26–28] Since then, there has been a dramatic increase in publications on the use of telehealth, telemedicine and digital technologies in MND care.[7–9,29–33] Mainly telemedicine through videoconferencing was proposed as method for the provision of care, as this could be set-up relatively quickly and replace regular in-clinic consultations. The increased availability of telehealth and improved reimbursement, as a result of the COVID-19 pandemic, will facilitate future development and implementation of novel telehealth services in MND care.

Patients

Besides proper reimbursement, the attitude of patients towards the use of telehealth is another essential determinant for the success of telehealth services.[23,24] We showed that patients with MND who have experience with telehealth, are positive about the use of telehealth or telemedicine, due to their benefits, such as reduced burden from travelling and visiting a clinic, more control over care, better continuity of care, and more personalized care (**Chapters 2 & 3**). Additionally, the majority of patients in the Netherlands and abroad, that for the most part did not have experience with a telehealth service, were willing to receive care remotely and perform assessments at home, and only few reported concerns with remote digital technology use (**Chapter 4**). Based on these findings we can conclude that the attitude of patients with MND is a facilitator for the adoption and implementation of telehealth, especially considering that the attitude of patients may positively influence the attitude of healthcare professionals.

An important aspect of a telehealth service, that promotes a positive attitude of patients towards the use of telehealth, is a user-centered telehealth design. A user-centered design includes the involvement of end-users, such as patients with MND and healthcare professionals, in the development process, and ensures that the telehealth service fits the needs of end-users.[34] Accordingly, the user-centered approach has been used to design telehealth services, which resulted in good adherence and positive experiences with telehealth from patients.[12,13] In addition, a recently published Roadmap, aimed at facilitating the adoption and utilization of remote digital health technologies in MND care and clinical trials, also used a user-centered co-design approach.[35] This roadmap outlines all the steps that are required to find a set of reliable digital outcome measures that

can be captured by patients with MND from home, and successfully implement remote digital health technology in care and research. One of the first steps in this roadmap is the evaluation of patients' attitude towards digital technology use and home-monitoring in care and clinical trials, which was investigated in **Chapter 4**. Patients considered improved communication with the multidisciplinary care team and more insight into the disease to be important as benefits of digital technology use. Interestingly, these aspects were improved by telehealth services that included self-monitoring at home and accessible communication with healthcare professionals (**Chapter 2 & 3**), indicating that these components are important to include when designing new telehealth services.

Healthcare professionals

Not only patients' attitude, but also the attitude of healthcare professionals towards the use of telehealth is an important determinant for the acceptance and implementation of telehealth in MND care.[23,24] Compared to patients, healthcare professionals have more doubts about telehealth use, mostly due to uncertainty about proper physical examination, and the lack of personal contact (**Chapter 2**). Similarly, in other healthcare settings it shows that healthcare professionals may believe that telehealth may interrupt/ not improve the delivery of care, or there may be a general resistance towards telehealth among healthcare professionals.[24] However, healthcare professionals who were experienced with a telehealth service that was integrated into the existing electronic health records were positive on the use of telehealth, and believed that telehealth was a valuable addition to MND care (**Chapter 3**). Therefore, changing the attitude of healthcare professionals, especially those who are skeptical about, or have little experience with telehealth, may be a primary aim in the implementation process.

An effective way of doing this is by first introducing telehealth to healthcare professionals who are eager to use telehealth, the so called early adopters. This subgroup is willing to help with troubleshooting and the development of telehealth. In turn, the early adopters may positively influence other, more skeptical, healthcare professionals. Moreover, it is important that a telehealth service is integrated with the existing electronic health records, since it makes telehealth easy to use and facilitates adoption by healthcare professionals.[36] In order to further improve telehealth acceptance and adoption among healthcare professionals, it is important to provide information, training and support, prior, during and after the implementation of telehealth (**Chapter 2**).[23,24] This ensures that healthcare professionals will be technically skilled to use digital technology, understand its benefits and be properly informed about topics such as patient data safety. Additionally, continuous evaluation of telehealth and demonstrating the benefits of telehealth may also improve the attitude of healthcare professionals.[24] Lastly, the implementation process should be guided by an implementation framework, since it describes 1) the process of translating research into practice, 2) the facilitators and barriers, and 3) the evaluation

of the implementation.[37] This systematic approach can improve the effectiveness of the implementation process and the sustainability of the telehealth service.

Remote monitoring of patients with MND

Two of the main goals of remote monitoring in MND care are: To enhance self-management by patients in care, and to provide healthcare professionals with data that will help with making clinical decisions remotely. In order for remote monitoring to be effective, home measurements should clinically relevant, feasible in a home setting, and provide accurate data (Figure 2). Firstly, the clinical relevance of an outcome measure is determined by what healthcare professionals and patients consider to be relevant, and to what extent the outcome measure is related to the disease (e.g. functional ability, respiratory function), and determines whether the monitored data is meaningful in clinical care. According to patients, respiratory function and muscle strength assessment are the most relevant outcome measures for home-monitoring (**Chapter 4**), which corresponds to the outcome measures that are considered to be important in clinical trials as well.[38–40] Secondly, an outcome measure is considered feasible when a patient (and their caregiver) is able and comfortable to perform an assessment at home without experiencing considerable physical or cognitive burden; this will be discussed in the next paragraph. Lastly, the accuracy of the remotely collected data is determined by the validity and reliability, and ensures that the data is appropriate for clinical decision-making. Examples of clinically relevant and feasible outcome measures that have been proposed in literature for home-monitoring are pulmonary function tests, quality of life questionnaires, muscle strength measurements, body weight measurements, physical activity monitors, functional impairment questionnaires, speech assessments and pain questionnaires.[7,41–47]

Feasibility

In **Chapters 2, 3 & 6** the feasibility of home-monitoring was assessed through the adherence to the assessments and the acceptability among patients. When devices or apps were easy to use, and home-monitoring was not burdensome or time consuming, patients with MND were accepting of and adherent to home-monitoring. Some aspects of remote monitoring that hinder adherence and negatively affect patient satisfaction, are cumbersome monitoring protocols, malfunctioning devices, non-user-friendly interfaces.[47–49] For these reasons, it is important to involve patients in the process of selecting and testing devices/assessments, and designing a remote monitoring protocol. Accordingly, patients were involved in **Chapter 4** to evaluate their perspective on home-monitoring, and found that most patients are willing to monitor several assessments at monthly or even weekly intervals at home. This shows that patients with MND are motivated to monitor disease-related outcome measures from home at frequencies that are higher

than usual in-clinic monitoring. In turn, this will aid healthcare professionals with clinical decision-making by providing more insight into patients' disease (progression), and it will make clinical trials more efficient by reducing the sample size.[41,50,51]

