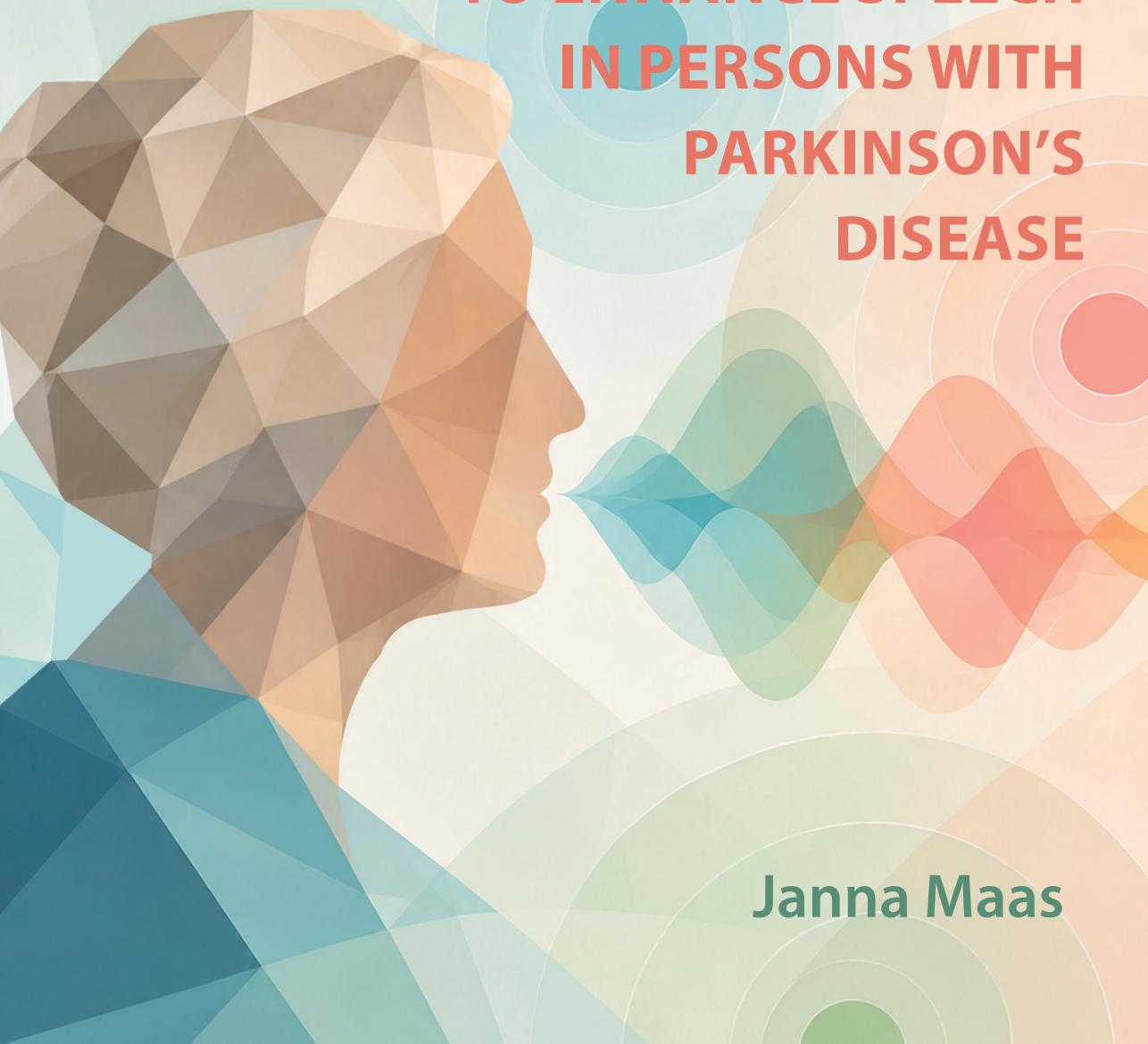
SPEAKING VOLUMES

A PERSONALISED APPROACH TO ENHANCE SPEECH IN PERSONS WITH PARKINSON'S DISEASE



Janna Maas

DONDERS SERIES

Stellingen

behorende bij het proefschrift

Speaking volumes

A personalised approach to enhance speech in persons with Parkinson's disease

1. Remotely delivered and personalised speech therapy can effectively improve communication-related quality of life in people with Parkinson's disease. (This thesis)

2. Persons with Parkinson's disease experience immediate benefit from personalised remote speech therapy, but achieving long-term improvements may require additional maintenance therapy. (This thesis)

3. Integrating the Voice Trainer app into speech therapy is valuable for people with Parkinson's disease to monitor and improve their speech themselves. (This thesis)

4. Supporting personal needs is critical for ascertaining the long-term effectiveness of speech therapy apps, meaning that an individually tailored approach is essential. (This thesis)

5. Specialised Parkinson-specific speech therapy can be made widely accessible through telerehabilitation. (This thesis)

6. 'Speaking loud and low' should not be the goal, but a means to regain communicative participation for people with Parkinson's disease. (This thesis)

7. Kortdurende intensieve logopedische interventie is de slijpsteen voor messcherp stemgebruik bij sociale interacties. (Carel van der Meer, study participant)

8. To speak is to be human. (Hannah Arendt)

9. Een bekwame logopedist spreekt goed, maar luistert nog beter.

10. De verdediging van dit proefschrift dient tevens als observationele case study naar de invloed van zwangerschap op de woordvinding.

Speaking volumes: a personalised approach to enhance speech in persons with Parkinson's disease

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Chapter 1

General introduction

General introduction

Parkinson's disease

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease, caused by loss of dopaminergic neurons in the substantia nigra [1]. The clinical diagnosis is based on the presence of bradykinesia (i.e. slowness of movement) combined with either rest tremor, rigidity, or both [2, 3]. Although the diagnostic criteria only include motor symptoms, many non-motor symptoms, such as cognitive decline, pain, and depression are present as well [2].

In the past two decades, the prevalence of PD has risen rapidly throughout the world [4, 5]. This increase is not yet fully understood, but can partly be explained by ageing of the general population, prolonged survival with PD and environmental pollution with toxins, such as pesticides [2, 6]. Up to now, no therapy can slow down or arrest disease progression. Treatment is therefore symptomatic and should ideally consist of a multifaceted approach, using both pharmacological (e.g. dopaminergic medication) and non-pharmacological interventions (e.g. physiotherapy, occupational therapy, and speech therapy), with speech therapy being the focus of this thesis [2].

Communication problems in Parkinson's disease

PD was described for the first time in 1817 by James Parkinson in his essay on the so-called 'shaking palsy' [7]. Even in this very first description at the time, Parkinson noticed how this disease impacted his patient's speech:

> *"What words he still could utter were monosyllables, and these came out, after much struggle, in a violent expiration, and with such a low voice and indistinct articulation, as hardly to be understood but by those who were constantly with him."*

Speech problems in persons with PD, called hypokinetic dysarthria, are common and occur in up to 70% of the people with PD, depending on the duration of the disease [8]. In later stages of PD, speech becomes almost invariably affected. Voice and speech problems consist of a reduction in both speech volume and pitch fluctuation, a hoarse voice, limited volume of breath, difficulties starting speech, and imprecise articulation [9, 10]. Most of these problems can be attributed to rigidity and hypokinesia (paucity of movement), which are considered to be the main features of PD [11]. Hypokinetic dysarthria results in a decreased speech intelligibility, impacting both the individual and the near ones [12].