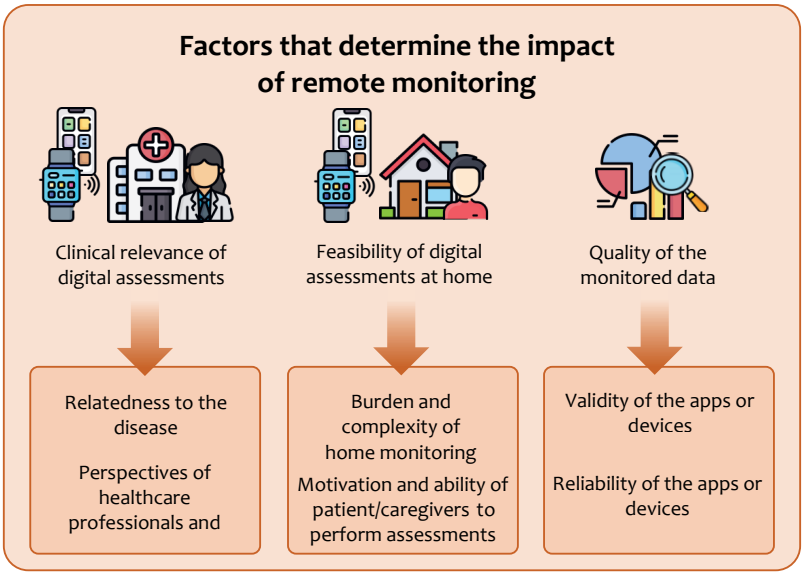

Figure 2 Factors that determine the effectiveness of remote monitoring, and what those factors are based on.

Adherence

In order to use the full potential of frequent monitoring, the adherence to the home-assessments needs to be sufficient. An important determinant of adherence, is the involvement of a multidisciplinary team and the provision of (personalized) feedback on the home-assessments (**Chapters 3 & 6**).[52] Patients will adhere better to a self-monitoring protocol when they know that a multidisciplinary care team monitors the data closely, and provides feedback and information when needed. There were two studies that investigated the home monitoring of various outcome measures outside of a clinical setting for research purposes, and required patients to complete assessments and transfer the data digitally to the investigators, without any feedback.[51,53] After several months adherence to the home measurements deteriorated, which was likely partly due to the lack of involvement of healthcare professionals and feedback. In contrast, the adherence to home monitoring was considerably better in healthcare settings where feedback was provided by a healthcare professional (**Chapter 3**).[12,13] Previous research reported that the minimum feedback that was expected by patients with MND, was a confirmation that the data was received by the medical team, and that their problems were acknowledged.[12] A negative determinant for adherence to home-monitoring is patients forgetting

measurements[12,47,52], however, this problem can be tackled by sending reminders on days that home measurements are scheduled, as discussed in **Chapters 3 & 6**. Important to note, is that the reminders are aligned with the monitoring protocol, and that they are adjusted to the preferences of the patient (e.g. day of the week, time of day, frequency, type of notification).

Home-monitoring of respiratory function

Home-monitoring of respiratory function is one of the most important aspects that needs to be included in a telehealth service, however, it was unknown which measures could best be used for home-monitoring of respiratory function. Out of the three most commonly used methods in the clinic, i.e. blood gas analysis, symptoms of hypoventilation and pulmonary function testing, the latter two were considered most suitable for the home-monitoring of respiratory function, due to their non-invasive nature and simplicity of assessment. In **Chapters 5 & 6** we have shown that both patient-reported symptoms of dyspnea and unsupervised vital capacity testing were valid and feasible for remotely monitoring respiratory function in cohorts of patients with MND. A previous clinical trial, which also included home-monitoring of vital capacity and patient-reported respiratory symptoms, showed that the use of telehealth was appropriate for tailoring medication adjustments in patients with Idiopathic Pulmonary Fibrosis.[13] To what extent home-monitoring of respiratory function can guide clinical decision-making in MND care, such as initiation of NIV, has not yet been investigated. However, when we look at current NIV practices in European countries, and in the United States, the FVC and dyspnea/orthopnea are important outcome measures for the indication of NIV.[54] These findings indicate that regular home-monitoring of vital capacity and dyspnea-related symptoms will likely facilitate the referral and timely initiation of NIV in patients with MND. Especially symptoms of dyspnea/orthopnea are important for the decision to start with NIV, since patients can be reluctant to start with NIV when they experience no or only mild respiratory symptoms.[55,56]

Methodological considerations

Study population - generalizability

We investigated the use of telehealth and home-monitoring in a sample of patients that received care at a University Medical Center specialized in MND. For this reason, results from these studies may not be fully generalizable to other, less specialized, healthcare settings. However, when we look at the data presented in **Chapter 4**, we see that a large proportion of the general MND population has a positive view towards performing home-assessments and remote monitoring by a medical team. Indicating that when telehealth

is implemented and used in other healthcare settings, it is likely that similar results will be found.

Study population - caregivers

In this thesis, caregivers' experiences with or attitudes towards telehealth are underemphasized, despite the importance of their role with assisting with remote monitoring and digital technology use. Considering the fact that caregiver burden is already high[10] and the continuity of telehealth is mainly dependent on caregiver assistance, they should be involved in the evaluation of home-monitoring and telehealth. This will help to determine how telehealth services can be tailored to the needs of caregivers.

Pulmonary function tests

Out of all pulmonary function tests we chose to assess the vital capacity test, in upright and supine position, in this thesis. One reason for choosing the vital capacity test, is that it has been well-documented that it is related to disease progression[57,58] (where vital capacity in supine position is more sensitive to detect respiratory muscle weakness compared to the upright position[40,57,59]). On top of that, the vital capacity is more widely available in MND care and more frequently assessed during regular visits to the clinic compared to the MIP or the SNIP.[54,60] As a result, multiple multidisciplinary centers could include patients during regular clinic visits, which enabled us to recruit a large cohort of patients with MND. Moreover, the vital capacity test shows lower variability compared to the MIP and SNIP[61], and handheld spirometers are much more affordable than respiratory pressure meters, making the vital capacity test ideal for home-monitoring. It should, however, be noted that the MIP and SNIP may be more sensitive in detecting respiratory muscle weakness, especially in patients with a bulbar onset.[40,57,61,62] Therefore, the MIP and SNIP could be valuable for home monitoring, but will require a larger budget and more extensive training. Lastly, the peak cough flow could be included in home-monitoring to help to detect ineffective cough and issues with airway clearance.

Clinical implications

This thesis has shown that telehealth can enhance current MND healthcare, through personalization of care, improved monitoring, reduced burden of care and increased patients' perceived control over the disease. As previously described, a roadmap was created to promote and give structure to the wide-scale adoption of digital health technologies in MND healthcare and clinical trials.[35] In the roadmap there are three main questions: 'what to measure?', 'how to measure?' and 'how to implement?'. This thesis contributes to the roadmap by formulating clinical implications that help to answer the

above-mentioned questions and facilitate the design and utilization of telehealth services in MND healthcare.

Standardizing remote digital health assessments

In order to optimize home-monitoring, a standardized set of remote digital health assessments should be developed, as it will improve the quality and uniformity of the remotely monitored data, and ensures that the data can be used for clinical decision-making and clinical research. For this reason, home-based studies should be set-up with the involvement of patients and caregivers to determine the validity, reliability and feasibility of a variety of home-assessments. Based on the data from this thesis, as well as existing literature, important home-assessments for care purposes are functional impairment [63–65], body weight/weight loss [66,67], vital capacity [57,58,68], symptoms of dyspnea and orthopnea [54,69,70], lower or upper limb muscle strength [38,44], and speech [71]. Besides the physical aspects of MND, it is also important to monitor mental well-being, and spirituality, since they are considered important to patients with MND, and may affect their quality of life and psychological well-being of their caregivers.[72–74] Therefore, a holistic care approach is recommended for remote monitoring to optimize psychological well-being in patients with MND and their caregivers.

Designing a telehealth service

Ideally, one centralized platform should be developed, which includes a telehealth service and a structured database (Figure 3). This will enhance the diffusion of telehealth, and facilitate clinical research by increasing the accessibility to real-world health data. The telehealth service and database should be co-designed with the involvement of relevant end-users (e.g. patients, caregivers, healthcare professionals, researchers). Each medical center can tailor the telehealth service to the needs of their multidisciplinary care team and patients, but should include at least: home-monitoring of disease related outcome measures, messaging between patient/caregiver and multidisciplinary care team, and a dedicated healthcare professional that monitors the data and provides feedback. To ensure equal quality of care for all patients, a standardized care protocol needs to be created by each multidisciplinary care team, describing what actions need to be taken, at what thresholds or changes in the outcome measures, and by who. These actions may include referring a patient to a specialist for further assessment, providing information, or initiating clinical interventions. The dedicated healthcare professional should use the standardized care protocol during monitoring as a guide to provide personalized information and feedback regularly to patients. This will help patients to gain insight into their disease (progression), and enables them to make independent decisions in care. Furthermore, a home-monitoring protocol needs to be developed, that describes which home-assessments have to be monitored and at what frequency. In clinical practice, the monitoring protocol can be tailored, through a shared decision making process between

the patient/caregiver and a healthcare professional, to fit the need of each individual patient/caregiver. For example, the monitoring frequency can be personalized at diagnosis to a slow or rapid rate of disease progression, based on the ENCALS prediction model, and can be adjusted as the disease progresses.[75] In addition, the number and selection of home-assessments may vary between patients due to differences in physical and cognitive abilities, or the availability of a caregiver at home.

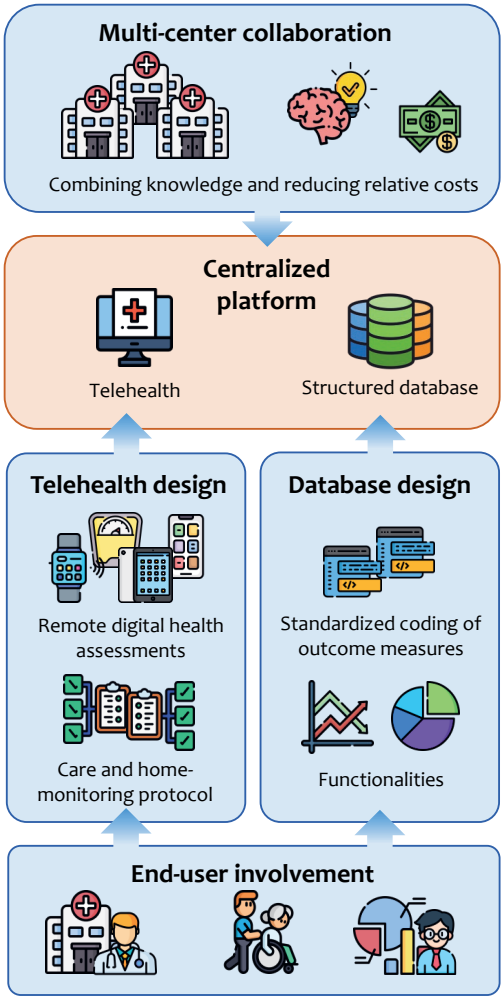

Figure 3 Designing and developing a centralized platform consisting of a telehealth service and a structured database using a user centered approach.

Implementation of telehealth in MND care

In order to accomplish wide-scale implementation in MND care, telehealth should be affordable and suitable for a variety of healthcare settings. This can be achieved when

multiple centers collaborate, and combine their knowledge to design a centralized telehealth platform, and reduce the relative financial investments. Once the centralized telehealth platform has been established, it will facilitate the onboarding process and implementation for other medical centers. To promote successful implementation, a theoretical framework should be used to give structure to the implementation process.[21] In addition to that, implementation scientists should evaluate what barriers and facilitators are expected by healthcare professionals, as this will help decide which strategy is most appropriate to change current care practices. The expected facilitators and barriers will determine how the telehealth service can best be used in conjunction with the existing care system and can help to define different roles for healthcare professionals during the implementation process. When the implementation plan is being executed, continuous evaluation and support is required to determine the needs of healthcare professionals and whether aspects of the process need to be changed. After the implementation has been completed, studies on the cost-effectiveness should be conducted in various healthcare settings, e.g. academic hospital, regional hospital, rehabilitation center, to provide insight into the (potential) cost-saving aspect of telehealth, making telehealth more appealing for insurance companies and other payers.

Furthermore there is a need to train the next generation of healthcare professionals. They are the key players in the digital transformation of healthcare. Their future practice is increasingly enabled by technology. Training medical students in personalized care through telehealth will prepare the next generation of physicians to conscientiously use these technologies and this will have a significant impact on the adoption and implementation of telehealth.