Persons with PD also often have cognitive impairments, and these can in turn influence language abilities like word fluency, understanding of language, and also dual tasks such as walking while talking [13, 14]. Seemingly simple things such as telling a story (which requires a logical organisation of reasoning) become more difficult for those with frontal executive dysfunction [14]. Moreover, non-verbal cues such as facial expressions and hand gestures diminish in PD, and these further compound the communication

problems as the disease progresses [15]. This aspect is also referred to as diminished social movements. For bystanders, this can inadvertently create a false impression that the person with PD is depressive, or uninterested. At the same, these diminished movements may induce negative feelings for persons with PD towards their interaction with others, such as the feeling of being ignored during conversations, feeling embarrassed when the words cannot get out, the feeling that others talked over them or for them, or even assumed they were daft [12]. One can imagine that these communication changes exert a strong influence on daily living for persons with PD and their loved ones.

Auditory feedback

Communication is a complex process, in which both production and perception of our speech and language is important. For optimal verbal communication, our auditory perception plays an essential role. Besides having to process acoustic features in order to monitor our own speech, we also have to process spatial cues that facilitate the grouping of sounds. Furthermore, auditory processing requires the selection of relevant auditory signals, while suppressing irrelevant auditory signals [16], for example while having a conversation in a context with loud background noise.

This component of communication creates further challenges for persons with PD, because this disease is not just characterised by motor deficits, but also by a range of sensory processing deficits [17]. Relevant in the context of this thesis is the result of multiple studies that identified an altered perception of auditory feedback in PD [18, 19], as well as an altered perception of characteristics of their own (and other's) voice and speech, resulting in an overestimation of persons with PD on their own speech volume [20]. This altered perception explains why studies reported a reduced awareness in persons with PD of their own speech deficiency [21] and that people with PD often fail to recognise that their voice is not loud enough to be understood by others [22]. Research shows that, although they are not able to appropriately increase speech volume as background noise increases, the ability to regulate their volume is normalised under explicit volume instructions (speaking as loudly as possible, but without shouting) [22]. This result suggests that persons with PD have the capacity to speak with normal volume, providing they consciously attend to speaking loudly. This outcome is not surprising, bearing in mind that by speaking in a conscious manner, people rely more on the cortical route in the brain, compensating for the more affected basal ganglia in PD. As such, this compensatory strategy resembles the many ways in which persons with PD an also overcome other motor deficits, like freezing of gait [23].

Speech therapy

Since pharmacological treatment with dopaminergic drugs typically has only limited beneficial effects on speech [24, 25], speech therapy is particularly relevant to treat hypokinetic dysarthria and enhance speech intelligibility. Current speech treatments for PD (Lee Silverman Voice treatment (LSVT)) [26-28], Speak Out [29], and Pitch Limiting Voice treatment (PLVT, see box 1) [30]) are all highly intensive treatment approaches, focusing on speaking louder to overcome hypokinetic speech, with therapy sessions that

take place three to four times a week. In the Netherlands, persons with PD receive specialised speech therapy with the PLVT by speech therapists participating in the nationwide ParkinsonNet (see box 2). Therapy with such a high intensity is imperative for people with PD in order to train and actively apply intelligible speech in daily life. However, this approach is not feasible for every person with PD, especially in later stages of the disease when endurance becomes limited and cognitive impairments become more prominent. In that case, a lower treatment intensity or setting lower treatment goals (i.e. speaking intelligibly with help from others instead of independently) may be more realistic. Systematic reviews show increasing evidence for the effectiveness of speech therapy in PD [15, 31, 32]. However, more research is needed to explore the full potential of speech therapy in PD, since previous studies had several limitations, i.e. most studies only included small samples, or had short follow-up periods. In addition, the outcome measures used in previous studies may have been suboptimal, with limited clinical relevance, and generalisability was restricted since mostly participants with mild to moderate PD were included (i.e. excluding those with more advanced disease stages) [15, 31, 32]. Until now, only high-intensive speech treatment approaches in PD have been studied, leaving a knowledge gap with regard to the effectiveness of speech therapy in patients who cannot comply to these programs.

Box 1: Pitch Limiting Voice treatment

Persons with PD have soft voices as a result of both decreased expiratory power and increased laryngeal resistance to air flow. The basic mechanism for improving loudness is to increase subglottal air pressure, leading to improved vocal fold vibration. However, greater expiratory effort might increase laryngeal muscle tone and pitch, resulting in a high-pitched and strained voice [30]. In order to increase loudness but at the same time preventing a strained voice, Dr. Bert de Swart from the Radboud University Medical Center developed the Pitch Limiting Voice Treatment (PLVT) in the late 1990s. This treatment method is taught to speech therapists specialising in treating persons with PD in the Netherlands through ParkinsonNet since 2007. The PLVT states that persons with PD have to: (1) learn how to sufficiently speak loud and low; (2) get used to this new technique with the use of specific biofeedback and dedicated exercise; and (3) frequently practice to actively integrate this speaking technique in daily life in order to speak intelligible independent of others. PLVT requires a treatment frequency of at least three times per week; for 30 minutes; for at least four weeks. To persons with PD who cannot comply with this high-intensity treatment, or to persons who are not able to reach the goal of independently speaking intelligible, PLVT-*light* can be provided. In PLVT-*light,* the same techniques as for PLVT are used ('speak loud and low'), but in a lower treatment frequency and/or with lower goals (speaking intelligible with help from relatives). Except the additional focus on pitch, these treatment principles for hypokinetic speech are comparable with other known and effective programs, like Lee Silverman Voice Treatment (LSVT LOUD) [27] and SPEAK OUT![29]. Vital for its clinical implementation, treatment intensity of PLVT aligns with the structural framework of the Dutch healthcare system, in which standard 30-minute treatment sessions are reimbursed by healthcare insurance providers. This is in contrast with SPEAK OUT! and LSVT LOUD, which require session durations of 45 to 60 minutes.

Box 2: ParkinsonNet

There is growing recognition that speech therapists ideally have received specialised training in the management of persons with PD, and attract a high case load, so that the hands-on experience grows cumulatively by treating many different individuals. This has been ascertained in the Netherlands via the development of the nationwide ParkinsonNet. This approach has evolved into a multidisciplinary network that now includes more than 20 specialised professional disciplines. All professionals receive disease-specific training and collaborate within regional networks to deliver consistent, high-quality, evidence-based care.

Concentrating expertise in this way improves clinical outcomes and efficient care delivery. For example, persons treated within ParkinsonNet experience fewer complications such as orthopaedic injuries or pneumonia, than those receiving generic care [33]. Moreover, the network structure facilitates knowledge dissemination and enhances interdisciplinary collaboration, which is particularly valuable in managing complex, progressive conditions such as PD. In addition, ParkinsonNet has proven to be cost-effective: a health-economic evaluation [34] reported substantial reductions in healthcare costs, driven primarily by fewer complications and lower use of non-specialised services.

The role of telemedicine and technology in managing PD

Face-to-face treatment, where persons with PD physically visit their therapist or vice versa, is often considered as the default way to deliver therapy. However, this approach is not feasible to everyone, as both persons with PD and therapists need to be located within a reasonable distance of each other. Moreover, the clinical presentation during in-clinic assessments may give a false impression of the person's actual functioning at home [35]. These considerations all contribute to the growing notion that it is important to take PD care out of the clinic, and back in the persons' own homes [35]. Telemedicine (see box 3) can serve as a relevant and attractive alternative for face-to-face treatment [36]. This especially applies to persons with PD in the later stages of the disease, who may have difficulty traveling, or persons who live in rural areas and who do not readily have access to therapy nearby. Moreover, therapy in the comfort of someone's own home can make it easier to comply with a high training frequency, since it reduces travel burden [37] and saves energy for people experiencing fatigue [38]. The use of telemedicine already has been studied widely in neurodegenerative diseases [39], and is increasingly becoming more common in managing PD. It took a giant leap during the COVID-19 pandemic [39, 40], when in-person visits were not allowed due to lock-down restrictions.