Recommendations for future research

Telehealth in MND care

Future research could compare the utilization and cost of care between telehealth and usual care, to determine the cost-effectiveness of telehealth. If telehealth is found to be cost-effective, this will promote the use of telehealth and facilitate implementation. Additionally, future studies could investigate how the use of telehealth affects the decision-making and psychological well-being in MND healthcare, and how this compares to usual in-clinic care. Specifically, studies should determine how telehealth affects the timing of information and clinical interventions (e.g. wheelchair, gastrostomy, non-invasive ventilation, speech assistance), and how telehealth can best used to improve patients' mood, feelings of depression, hopelessness and perceived control over the disease.

Caregivers and home-monitoring

This thesis has been mainly focused on the home-monitoring of patients with MND. However, caregivers experience considerable care burden, accompanied with mental distress, and are therefore in need of support. Hence, more research is needed to evaluate how caregivers can best be monitored and supported through telehealth. In turn, this will help develop a telehealth service that includes information for, and support to, caregivers. Additionally, the burden that caregivers experience from assisting with home-monitoring should compared to the burden from usual in-clinic care, to determine whether telehealth reduces care burden on caregivers.

Home-monitoring for clinical trials

Besides the benefits of home-monitoring for MND care, it can also greatly benefit the efficiency of clinical trials, since more patients will be able to participate and more frequent follow-up can reduce the sample size required for a trial. For these reasons, future research could assess to what extent long-term home-monitoring of disease-related outcome measures (e.g. vital capacity, muscle strength, functional ability, physical activity) reflects disease progression in patients with MND.

Pulmonary function tests

In this thesis we have shown that the upright vital capacity test is a valid and feasible method for the remote monitoring of respiratory function. However, future research should assess whether other pulmonary function tests, such as the SNIP, MIP, peak cough flow and supine vital capacity test, are valid and feasible for home-monitoring in patients with MND.

Summarizing the recommendations for telehealth

An optimal telehealth service should:

- be co-designed by patients, caregivers, healthcare professionals and researchers, to ensure that telehealth fits the needs of end-users.
- be personalized to the individual patient and aimed at giving patients more control throughout the care process.
- include at least home-monitoring, messaging between patients and care team, and regular provision of personalized information and feedback.
- include a standardized set of remote digital health assessments, to make sure that the monitored data can be used for both care an research purposes.

To optimize uptake and sustainability of telehealth in MND care:

- multidisciplinary clinics could collaborate to develop a centralized telehealth platform, as it makes telehealth services more affordable and widely accessible.
- a theoretical implementation framework should be used, as it gives structure to the implementation process and can result in more sustainable telehealth services.
- potential barriers and facilitators to implementation of telehealth should be identified, and appropriate strategies should be chosen accordingly.
- telehealth services should be integrated the existing electronic health records used in clinical practice.
- education on telehealth should be provided to medical students, to increase their knowledge on telehealth and improve adoption among healthcare professionals.

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SUMMARY

Summary

Motor neuron disease (MND) is a rapidly progressive neurodegenerative disease that leads to loss of motor neurons and eventually leads to paralysis of most voluntary muscles. The initial symptoms of MND may occur in the arms or legs, known as a spinal onset, or show in difficulties with speech and swallowing, known as a bulbar onset. The average disease duration is 2 to 4 years, and the main cause of death in patients with MND is respiratory failure, due to severe respiratory muscle weakness. Patients with respiratory muscle weakness, can develop hypoventilation, which leads to shortness of breath, fatigue and sleepiness during the day, and restless sleep during the night.

Patients with MND require multidisciplinary care, which is aimed at optimizing participation and quality of life and includes 3 to 4 monthly visits to a multidisciplinary clinic. Besides improving quality of life, multidisciplinary MND care has shown to also prolong survival, compared to non-specialized care. One of the most effective treatments for improving survival in patients with MND is non-invasive ventilation (NIV), as it provides ventilatory support when patients are respiratory insufficient. A drawback of multidisciplinary MND care, is that accessing and receiving care at a multidisciplinary clinic can be time-consuming and physically challenging for patients with MND, due to their physical disability. This results in considerable burden of care, and may hinder the continuity of care, which can increase distress and negatively affect patients' psychological well-being.

Telehealth, which is the remote provision of care, holds the potential to improve accessibility and personalization, and reduce burden of multidisciplinary MND care, by enabling frequent monitoring of patients from home. Despite these promising benefits of telehealth and the wide availability of digital technologies, the use of telehealth in care for patients with MND is limited. For these reasons it would be of great benefit to know what factors determine the success of the implementation of telehealth in MND care, and what methods can best be used for remote monitoring of patients with MND. In particular, the remote monitoring of respiratory function is important, as it can help healthcare professionals to detect respiratory decline earlier and optimize the timing of NIV. In order to determine which respiratory measures are appropriate for remote monitoring in a home setting, their validity and feasibility should be investigated.

This thesis aims to expand the knowledge on the use and implementation of telehealth in multidisciplinary MND care, and identify adequate methods for the remote monitoring of patients with MND.

Chapter 1 provides a general introduction on MND and multidisciplinary care. Furthermore, we introduce telehealth and remote monitoring as a way to improve multidisciplinary in MND care and highlight areas that require further investigation.

Part 1 Telehealth and digital technology

Chapter 2 describes a systematic review on the use of telehealth in the care for patients with ALS, and the barriers to and facilitators of telehealth implementation. We identified three types of telehealth: videoconferencing, home-based self-monitoring and remote NIV monitoring. Telehealth was mainly used by patients with respiratory impairment and focused on monitoring respiratory function. Facilitators for telehealth implementation were a positive attitude of patients and caregivers toward telehealth and the provision of training and ongoing support. Healthcare professionals were more likely to have a negative attitude toward telehealth, due to the lack of personal evaluation/contact and technical issues. Other important barriers to telehealth were lack of reimbursement and cost-effectiveness analyses. Based on these finding future endeavors should focus on improving the attitude of healthcare professionals towards telehealth, and investigate the cost-effectiveness of telehealth.

In **Chapter 3** we evaluated the use of telehealth as part of specialized care for patients with ALS and the user experiences of patients and healthcare professionals. In total 50 patients with ALS used a telehealth service, which consisted of an ALS-app for self-monitoring and messaging, alerts for symptom-worsening, and regular nurse practitioner follow-up with personalized feedback and information. Patients self-monitored their well-being, body weight and functional status on average for 11 months. The adoption rate was high (80%), dropout rate was low (4%) and patients showed good adherence to home-monitoring protocol. Patients continued to use telehealth until shortly before death. Most patients experienced using telehealth as easy, helpful, not burdensome, and reported satisfaction with flexible clinic visits and the continuity of care. Healthcare professionals reported that telehealth was of added value in ALS care. From these findings we concluded that ALS care supplemented by home-monitoring and nurse practitioner follow-up was suitable and widely accepted by patients and healthcare professionals in our ALS clinic. Success factors were low self-monitoring burden, a user-friendly platform and the provision of personalized feedback.

Chapter 4 aimed to capture the opinion of patients with MND about remote monitoring in care and clinical trials, and their concerns and preferences regarding the use of digital technology. A multi-centre survey study was conducted in three MND clinics in The Netherlands, the United Kingdom (UK) and Australia. The survey was co-developed by investigators from participating clinics and eight patients with MND. The main topics included: patients' attitude towards receiving remote care, monitoring frequency and devices, participating in decentralized clinical trials, and their preferences for and concerns with digital technology. Patients were invited either by e-mail or mail to participate in this study. In total, 332 patients with MND participated, of which most would like to self-monitor their health from home (70%), be remotely monitored by a multidisciplinary care

team (75%), and would be more willing to participate in clinical trials from home (65%). Patients considered respiratory function and muscle strength to be most valuable for home-monitoring, and considered 3-4 measurements at a weekly frequency as acceptable for home-monitoring. Of all patients, 15% would not like to perform home-measurements; this subgroup was more concerned about the burden, distress due to self-monitoring of disease progression, privacy and data security. Our findings show that the majority of patients with MND holds a positive attitude towards the use of digital technology in both care and clinical trial settings. However, a subgroup of patients described a number of concerns that unless addressed risk being barriers to universal adoption. Addressing these barriers early in the design and implementation of remote digital technology with a user centred design approach will reduce the risk of technology exclusion.

Part 2 Remote monitoring and management of respiratory function

In **Chapter 5** we determined which patient-reported hypoventilation symptoms are best for screening reduced respiratory function in patients with MND, and compared them to the respiratory domain of the amyotrophic lateral sclerosis functional rating scale (ALSFRS-R). We developed a 14-item hypoventilation symptom questionnaire (HYSQ) based on guidelines, expert opinion and think-aloud interviews with patients. Symptoms of the HYSQ were related to dyspnea, sleep quality, sleepiness/fatigue and pneumonia. A total of 100 patients with MND were included from 6 medical centers, who performed a supine vital capacity test and filled-out the HYSQ and ALSFRS-R. A supine vital capacity <80% of what is predicted was considered reduced respiratory function. Dyspnea-related symptoms were combined into the MND Dyspnea Scale (MND-DS), which showed better diagnostic performance than the sleep-quality symptoms, sleepiness/fatigue-related symptoms, and the respiratory domain of the ALSFRS-R. For this reason, we recommended the MND-DS for remotely monitoring respiratory function.

In **Chapter 6** we evaluated the validity and feasibility of home-monitoring vital capacity in patients with MND. We included 33 patients with MND who completed a 12-week home monitoring protocol, consisting of 4-weekly unsupervised home assessments of vital capacity and a functional rating scale. Patients and caregivers were trained in performing a vital capacity test during a home visit, and the investigator performed a supervised vital capacity test, which was repeated at final follow-up during a second home visit. In 88% of patients the difference between supervised and unsupervised vital capacity was less than 10%. Home-monitoring of vital capacity was generally experienced as easy and not burdensome, however, some patients were insecure about their vital capacity test performance without supervision. The majority of patients would like home-monitoring of vital capacity in MND care. In conclusion, unsupervised vital capacity testing at home, with prior face-to-face training, is a valid and time-efficient method for the remote

monitoring of respiratory function, and well-accepted by patients with MND and their caregivers.

In **Chapter 7** we discuss the main findings of this thesis, which include the current use and (perceived) benefits of telehealth in MND healthcare, determinants of the implementation of telehealth in MND healthcare, and how to optimize remote monitoring of patients with MND. Furthermore we provide clinical implications for designing and developing the optimal telehealth platform, and how telehealth can best be implemented in MND healthcare. Lastly, we provide recommendations for future research.

SAMENVATTING

Samenvatting (Summary in Dutch)

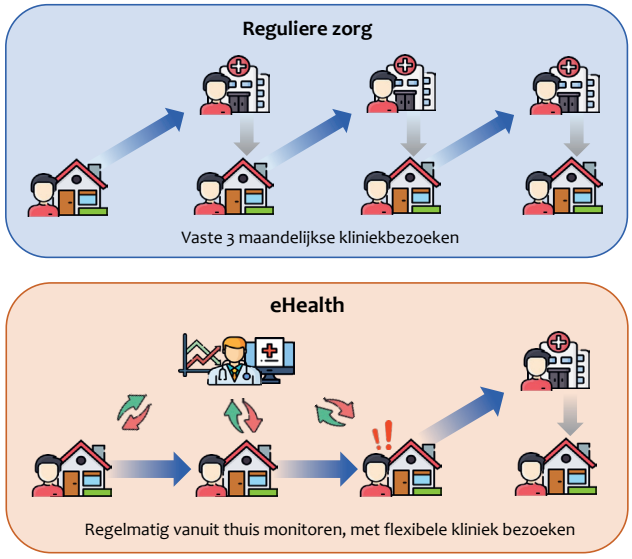
Hoofstuk 1 Introductie

Amyotrofe laterale sclerose (ALS), progressieve spinale musculaire atrofie (PSMA) en primare laterale sclerose (PLS) zijn progressieve zenuwziektes, dit houdt in dat de zenuwen die de spieren aansturen steeds minder goed werken en uiteindelijk afsterven. Dit leidt tot verlamming van heel veel spieren in het lichaam, waardoor mensen met ALS, PSMA of PLS steeds meer moeite ervaren met dagelijkse activiteiten, zoals lopen, schrijven, praten, eten en zichzelf wassen. De eerste symptomen van een zenuwziekte zijn te merken in de armen of benen *(bijv. niet meer een sleutel kunnen omdraaien of een klapvoet tijdens het wandelen)*, of in het spreken en slikken *(bijv. moeilijk kunnen articuleren, of snel verslikken tijdens het drinken)*. ALS is de meest agressieve zenuwziekte waarbij mensen gemiddeld 2 tot 4 jaar na de eerste symptomen overlijden, al is er een kleine groep die langer dan 10 jaar met de ziekte leeft. Mensen met PSMA en PLS leven gemiddeld langer dan mensen met ALS, en in een deel van de mensen met PLS is de ziekte niet fataal. De meest voorkomende doodsoorzaak bij patiënten met een zenuwziekte is het niet meer zelfstandig kunnen ademhalen als gevolg van ernstige zwakte van de ademhalingsspieren. Patiënten met zwakte van de ademhalingsspieren kunnen hypoventilatie ontwikkelen, wat leidt tot kortademigheid, vermoeidheid en slaperigheid gedurende de dag en rusteloos slapen tijdens de nacht.