Besides videoconferencing, other digital tools such as wearable devices or mobile phone applications can be used for remotely treating and monitoring disease symptoms in PD. In an interview study about the perspectives of patients and healthcare professionals towards wearables in PD [41], persons with PD turned out to be positive toward using wearables. They did not have any concerns regarding device visibility or health-related data privacy transmitted over the internet. In the same study, healthcare professionals mentioned a need for an economical solution that is easy to interpret.

Although many benefits are reported, telemedicine can also bring several challenges. Multiple studies on telemedicine in PD reported technical problems as a negative factor [37, 38, 42, 43]. Moreover, some persons may experience a lack of hands-on care [43, 44], or miss the personal contact [42, 43]. Overall, the advantages of telemedicine seem to outweigh the challenges [40]. The use of telemedicine is promising, although finding a balance between benefits and burden for individual persons with PD remains important [39, 40].

Box 3: Telemedicine

Telemedicine refers to the use of information technologies and electronic communications to provide remote clinical services to patients (e.g., video consultations, evaluation of medical imaging) [39]. Telemedicine can be broadly divided in three approaches: teleconsultation (remote consultation between patient and clinician, e.g. through telephone or video conferencing), telemonitoring (remote gathering of information about a patient which is used to inform healthcare providers), and tele-treatment (treatment delivered remotely, such as physical exercises, cognitive training, or speech therapy) [40].

The use of telemedicine has been examined as a way of delivering speech therapy to persons with PD. Previous studies showed the noninferiority of online delivery of speech therapy in small groups [45-47]. In all studies, videoconferencing was used to deliver high-intensity treatment. One study found similar improvements for clinical outcomes and quality of life in persons with PD receiving online treatment, as well as persons receiving face-to-face treatment [46]. Two studies also examined satisfaction of persons with PD: one study reported that all patients were satisfied with online treatment and even had a preference for telemedicine compared to face-to-face treatment, despite some technological adversities [47]. The other study reported that there was no difference between satisfaction of the group who received online treatment and the group who received face-to-face treatment [45]. Both findings underpin the feasibility of using telemedicine to deliver speech therapy remotely to persons with PD.

In terms of technology, biofeedback can also be a useful method in treating persons with PD [25]. Biofeedback using visual modalities has been applied successfully to improve swallowing in persons with PD [48]. Biofeedback can also support them to monitor their speech, which is particularly relevant since, as mentioned previously, their own auditory feedback is affected. Multiple studies have examined the use of biofeedback to improve speech in PD, providing feedback about vocal loudness. One of the studies used a microcomputer-based wearable biofeedback mechanism providing auditory cues. It turned out that this mechanism improves perceptual and acoustic assessments [49]. In contrast, another study examining the effectiveness of vibrotactile feedback using a wearable device to improve conversational vocal intensity in PD found that using vibrotactile feedback is limited in improving vocal intensity [50].

In the integrated allied health care guideline for Parkinson disease [51], use of a real-time visual feedback app (named the Voice Trainer) has been integrated. Following the instructions of the PLVT (see box 1),

the Voice Trainer provides visual feedback on vocal loudness and pitch to persons with PD (see Figure 1). The Voice Trainer can support them during speech exercises as well as beyond speech therapy sessions, for example during conversational situations.

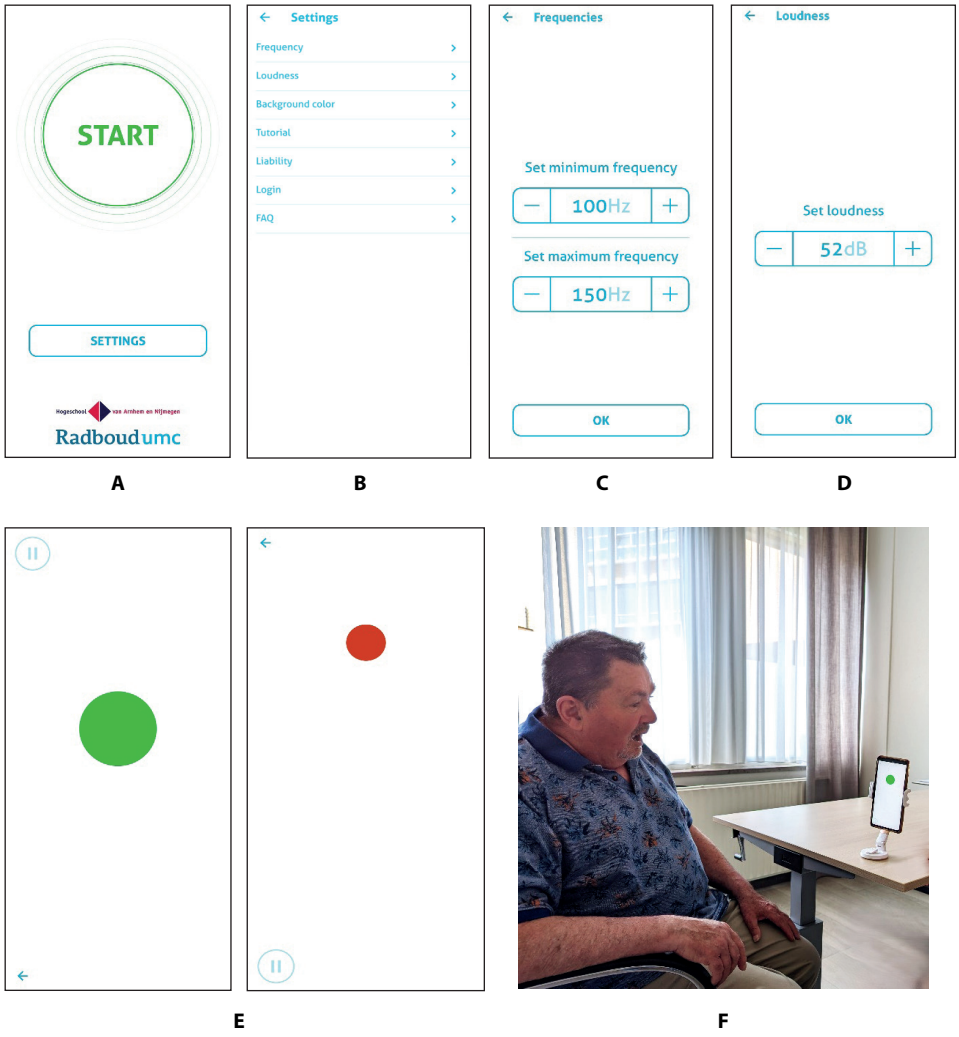


Figure 1. Interface of the Voice Trainer. **A.** Home screen. **B.** Settings overview. **C.** Setting the frequency range (Hz). **D.** Setting the minimum loudness level (dB). **E.** Visual feedback about pitch and loudness. When the circle is large and green, it means the speech is loud enough. Red and small means speaking too softly. The placement of the circle reflects pitch: when the circle moves upward in the screen, the pitch is too high. Ideally, the circle is place in the middle of the screen to support intelligible speech. **F.** Person with PD using the Voice Trainer.

Besides biofeedback, masking noise (i.e. background noise that masks the speaker's own voice and elicits the Lombard effect) has also been used to increase patients' vocal loudness [52]. Although significant

improvements in vocal loudness have been reported, it seems difficult for persons with PD to voluntarily control this increase in the absence of masking noise, making it a less feasible treatment solution.

To summarise, I conclude that the use of telemedicine in PD is feasible. Treatment using videoconferencing makes specialised treatment easily accessible and reduces travel burden. Besides, technologies such as wearables and mobile applications might support persons with PD in improving their speech.

Aim and outline of this thesis

Based on the challenges regarding speech therapy and PD, the methodological limitations of previous studies, and the opportunities brought forth by technological developments, the aims of this thesis are:

1. to study the effectiveness of remote personalised speech therapy in persons with PD, irrespective of disease stage;
2. to evaluate how persons with PD experience a real-time visual feedback app regarding its use and usability.

In Part I, I address the first aim: **Chapter 2** presents the study protocol of a randomised controlled trial (RCT) examining the effectiveness of personalised speech therapy in PD. When designing the study, I addressed the need for a large RCT [15, 32], including outcome measures relevant to persons with PD and a follow-up period of at least 6 months to determine the duration of any improvement. **Chapter 3** presents the results of this large RCT, in which I opted to deliver speech therapy remotely using videoconferencing instead of face-to-face treatment, to enhance the accessibility of specialised speech therapy. I included persons with PD regardless of disease stage, which provides us unique insights in the effectiveness of speech therapy among a group of persons with different disease stages of PD.

In Part II, I address the second aim. A real-time visual feedback app has been implemented in specialised speech therapy in the Netherlands (the Voice Trainer). In **Chapter 4,** I will describe its development, and the experiences of persons with PD regarding its use, and I present the usability.

In Part III, I provide a summary of the findings of this thesis (**Chapter 5** and **Chapter 7**). In **Chapter 6**, I put all findings into perspective and I offer directions for future research.

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PART I

Effectiveness of personalised, remotely delivered speech therapy in people with Parkinson's disease



Chapter 2

Design of the PERSPECTIVE study: Personalised SPEeCh Therapy for actIVE conversation in Parkinson's disease (randomised controlled trial)

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Abstract

Objective: To evaluate the effectiveness of personalised and home-based speech therapy on quality of life, intelligibility and social participation for people with Parkinson's disease (PD) who have a reduced intelligibility of speech.

Background: Speech problems in PD have a profound negative impact on social interaction and quality of life. Evidence for speech therapy in PD is growing, but more work remains needed to explore its full potential. Efficacy exists for highly intensive standardised speech treatment programs, but not all patients can comply with this rather intense intervention, especially the more severely affected ones. Here, we aim to study the effectiveness of personalised and home-based (remote) speech therapy in PD on quality of life and speech. The intervention will be supported by a dedicated speech training app. We expect that this approach will improve speech intelligibility and quality of life in patients irrespective of disease stage.

Methods: We will perform a single blind, randomised controlled trial, comparing 8 weeks of speech therapy to no intervention using a waiting list design. 215 PD patients with problems in intelligibility will be recruited by 12 highly experienced speech therapists. All patients will be measured at baseline and after 8 weeks (primary endpoint). Additionally, the experimental group will be re-assessed one more time, after a wash-out period of 24 weeks. The control group will receive deferred treatment after 8 weeks, but without additional follow-up assessments. Our primary outcome is quality of life (as measured with PDQ-39). Secondary outcomes include speech and voice quality, intelligibility, severity of voice and speech complaints, and caregiver burden.

Results: The inclusion of participants has started in March 1st 2019 and is expected to be finalised in April 1st 2021. We expect to have the first results in January 2022.

Conclusions: We will investigate the effectiveness of speech therapy in PD. Particular strengths of our study include a randomised and single blinded design, the personalised treatment approach, the inclusion of PD patients irrespective of disease stage or severity of the speech complaint, the long term follow-up, the adequate power and the use of a patient relevant primary endpoint. This will allow us to draw firm conclusions about the effectiveness of personalised and remote speech therapy for PD patients in all disease stages.

Background

Parkinson's disease (PD) is a progressive neurological disorder, with a large variety of motor and non-motor problems, including reduced speech intelligibility which may occur in up to 70% of patients (1). Even patients without explicit intelligibility problems can have difficulties conducting a routine conversation. Reduced intelligibility and poor communication skills can have a profound negative impact on social interaction and quality of life (2). Since pharmacological treatment only has limited beneficial effects on speech (3, 4), speech therapy is particularly relevant to improve speech quality and to enhance intelligibility.

Currently, there is level II evidence to support existing speech treatment programs in PD (5, 6). The most recent Cochrane reviews from 2012 on this subject showed that evidence is growing, but more work remains to explore its full potential due to small sample sizes, inadequate methodology, lack of outcomes relevant to PD patients and insufficient follow-up to determine the duration of any improvement (6, 7). Since 2012, three further RCTs have been initiated (8-10), all aiming to evaluate Lee Silverman Voice Treatment LOUD (LSVT-LOUD) versus another or no treatment in a small sample (20 and 30 patients per treatment arm).

It seems that current speech treatments that show positive outcomes are not suitable for all PD patients: LSVT-LOUD (10-12), Pitch Limiting Voice Treatment (13), and SPEAK OUT!(14)) are all highly intensive (3-4 times a week in a professional setting, plus home exercises) and generally follow the same program for all patients. A recent LSVT analysis reported that, in routine care, some patients refuse this high-intensity treatment or do not adhere to the entire protocol because of physical limitations or fatigue, suggesting that this intensive approach is most suitable for only a select group of patients (15). Offering treatment remotely (i.e. delivered at home) may be an attractive solution to increase treatment intensity, while reducing travel burden. Recently, studies using telerehabilitation have shown the feasibility of online delivery of speech therapy in small samples of PD patients (16, 17), but dedicated speech therapy is still not available for many PD patients, in particular for those with advanced PD.

In addition to the research challenges mentioned above, it is also common to experience various unmet challenges related to speech therapy in PD itself. First, although it is relatively easy to temporarily increase intelligibility in PD patients with the right instruction, it takes intensive exercise and specific feedback for patients to get used to normal loudness again, and to apply it independently in an everyday conversation. A second challenge is that speech exercise can make speech more intelligible, but patients may remain dependent on cueing. It is uncertain how to deliver such cueing at home, outside the therapeutic settings. Thirdly, conveying a message through speech requires producing both comprehensible language and intelligible speech at the same time. This dual tasking becomes increasingly difficult for patients with PD (18), making them progressively more dependent on caregivers. To help patients to monitor their speech, we have developed a sophisticated app, named the Voice Trainer (19), that provides real-time visual feedback aiming to improve intelligibility. Several

user tests were conducted with both patients and speech therapists to optimise the usability of the application and before introducing and implementing the app in the training of speech therapists in the Netherlands. In this study, patients use the Voice Trainer to practice their speech quality and maintain their intelligibility during daily conversation and social interaction as well.

In an experimental design, our main aim is to address all these challenges by evaluating a multifaceted approach of home-based speech therapy in a single blind, randomised and controlled trial, using quality of life as the primary outcome. Specifically, our approach combines the following elements: (1) personalised treatment, based on (internationally) established speech treatment programs and guidelines (20, 21), making speech therapy available for every PD patient regardless of disease stage; (2) consistent use of the Voice Trainer app to enable cueing during treatment and outside the therapeutic setting; and (3) treatment delivery within the patients' home using telerehabilitation, and delivered by highly experienced therapists who work as part of the Dutch ParkinsonNet (a professional network of allied health therapists with dedicated expertise in the management of PD (22, 23)), to enable patients to follow the program with adequate intensity at home.

We expect an improvement in both quality of life (primary outcome) and speech quality (secondary outcome) for patients across all disease stages. Moreover, we hypothesise that improvements will be maintained at follow-up, since long-term effects in improvements of speech in PD have been found in previous studies (10) Therefore, our primary objectives are (1) to study the effectiveness of personalised speech therapy on quality of life in patients with Parkinson's disease, and (2) to explore whether the effects of speech therapy remain after long-term follow-up (six months).