Patiënten met ALS, PSMA of PLS hebben multidisciplinaire zorg nodig. Dit houdt in dat de zorg wordt gegeven door meerdere disciplines, zoals revalidatie, fysiotherapie, psychologie en ergotherapie. De zorg is gericht op het behoud van participatie en kwaliteit van leven, waarbij patiënten regelmatig (elke 3 – 4 maanden) een ALS behandelteam bezoeken in een multidisciplinaire kliniek. Naast kwaliteit van leven verbetert de multidisciplinaire zorg ook de levensduur wanneer dit wordt vergeleken met reguliere (non-specialistische) zorg. Een van de meest effectieve behandelingen voor het verlengen van de levensduur van patiënten met een zenuwziekte is non-invasieve beademing. Dit is een vorm van ademhalings-ondersteuning, die patiënten gebruiken wanneer zij onvoldoende zelfstandig kunnen ademhalen. Om te bepalen wanneer patiënten moeten starten met beademing, is het belangrijk dat de longfunctie regelmatig gemeten en gecontroleerd wordt.

Mensen met ALS, PSMA of PLS zijn over het algemeen positief over de multidisciplinaire zorg die zij ontvangen, al zijn er wel enkele tekortkomingen. Voor een deel van de patiënten is het reizen naar een kliniek niet vanzelfsprekend, aangezien het fysiek belastend en tijdrovend kan zijn door lichamelijke beperkingen, en soms überhaupt niet mogelijk is door de Corona pandemie. Hierdoor kunnen patiënten niet optimaal zorg ontvangen. Daarnaast worden patiënten relatief weinig gemonitord tussen de bezoeken door, waardoor de gezondheid van patiënten, die minder vaak naar de kliniek (kunnen) komen, in het geding kan komen. Verder sluiten de vooraf geplande 3-maandelijkse bezoeken vaak niet aan bij de behoeftes van patiënten, aangezien de snelheid van de

ziekte (en ziekteduur) aanzienlijk kan verschillen per patiënt. Deze zaken laten zien dat de multidisciplinaire zorg voor mensen met een zenuwziekte moet veranderen, om het bieden van specialistische zorg te optimaliseren.



Figuur 1 Verschillen in het monitoren van patiënten tussen reguliere zorg en eHealth

eHealth is het verlenen van zorg op afstand, en heeft de potentie om de toegankelijkheid en regelmatigheid van de zorg te verbeteren en de zorglast voor de patiënt te verminderen, bijvoorbeeld door het mogelijk te maken dat patiënten thuis regelmatig gemonitord worden. Ondanks deze veelbelovende voordelen van eHealth en de beschikbaarheid van digitale technologie, is het gebruik van eHealth in de zorg voor patiënten met een zenuwziekte op dit moment nog beperkt. Om deze redenen zou het van groot belang zijn om te weten welke factoren het succes van de implementatie van eHealth in de zorg bepalen en welke methoden het beste kunnen worden gebruikt om patiënten met een zenuwziekte op afstand te monitoren. In het bijzonder is het op afstand monitoren van de ademhalingsfunctie belangrijk, omdat het zorgverleners kan helpen om de achteruitgang van de ademhaling eerder op te sporen en de timing van non-invasieve beademing te optimaliseren. Om te bepalen welke metingen voor de longfunctie het beste thuis gebruikt kunnen worden, moeten de validiteit en haalbaarheid in een thuissituatie worden onderzocht.

Doel van proefschrift

Dit proefschrift heeft als doel de kennis over de implementatie en het gebruik van eHealth in multidisciplinaire zorg te vergroten en geschikte methoden te vinden om mensen met een zenuwziekte op afstand te kunnen monitoren.

Deel 1

In het eerste deel van dit proefschrift zal worden gekeken naar het huidige gebruik van eHealth in de multidisciplinaire zorg voor mensen met ALS, PSMA en PLS, welke factoren de implementatie belemmeren en bevorderen, en hoe patiënten het gebruik van digitale technologie en het monitoren vanuit huis ervaren.

Hoofdstuk 2 beschrijft een literatuuronderzoek naar het gebruik van eHealth innovaties in de zorg voor patiënten met ALS, en de belemmerende en bevorderende factoren voor de implementatie van eHealth. We vonden dat drie soorten eHealth werden gebruikt voor ALS: digitale consulten via video, zelfstandig metingen uitvoeren vanuit huis, en het op afstand monitoren van non-invasieve beademing door artsen. eHealth werd voornamelijk gebruikt door patiënten met ademhalingsproblemen en was gericht op het monitoren van de longfunctie in een vergevorderd stadium van de ziekte. Bevorderende factoren voor de implementatie van eHealth waren een positieve houding van patiënten en zorgverleners richting eHealth, en het bieden van training en ondersteuning aan de gebruikers van eHealth (zorgverleners en patiënten). Zorgverleners hadden vaker twijfels en een meer negatieve houding richting eHealth, vanwege het gebrek aan fysiek en persoonlijk contact, en door technische problemen. Andere belangrijke belemmeringen voor de implementatie van eHealth waren het gebrek aan financiële vergoeding van de zorg en informatie over de kosteneffectiviteit. Op basis van deze resultaten raden wij aan dat men zich in de toekomst moet richten op het verbeteren van het gebruik van eHealth onder zorgverleners, en de kosteneffectiviteit van eHealth.

In **Hoofdstuk 3** is het gebruik van eHealth in de zorg voor patiënten met ALS en PSMA geëvalueerd, en de gebruikerservaringen van patiënten en zorgverleners uitgevraagd. In totaal deden 50 patiënten met ALS of PSMA mee met het onderzoek, zij maakten gebruik van de eHealth service 'ALS Thuismeten en Coachen'. Deze service bestaat uit een ALS app waarmee patiënten zichzelf kunnen monitoren en berichten naar het medische team kunnen sturen. Daarnaast werden er waarschuwingen bij het medische team geactiveerd wanneer er een achteruitgang van de symptomen werd gemeten, hierop ontvingen de patiënten informatie en feedback van een verpleegkundig specialist. Ongeveer 80% van de patiënten, die werd gevraagd om de eHealth service gebruiken, is er daadwerkelijk mee gestart. Slechts 2 mensen zijn vroegtijdig gestopt, omdat zij eHealth niet geschikt vonden voor hun wensen. In dit onderzoek maakten patiënten gemiddeld 11 maanden gebruik van eHealth, en voltooiden zij regelmatig thuis de metingen. Patiënten die zijn overleden, gebruikten eHealth tot gemiddeld 19 dagen voor hun dood. De meeste patiënten ervoeren het gebruik van eHealth als gemakkelijk, nuttig en niet belastend, en gaven aan tevreden te zijn over flexibele kliniekbezoeken en de continuïteit van de zorg. Zorgverleners rapporteerden dat eHealth van toegevoegde waarde was in de ALS zorg. Op basis van deze bevindingen concluderen we dat ALS zorg, aangevuld met

thuismonitoring en regelmatige feedback van een verpleegkundig specialist, geschikt is en positief ervaren wordt door patiënten en behandelaren. Succesfactoren van 'ALS Thuismeten en Coachen' waren het gebruiksvriendelijke platform, eenvoudige metingen die niet belastend waren en de persoonlijke feedback.

In **Hoofdstuk 4** hebben we de mening van patiënten met ALS, PSMA of PLS uitgevraagd over het monitoring op afstand in de zorg en onderzoek, en de zorgen en voorkeuren die patiënten hebben met betrekking tot het gebruik van digitale technologie. Er is een vragenlijstonderzoek gedaan in drie multidisciplinaire klinieken in Nederland, het Verenigd Koninkrijk (VK) en Australië. De vragenlijst is ontwikkeld door onderzoekers van de deelnemende klinieken en acht patiënten. De belangrijkste onderwerpen van de vragenlijst waren: de houding van patiënten ten opzichte van het ontvangen van zorg op afstand, de frequentie van het thuis monitoren, het aantal apparaten om te meten, deelname aan onderzoeken op afstand en de voorkeuren en zorgen wat betreft digitale technologie. In totaal deden er 332 patiënten met ALS, PSMA of PLS deel aan dit onderzoek. De meeste patiënten stonden ervoor open om thuis zelf hun gezondheid te monitoren/meten (70%) en om op afstand te worden gemonitord door het multidisciplinaire zorgteam (75%). Ook waren patiënten meer bereid om deel te nemen aan onderzoeken als deze vanuit huis zouden kunnen plaatsvinden (65%). Patiënten vonden de longfunctie en spierkracht het meest waardevol om thuis te monitoren, en hadden de voorkeur voor het wekelijks meten van 3 á 4 verschillende metingen. Van alle patiënten had 15% geen behoefte aan het doen van thuismetingen; deze groep patiënten verwacht dat thuismetingen te belastend of confronterend zijn, en maakt zich zorgen over privacy en data veiligheid. Al met al, is de meerderheid van de patiënten uit verschillende landen bereid om een aantal digitale apparaten/apps te gebruiken om regelmatig thuis hun gezondheid te meten, en is er een positieve houding ten opzichte van zorg en onderzoek op afstand.

Deel 2

In het tweede deel van dit proefschrift hebben we onderzocht we op welke manieren we de longfunctie het beste op afstand kunnen monitoren.

In **Hoofdstuk 5** is er bepaald welke symptomen het beste gebruikt kunnen worden om een verminderde longfunctie bij patiënten met ALS, PSMA en PLS op te sporen. Voor dit onderzoek hebben we symptoomvragenlijst ontwikkeld op basis van ALS richtlijnen, kennis van experts en interviews met patiënten. De vragenlijst bestaat uit symptomen die gerelateerd zijn aan kortademigheid, slaapkwaliteit, vermoeidheid en longontsteking. In totaal werden 100 patiënten met ALS, PSMA of PLS uit 6 verschillende medische centra betrokken bij dit onderzoek. Tijdens het onderzoek werd er bij elke patiënt een longfunctietest in een liggende positie uitgevoerd om de longinhoud te

meten, deze methode is gevoeliger om ademhalingszwakte op te sporen ten opzichte van de longfunctietest in zittende positie. Daarnaast vulden patiënten twee vragenlijsten in over de symptomen van een verminderde longfunctie en het algeheel lichamelijk functioneren. Uiteindelijk bleken klachten van kortademigheid het beste te zijn om een verminderde longfunctie op te sporen. Van deze symptomen is er een korte vragenlijst gemaakt, de MND-DS, die beter was dan de standaard ALS vragenlijst in het opsporen van een verminderde longfunctie. Om deze reden hebben we de MND-DS aanbevolen voor het op afstand monitoren van de longfunctie bij patiënten met ALS, PSMA en PLS.

In **Hoofdstuk 6** hebben we bepaald of het thuis meten van de longinhoud bij patiënten met ALS, PSMA en PLS valide en haalbaar is. Er deden 33 patiënten mee met het onderzoek, zij volgden 12 weken lang thuis een meetprotocol, bestaande uit 4-wekelijkse zelfstandige longfunctiemetingen en een vragenlijst over algeheel lichamelijk functioneren. Patiënten en mantelzorgers kregen tijdens een huisbezoek instructies van de onderzoeker over hoe ze de longfunctietest moesten uitvoeren. Tevens voerde de onderzoeker een begeleide longfunctiemeting uit; deze werd nog een keer gedaan aan het einde van het onderzoek tijdens een tweede huisbezoek. Bij 88% van de patiënten was het verschil in longinhoud tussen de zelfstandige en begeleide longfunctiemeting minder dan 10%. Het thuis monitoren van de longinhoud werd over het algemeen als gemakkelijk en niet belastend ervaren, maar sommige patiënten waren onzeker over de juiste uitvoering van hun longfunctietest zonder begeleiding. De meerderheid van de patiënten zou graag willen doorgaan met het thuis monitoren van de longfunctie voor zorgdoeleinden. Uit deze resultaten trekken we de conclusie dat het zelfstandig thuis monitoren van de longinhoud een valide en haalbare methode is voor het op afstand monitoren van de longfunctie, en dat patiënten en hun mantelzorgers het thuismonitoren als positief ervaren.

In **Hoofdstuk 7** bediscussiëren we alle bevindingen uit dit proefschrift en doen we aanbevelingen voor het gebruik en de implementatie van eHealth in de zorg voor mensen met ALS, PSMA of PLS:

- Een eHealth service moet mede ontworpen zijn door patiënten, zorgverleners, zorgverleners en onderzoekers, om ervoor te zorgen dat deze manier van zorgverlening aansluit bij de behoeften van gebruikers. Daarnaast moet de zorg die met eHealth geleverd wordt gepersonaliseerd zijn en erop gericht zijn de patiënt meer controle te geven gedurende het zorgproces. Hierdoor zijn patiënten beter op de hoogte van het verloop van hun ziekte en kunnen ze beter keuzes maken gedurende het zorgproces.