Methods/Design

Trial design

Here, we will perform a single blinded randomised controlled trial comparing speech therapy to no intervention using a waiting list design. We opted for this design because this enables us to properly compare patients who have received therapy with patients who have not received therapy (yet), thereby answering our primary research question addressing the effectiveness of speech therapy in patients with PD. The control group receives deferred treatment directly after reassessment, which is a realistic waiting period in usual care. Patients will be assigned to either the experimental group or the control group in a 1:1 manner, by means of a computerised validated variable block randomization model using Castor EDC (24) with automatically generated block sizes of 4, 6, and 8. Stratification will take place for gender, speech therapist, Hoehn & Yahr stage, and age (<46 years, 47-55 years, 56-65 years, >66 years). To ensure blinding, allocation of the participants is made invisible for assessors in the data collection program Castor EDC. Furthermore, patients and speech therapists are instructed to refrain from discussing the treatment with the assessors. Measurements will be performed at baseline (T0) and

after 8 weeks (T1). For the intervention group only, an additional follow-up measurement takes place 32 weeks after baseline (T2) (Figure 1) to study whether effects are retained at the long term. The T1-measurement is the primary endpoint at which we will compare the intervention group with the control group. The T2-measurement is the secondary endpoint at which we will compare the within-group differences of the intervention group after follow-up.

Full ethical approval has been granted by the medical ethical committee of Arnhem-Nijmegen (NL67867.091.18) and the PERSPECTIVE trial is registered at clinicaltrials.gov (NCT03963388) on May 24 2019. Important protocol modifications will receive a written notice to the relevant parties (medical ethical committee, trial register, speech therapists, and/or participants).

Procedure

Patients are asked to participate by highly experienced speech therapists, and we will recruit these speech therapists throughout the Netherlands, using the nationwide ParkinsonNet infrastructure (25). ParkinsonNet is a national health care model that consists of 70 regional networks, with over 3,000 health professionals with specific expertise in the treatment of PD patients (22). Twelve speech therapists who participate in ParkinsonNet will be selected based on their caseload, who will each treat 16-20 patients, which is approximately 1 patient per month during the inclusion period.

During the first visit, speech therapists inform eligible patients about the study with the formal information letter. The speech therapists explicitly do not give any therapeutic advice to patients during this first visit, since patients can already benefit from education. To provide the patients enough time to consider participation, the research team calls the patients after seven days to verify willingness to participate and to check for eligibility. When a participant is willing and eligible, the baseline measurement (T0) is scheduled. One day after baseline measurement, randomization is performed by a researcher who is not involved in any of the measurements, and who also subsequently informs both the therapist and patient about group allocation. If the patient is allocated to the intervention group, treatment will start within a week. If the patient is allocated to the control group, treatment will start after the second measurement (T1), as shown in the flowchart (Figure 1).
The intervention is delivered during a maximum period of 8 weeks. The number of sessions depends on the complexity of goals and possibilities of the patient (i.e. time and availability). Between T1 and T2 (only for the intervention group), patients will not receive speech therapy, but still can use the Voice Trainer app.

Participants

Eligible patients have PD according to the MDS criteria (26) as confirmed by their own treating neurologists. Other inclusion criteria are (1) reduced intelligibility bothering daily communication according to the patient and/or informal caregiver(s), (2) a desire to improve their speech, and (3) willingness and ability to receive online treatment. Importantly, patients who do not own a device that is suitable for online treatment can still participate in the study, because in those cases we will provide

them with a loan device. Exclusion criteria are: (1) recently received (<1 year) speech therapy, (2) voice or speech problems due to other causes, (3) communication difficulties based on language problems without predominantly reduced intelligibility, and (4) (technical) inability to receive online treatment. Patients are not excluded by disease stage or the severity of their speech complaint, because we aim to study the effectiveness of the intervention irrespective of dysarthria severity.

Drop-out criteria are (1) withdrawal from consent, (2) health problems of such severity that conducting assessments is not possible. When willing and available, a primary informal caregiver of each patient can participate in the study by completing two questionnaires about speech and caregiver burden. Inclusion will take place over a period of 25 months, starting at March 1st 2019 and ending in 31 March 2021. Informed consent of both patient and caregiver (when applicable) is obtained by the researcher before the baseline assessment.

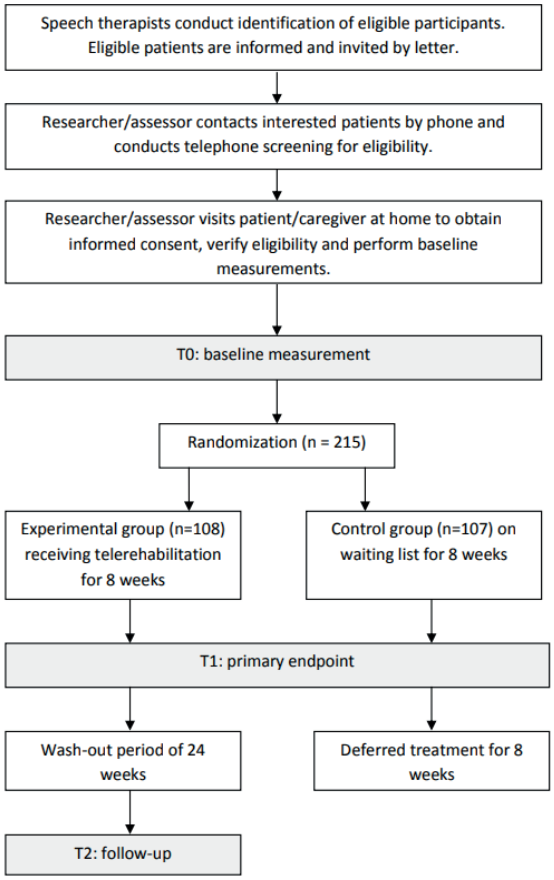


Figure 1. Flowchart of design and enrolment procedures.

Intervention

The PERSPECTIVE treatment approach combines three elements: (1) personalised treatment; (2) consistent use of a feedback-app for smartphone or tablet that delivers real-time visual feedback (the Voice Trainer app); and (3) treatment delivery in the patient's home using telerehabilitation.

1. Personalised treatment

Based on the Guidelines for Speech-Language Therapy in Parkinson's Disease (27) and Pitch Limiting Voice treatment protocol (20), the intervention consists of 12-16 sessions (30-60 minutes each) in up to eight weeks, with a maximum of three times a week and daily home exercise. The first treatment session includes an extensive assessment of the patient's personal conversational goal (28, 29), taking into account personal circumstances and (social) environment. The caregiver is also explicitly involved and, when necessary, instructed on how to help or support the patient in doing exercises or providing trained cues. The technique to improve intelligibility will be personalised, based on the patient's individual treatment goal. This treatment paradigm makes the treatment suitable for patients with mild to advanced hypokinetic dysarthria and has been successfully implemented in the Dutch ParkinsonNet for over a decade.

2. Support by feedback-app

People with PD are highly dependent on feedback to improve motor control (30). We therefore developed a dedicated app that provides real-time visual feedback about speech loudness and pitch: the Voice Trainer app (19). The app supports patients and therapists to correctly practice and maintain voice loudness and pitch, during exercises as well as during conversation. As such, it supports patients in self-management and treatment compliance beyond the therapy sessions. Feasibility of the app has been confirmed by patients, caregivers and speech therapists (31) and use of the app has been integrated in the recently updated Guidelines for Speech-Language Therapy in Parkinson's Disease (32).