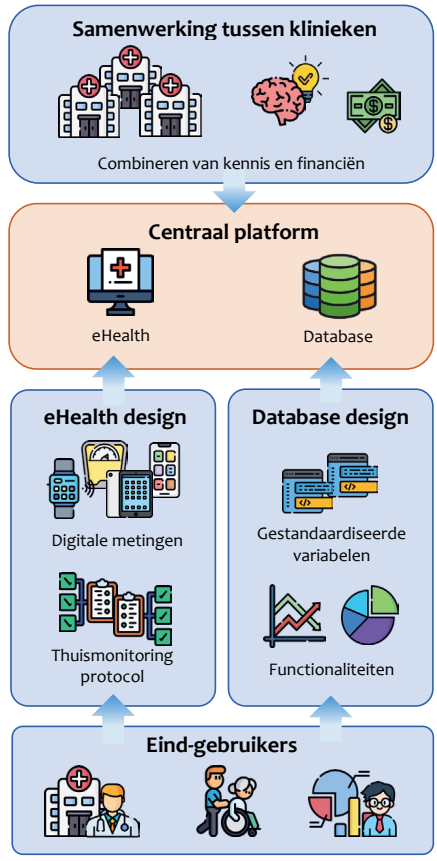
- De minimale functionaliteiten die een eHealth service zou moeten bevatten zijn 1) zelfstandig thuis metingen uitvoeren met gebruik van digitale technologie, 2)

berichtenuitwisseling tussen patiënt en het behandelteam, en 3) het regelmatig versturen van gepersonaliseerde informatie en feedback naar de patiënt. De metingen die thuis worden uitgevoerd moeten gestandaardiseerd zijn, aangezien dit ervoor zorgt dat de data die wordt gemonitord zowel voor zorg- als onderzoeksdoeleinden gebruikt kunnen worden.

- Om eHealth betaalbaarder en breder toegankelijk te maken zouden meerdere multidisciplinaire klinieken gezamenlijk een centraal eHealth platform kunnen ontwikkelen. Dit zal tevens de implementatie van eHealth in de zorg voor mensen met ALS, PSMA en PLS vergemakkelijken.

- Tijdens het implementatieproces moet de focus liggen op het veranderen van de houding of mening van zorgverleners die sceptisch zijn tegenover het gebruik van eHealth, dit is namelijk een van de grootste belemmeringen voor de implementatie van eHealth. Dit probleem zou vroegtijdig aangepakt kunnen worden, door 'eHealth' op te nemen in het curriculum van geneeskunde studies. Dit zal de kennis over en de bekendheid van het gebruik van eHealth vergroten, en geneeskunde studenten voorbereiden op de klinische praktijk.

- Als laatste is het belangrijk dat eHealth geïntegreerd is met het bestaande elektronische patiënten dossier (EPD), aangezien zorgverleners het als een grote barrière zien, als ze naast het EPD apart moeten inloggen om de eHealth gegevens in te zien.



Figuur 2 Het ontwikkelen van een centraal platform

DANKWOORD

Dankwoord

Yes mijn proefschrift is af! Ik zeg nu wel 'mijn proefschrift', maar ik had dit natuurlijk nooit gered zonder de hulp en bijdrage van een hele hoop mensen. Daarom wil ik graag alle mensen bedanken die direct of indirect betrokken zijn geweest bij mijn promotietraject en het realiseren van dit proefschrift.

Deelnemers

Ten eerste zou ik graag alle deelnemers willen bedanken die mee hebben gedaan aan mijn onderzoeken, zonder jullie had ik dit proefschrift natuurlijk niet kunnen schrijven. Ik heb veel respect voor iedereen die zijn steentje heeft bijgedragen aan onderzoek, om op deze manier andere mensen te kunnen helpen. Naarmate ik meer in contact ben gekomen met mensen met ALS, PSMA of PLS, is mij vooral duidelijk geworden dat ondanks het uitzichtloze aspect van deze ziektes, deze mensen ontzettend sterk, daadkrachtig en inspirerend zijn. In het bijzonder heb ik genoten van het contact met de mensen tijdens het onderzoek naar het thuis meten van de longfunctie. Voor dit onderzoeken kwam ik twee keer per deelnemer op huisbezoek, waardoor ik de kans kreeg om elke deelnemer en hun naaste wat beter te leren kennen. Ik was vaak 2 keer zo lang op huisbezoek dan nodig door alle mooie, interessante en ontroerende gesprekken die ik had met patiënten en hun naasten. Iedereen ontzettend bedankt voor jullie bijdrage!

Promotiecommissie

Prof. Dr. Visser-Meily, Beste Anne, bedankt voor jouw begeleiding en de vele lessen die ik van je heb geleerd tijdens mijn PhD. Ik bewonder jouw passie en enthousiasme voor de revalidatie en de manier waarop je altijd de focus weet te houden op het belang en het welzijn van patiënten. Ik vond het erg fijn dat je elk week tijd wist te maken voor het beantwoorden van vragen of het geven van feedback via de mail. Jouw kritische vragen tijdens onze meetings hebben het onderzoek tot een hoger niveau getild en hebben mij geholpen om 'het grotere plaatje' goed in kaart te brengen.

Prof. Dr. Van den Berg, beste Leonard, bedankt voor al jouw waardevolle advies en feedback die ik heb mogen ontvangen op mijn artikelen en onderzoeken. Ik bewonder jouw unieke visie op de verschillende vraagstukken die spelen binnen het ALS onderzoek en jouw kijk op het communiceren van onderzoek naar de buitenwereld. Alle dingen die je voor mensen met ALS hebt gedaan zijn van onschatbare waarde, en ik wens je veel succes met de zoektocht naar het geneesmiddel, met zoveel doorzettingsvermogen gaat dat sowieso lukken.

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ABOUT THE AUTHOR

About the author

Curriculum vitae

Jochem Helleman was born on 24th January 1993 in Den Helder, The Netherlands. In 2012 he graduated bilingual VWO at the Wateringseveld College. To pursue his interest in the human body, sports and rehabilitation Jochem started the Bachelor Human Movement Sciences at the Vrije Universiteit Amsterdam, and obtained his master's degree in Human Movement Sciences in 2016. During his master he conducted a research study on the mobility of wheelchair basketball players, which resulted in a published research paper and his first co-authorship.

After university Jochem worked as a research assistant at Capri Heart rehabilitation while trying to obtain a PhD position. In 2017 he started his PhD at the University Medical Center in Utrecht on the project 'ALS Home-monitoring and Coaching'. During his PhD Jochem presented his research on national and international conferences, as well as open days that were organized for and attended by patients with ALS and their caregivers.

Currently Jochem is working as a Product Owner at Heart for Health where he works together with a team of developers, testers and consultants, aimed at developing mobile applications for home-monitoring of cardiology and diabetes patients.

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