3. Highly experienced therapists who deliver online treatment

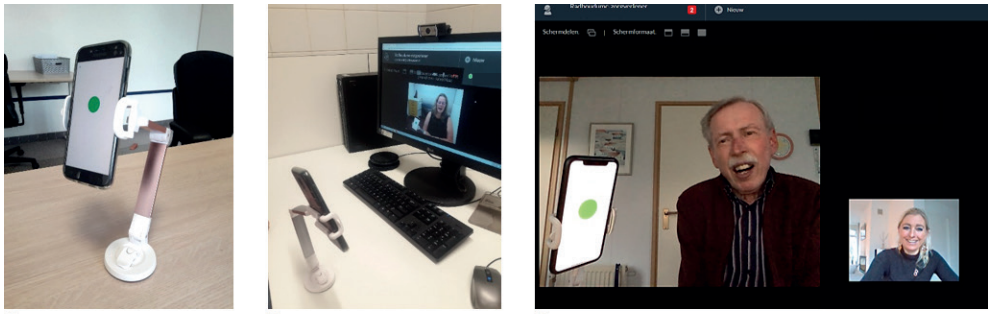
The intervention will be delivered by highly experienced speech therapists who participate in the Dutch national ParkinsonNet, who have all received a dedicated three day training programme in treating PD patients according to evidence-based guidelines, and who all treat a high caseload in their daily practice which further increases their treatment quality (22, 23). Delivery of the online treatment will be done using a reliable, certified and secured online platform, which is easy to use without extra costs for patients (software provided by Zaurus B.V.). Speech therapy itself will be reimbursed by the Dutch healthcare insurance, but every participating therapist is offered a small fee of €50,- per patient to compensate for the extra time they spend on training and coaching (see next paragraph), thereby facilitating them to participate in the study.

Training and coaching of trial therapists

Before the start of the trial, participating speech therapists follow a two-day training in which they are informed about the study procedures and the PERSPECTIVE intervention protocol, including delivering online treatment. During the study period, speech therapists will be coached online by one of two experts to ensure that every patient receives optimal speech therapy. These experts have been responsible for the education of speech therapists in ParkinsonNet and the development of the Voice Trainer. Coaching of speech therapists takes place in a group video call with the coach, speech therapist and patient during three online treatment sessions (week 1, 3 and 5), in which the coach provides live feedback to the speech therapist.

Assessment procedures

Two assessors, who are kept blinded for group allocation, will collect the data in the patient's home. Questionnaires are completed online by the patient within three days after the assessor's visit. Also at T0, patients receive explanation on how to use the online platform and the Voice Trainer app. To use the Voice Trainer app and the online platform at the same time, patients need two devices (preferably a smartphone and a tablet or computer).



A B C

Figure 2. Set-up of using Voice Trainer app and online platform. **A.** Smartphone with Voice Trainer is correctly placed in smartphone holder. **B.** Smartphone is aimed at the camera of second device (computer or tablet). **C.** Voice Trainer is visible for both patient and speech therapist in their computer screen.

Outcome measures

Primary outcome measure

Our primary endpoint is quality of life using the summary index score of the Parkinson's Disease Questionnaire (PDQ-39) at 8 weeks follow-up (T1) (33, 34). We have chosen the PDQ-39 as primary outcome, because a positive impact of speech therapy on the lives of patients with PD is our highest goal. The PDQ-39 is a disease-specific measure of subjective health status and contains 39 questions, divided over eight important areas of health status: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. Patients indicate for every question how often they experience problems on a five point scale (never, seldom, sometimes, often, or

always). A profile of scores can be calculated, indicating the impact of PD in the eight dimensions. The summary index score (SI) is calculated from the eight profile scores and provides an indication of the global impact of PD on health status. Studies evaluating the PDQ-39 show high levels of validity and reliability (33, 35). The PDQ-39 is known as the most widely used PD-specific health-related quality of life questionnaire (36).

Secondary outcome measures

All secondary outcome measures are listed in Table 1 and include evaluation of speech and voice quality, voice handicap, speech intelligibility, severity of voice and speech complaints, mood and anxiety, health-related quality of life, and swallowing speed (the latter because of the possible impact of speech improvement on swallowing efficiency (37). Outcome measures at caregiver level are caregiver burden, and caregiver reported severity of voice and speech complaints.

Background variables

Demographic data are collected at baseline and consist of age, gender, disease duration, and possible presence of advanced therapy, e.g. deep brain stimulation, subcutaneous apomorphine infusion, or levodopa-carbidopa intestinal gel). Patient's disease severity will be measured with the Movement Disorder Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS; (41)), including the Hoehn and Yahr scale. The Mini Mental State Examination (MMSE; (38)) and a category fluency task are used to assess general cognitive functioning. Demographic data, disease severity and cognitive functioning will be used to describe the study population.

Table 1. Schedule of measurements and outcome measures

Background variable	**Instrument**	**Baseline**	**8 weeks**	**32 weeks**[1]
Age, gender, disease duration, presence of advanced therapy	n.a.	√		
Cognitive functioning	Mini-Mental State Examination (MMSE) (38)	√		
	Category fluency task (animals)(39)	√		
Disease severity	Hoehn & Yahr stage (40)	√	√	√
	Total score on Movement Disorder Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS)(41)	√	√	√
Outcome measure	**Instrument**			
Health-related quality of life	Parkinson's Disease Questionnaire (PDQ-39) (33-35)	√	√	√
	EuroQol-5D (EQ-5D)(42)	√	√	√
Speech quality	Radboud Dysarthria Assessment (RDA)(43)	√	√	√
Voice quality	Acoustic Voice Quality Index (AVQI)(44)	√	√	√
Voice handicap	Voice Handicap Index (VHI)(45)	√	√	√
Severity of voice and speech complaints, reported by patient	Radboud Oral Motor inventory for Parkinson's disease (ROMP)(46)	√	√	√
Severity of voice and speech complaints, reported by caregiver	Radboud Oral Motor inventory for Parkinson's disease (ROMP), adapted to caregiver	√	√	√
Speech intelligibility	Dutch intelligibility test – sentence level (NSVO-Z) (47)	√	√	√
Caregiver burden	Zarit caregiver Burden Interview Short Form (ZBI-12)(48)	√	√	√
Mood and anxiety	Hospital Anxiety and Depression Scale (HADS)(49)	√	√	√
Swallowing	Maximum swallowing speed (timed test)(50)	√	√	√

1 T2 will only be performed in patients who were allocated to the intervention group.

Sample size calculation

Based on a trial on the effectiveness of multidisciplinary care (51), we have calculated the sample size on our primary outcome with a conservative estimated PDQ-39 total score improvement of 2.5 points (SD = 5.8) in the intervention group, and no difference in controls. This estimated improvement exceeds the minimally important difference of 1.6 points (34). A sample of 170 patients would be needed to show this expected difference. Allowing for 20% drop-out, we will include 215 patients.

Statistical analysis

Descriptive statistics

Means, standard deviations and frequencies will be used to describe outcome, background and baseline variables.

Analysis effectiveness

Based on our hypothesis and design, two comparisons will be made: (1) the between-group differences at the primary endpoint (T1); and (2) the within-group differences in the experimental group after 24 weeks of follow-up (T1 versus T2). Statistical analyses will be performed based on the intention-to-treat principle. Analysis of covariance will be used with each of the outcomes as dependent variable and group allocation as fixed variable. Baseline values, age at baseline, Hoehn & Yahr stage and disease duration will serve as covariates. We will also perform a process analysis and a planned post-hoc analysis to identify which factors predict a successful outcome.

Data management and monitoring

The assessors will enter all data electronically in clinical data management system Castor EDC (24). Participants will receive a unique consecutive personal identification code based on the order of enrollment. Original study forms will be entered and kept on file at the university medical center. Personal information about potential and enrolled participants is saved electronically on the server of the university medical center and is only accessible for the researchers. Personal data will not be shared. An independent data monitor will conduct three to four visits (after inclusion of the first three participants, during inclusion period at least once a year, and after the follow-up measurement of the last participant) to randomly check records for inaccuracies and errors in source data verification, serious adverse events, and inclusion and exclusion criteria. Furthermore, data collection program Castor EDC (24) keeps an audit trail log, which allows the data monitor to view all changes made to the study and reasons for change Since patients are at negligible risk during participation in this study, a data monitoring committee is not needed and there is no ancillary and post-trial care for participants. In case of serious adverse events, the investigator will report them to the medical ethical committee without undue delay after obtaining knowledge of the events.

Dissemination and implementation

Trial results will be shared with the participating patients, speech therapists, and the general medical community by newsletters, with the Michael J Fox Foundation via a study report and with the academic community via a scientific paper. Additionally, trial findings will be shared with relevant therapist via web-based communities for medical professionals specialised in Parkinson care in the Netherlands and with a wider audience via social media. The principles of speech treatment are generated from the guideline-based treatment that is considered as usual care, delivered by the speech therapist who are affiliated with the Dutch ParkinsonNet. However, the combination of the three specifications (personalised treatment, support by feedback app and delivery of online treatment) are new and are studied here. Any results will be re-implemented via the continued education programs as delivered by the Dutch national ParkinsonNet approach.

Discussion

The PERSPECTIVE study is a large randomised controlled trial evaluating the effectiveness of speech therapy in persons living with PD. Particular strengths of our study include the randomised and controlled design, the personalised treatment approach, the inclusion of PD patients irrespective of disease stage, the long term follow-up, the adequate power and the choice for a patient-relevant primary endpoint.

We believe that the ultimate goal of any treatment for persons with PD is a relevant improvement of their quality of life. Intelligible speech is certainly thought to contribute to this, because we expect that patients are better able to handle communicative and social situations when their speech is more intelligible, which in turn will likely have a positive impact on quality of life. Obviously, there are many other factors that could affect the quality of life, like mobility, emotional wellbeing, or bodily discomfort. Taken together, choosing quality of life as our primary endpoint is highly relevant for patients but also challenging at the same time, because it is only partially dependent on intelligibility. That is why we based our power calculation on finding a small, but clinically relevant improvement of quality of life after speech therapy.

The PERSPECTIVE study is a complex study, because we conduct our research in daily practice, with patients receiving the treatment within their own homes, instead of in a fully controlled situation within a hospital environment. While challenging, this remote home-based approach allows us to gain a realistic and generalizable view on the effectiveness of speech therapy in PD. We will discuss some of these challenges here.

The first challenge is that therapy is delivered by multiple speech therapists, which may be accompanied by inter-individual differences in treatment quality, which may in turn impact the results of the trial. In order to minimise this treatment variability, all speech therapists are being coached by an expert speech

therapist for every single patient that is allocated to the experimental group. Moreover, all participating therapists are part of a professional network, that includes a thorough three day Parkinson-specific training course according to the latest guidelines prior to participation, as well as ascertainment of a high caseload in daily practice. In this way, we have taken specific measures that help to ascertain a delivery of high-quality treatment for every patient participating in the trial. An advantage is that we may be able to extrapolate the trial findings more readily to everyday clinical practice, as compared to studies that were performed on the more carefully controlled in clinic situations.

The second challenge is that we aim to include patients in all disease stages and with all grades of dysarthria severity, because we want to understand the effectiveness of the intervention for the full severity range, like it is presented in day-to-day clinical practice (52). This leads to a heterogeneous study population, and therefore to more variation in the data, which could impact on the power of our analysis. However, although the size of treatment results will differ between patients, we anticipate to show that dedicated speech therapy can make a difference for every PD patient with speech problems.

Although a non-inferiority trial has shown that telerehabilitation is feasible in patients with PD, also for speech therapy (17), this approach can still be a challenge for individual patients, e.g. due to a lack of technical skills, unstable internet connection or cognitive problems, especially in advanced stages of PD. As a result, speech therapy could still be a challenge for individual patients and may lead to inclusion bias for our trial. However, we preferred online treatment over face-to-face treatment because of several advantages. First, online treatment reduces travel burden and costs and therefore saves patients' valuable time, energy and expenses. Furthermore, online treatment has no limitations related to distance; as long as both patient and therapist have a stable internet connection, it does not matter where they are located. This is in particular relevant for patients who do not have physical access to a highly experienced speech therapist, which would make our remote speech therapy suitable for many patients, even for those living in remote areas. To overcome technical challenges and reduce potential inclusion bias, we will optimally support all participants by educating them as well as by testing a video call combined with use of the Voice Trainer on the participants' own devices during the baseline home visit,. We realise that this is not always feasible in daily practice, e.g. when there is too much travel distance between speech therapist and patient. However, based on the experiences from this trial, we expect to be able to give specific recommendations on how to use the set-up and to draw conclusions about what type of patients will be able to use remote speech therapy, and what sort of external support would be needed for this.

One of the limitations of a non-pharmacological trial is that blinding is a challenge. The assessor may notice an improvement in speech at the T1-measurement compared to the baseline measurement. Also, it is possible that patients or speech therapists accidentally reveal their group allocation (experimental or control group) to the assessor. To minimise this risk, patients and speech therapists are repeatedly

requested to keep their group allocation secret to the assessor. We will assess the success of this blinding procedure after the trial by debriefing both the participants and the assessors.

Finally, we would like to mention that the trial will be conducted in part during the COVID-19 pandemic. Therefore, home-based measurements were not allowed during a few months when we started the study. We decided to proceed with the planned T1- and T2-measurements using online measurements. No new patients were included during lock-down. This strategy has resulted in missing data for several secondary outcome measures, e.g. voice and speech quality. However, our primary outcome and other surveys could be collected as planned without any problems. Importantly, a great advantage of the remote therapy that we study here is that all treatments could be continued online, making our approach future proof.

Acknowledgment

This study is made possible by a grant of the Michael J. Fox Foundation.

Ethical approval and consent to participate

Full ethical approval has been granted by the medical ethical committee of Arnhem-Nijmegen (NL67867.091.18) and the PERSPECTIVE trial is registered at clinicaltrials.gov (NCT03963388) on May 24, 2019.

Trial registration: data set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03963388
Date of registration in primary registry	May 24 2019
Secondary identifying numbers	NL67867.091.18
Source(s) of monetary or material support	Michael J Fox Foundation for Parkinson's Research
Public title	Personalised SPEeCh Therapy for actIVE Conversation
Scientific title	The PERSPECTIVE Study: Personalised SPEeCh Therapy for actIVE Conversation
Countries of recruitment	The Netherlands
Health condition(s) or problem(s) studied	Parkinson's disease, speech problems
Interventions	Online speech therapy, delivered by specialised speech therapists. Speech therapy will be complemented by a real-time visual feedback app (the Voice Trainer app).
Key inclusion and exclusion criteria	Inclusion criteria: A diagnosis of idiopathic PD, problems in intelligibility affecting daily communication (as indicated by the patient and/or the caregiver), a desire for improvement, willing and able to receive online treatment. Exlusion criteria: Recent (<1 year) speech therapy, voice or speech problems due to other causes, communication difficulties based on language problems without predominantly reduced intelligibility, inability to receive online treatment.
Study type	Interventional Allocation: randomised intervention model. Single blinded (outcomes assessor).
Date of first enrolment	March 2019
Target sample size	215
Recruitment status	Recruiting
Primary outcome(s)	Total score of the Parkinson's Disease Questionnaire (PDQ-39)

Key secondary outcomes	Radboud Dysarthria Assessment (RDA) • Speech quality [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Acoustic Voice Quality Index (AVQI) • Voice quality [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Voice Handicap Index (VHI) • Voice handicap [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Radboud Oral Motor inventory for Parkinson's disease (ROMP) • Severity of voice and speech complaints, reported by patient [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Radboud Oral Motor inventory for Parkinson's disease (ROMP), adapted to caregiver • Severity of voice and speech complaints, reported by caregiver [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Dutch intelligibility test - sentence level (NSVO-Z) • Speech intelligibility [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Zarit caregiver Burden Interview Short Form (ZBI-12) • Caregiver burden [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Hospital Anxiety and Depression Scale (HADS) • Mood and anxiety [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2). Minimum score = 0 (no anxiety or depression), maximum score = 42 (most anxiety or depression).] EuroQol-5D (EQ-5D) • Health-related quality of life [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)] Maximum swallowing speed (timed test) • Swallowing [Time Frame: Baseline (T0), primary endpoint after 8 weeks (T1), follow-up after 32 weeks (T2)]

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Chapter 3

Effectiveness of remotely delivered speech therapy in persons with Parkinson's disease – a randomised controlled trial

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Abstract

Background: Increasing evidence supports the merits of speech therapy in Parkinson's disease, but the current practice of multiple in-house treatments is demanding for patients. We therefore assessed the effectiveness of remotely delivered and personalised speech therapy on improving quality of life and speech quality in persons with Parkinson's disease.

Methods: We performed a single blinded randomised controlled trial (the PERSPECTIVE study), comparing 8 weeks of personalised remote speech therapy to no intervention (waiting list design). Patients with reduced speech intelligibility were included, regardless of disease stage or dysarthria severity. Patients were assigned randomly (1:1) to the intervention or control group. Measurements took place at baseline and after 8 weeks (both groups), and after 32 weeks (intervention group only). Patients were treated remotely by 20 experienced speech therapists. The primary outcome was disease-related quality of life at 8 weeks, assessed with the Parkinson's Disease Questionnaire 39 (PDQ-39). Data were analysed using analysis of covariance based on the intention-to-treat principle. This trial is registered in ClinicalTrials.gov, NCT03963388.

Findings: Between March 1, 2019, and March 27, 2021, 214 patients were enrolled in the intervention group (n=109) or control group (n=105). At the primary timepoint, the adjusted mean difference in PDQ-39 was -2.0 in favour of the intervention group (95% CI -4.0 to 0.1); p=0.056). The intervention group scored better on the communication index score of the PDQ-39 (post hoc analysis), with an adjusted mean difference of -5.3 (95% CI -9.4 to -1.2; p=0.011). We found no between-group differences on any other PDQ-39 domain. Follow-up measurements showed a significant reduction of the PDQ-39 compared to the primary timepoint with a difference of 2.40 (95% CI 0.77 to 4.02; p=0.004).

Interpretation: Personalised remote speech therapy improved communication-related quality of life, but not overall quality of life.

Introduction

Up to 70% of persons with Parkinson's disease (PD) may encounter problems in speech intelligibility due to hypokinetic dysarthria (1), affecting social interaction and quality of life. Hypokinetic speech is characterised by a soft and monotonous voice and small articulation movements, which worsens when tired (2). Since pharmacological treatment offers limited improvement (3), speech therapy is the preferred option to improve speech quality and intelligibility. This is now deemed to be an integral part of comprehensive care for PD across all disease stages (4). Recent systematic reviews (5-7) conclude that the evidence for the effectiveness of speech therapy in PD is increasing. However, more research is needed to explore its full potential since previous studies had certain limitations, including small samples or short follow-up periods. Also, the outcome measures used in previous studies were suboptimal because of their limited clinical relevance. Finally, generalizability was restricted because mostly participants with mild to moderate PD were included (i.e. excluding those with more advanced disease stages) (5-7).

Current speech treatments (Lee Silverman voice treatment (LSVT) (8, 9), Pitch Limiting Voice Treatment (PLVT) (9, 10), and SPEAK OUT! (10)) generally focus on speaking louder to overcome the hypokinetic speech. Intensive training in these programs is imperative for patients to gain and preserve a better intelligibility. This requires a highly intensive treatment program, typically involving in-house treatment sessions three to four times a week, for a duration of on average four weeks. However, such a high-intensity approach is less feasible for patients with severe PD, so a more personalised and convenient approach is needed. In that regard, telerehabilitation has become an attractive way to offer treatments remotely, into the home of affected individuals. This is particularly attractive for more severely affected patients with difficulties traveling and for patients living in loosely populated areas where physical access to specialised care is challenging. The COVID-19 pandemic has shown that telerehabilitation can be a suitable solution for delivering treatments during times of lockdown (11). Treatment in the comfort of the patients' own home makes it easier to achieve a high frequency of training. Previous studies already suggested a non-inferiority of online speech therapy and an acceptable feasibility of other speech-related activities such as therapeutic singing in small groups of PD patients, as compared to the traditional in-house treatment programs (12-15).

Here, we report the results of the PERSPECTIVE study (PERsonalised SPEech therapy for aCTIVE conversation), a Randomised Controlled Trial (RCT) evaluating the effectiveness of a remotely delivered speech therapy program in persons with PD who experienced a reduced speech intelligibility, but irrespective of dysarthria severity and across all disease stages. We expected speech therapy to improve both quality of life and speech quality in patients across all disease stages. Moreover, we hypothesised that the improvements would be maintained at the six-month follow-up.

Methods

We conducted a single blinded RCT, comparing remotely delivered speech therapy with a waiting-list control group. The study protocol, approved by the medical ethical committee of Arnhem-Nijmegen (NL67867.091.18), has been detailed previously (16).

We recruited patients diagnosed with PD according to the Movement Disorder Society criteria (17), in all disease stages. Potential participants were asked to participate by their own speech-language therapist (from now on referred to as speech therapist) at the time of initial referral, or they volunteered to participate via the Dutch online recruitment platform ParkinsonNext (www.parkinsonnext.nl) which matches patients to suitable research projects. Interested patients received an information letter with detailed information about the study. To provide the patients enough time to consider participation, the research team called the patients seven days after having received the information letter, to verify their willingness to participate and to check for eligibility. When a participant was willing and eligible, the baseline measurement (T0) was scheduled. Eligibility criteria were: (1) reduced intelligibility that negatively impacted daily communication, as indicated by the patient or informal caregiver(s); (2) a desire to improve their speech; and (3) willingness and ability to receive online treatment. Exclusion criteria were: (1) recently (<1 year) having received speech therapy; (2) voice or speech problems due to other causes; (3) communication difficulties based on language problems without predominantly reduced intelligibility; and (4) (technical) inability to receive online treatment. When willing and eligible, a primary informal caregiver was also asked to participate. Both patient and caregiver signed informed consent in twofold before the start of the baseline measurement.
For detailed descriptions of the procedures and outcomes, we refer to a previous publication of the study design (16).

Randomisation and masking

After the baseline visit, patients were randomised to either the intervention or the waiting list control group in a 1:1 manner by means of a computerised validated variable block randomization model with automatically generated block sizes of 4, 6, and 8. Stratification took place for sex, current age (<46 years, 47-55 years, 56-65 years, >66 years), speech therapist, and Hoehn & Yahr stage. Randomisation was performed by a researcher who was not involved in any of the measurements, and using the electronic data capture system Castor EDC (Amsterdam, NL). This researcher subsequently informed both the therapist and patient about group allocation, keeping the researchers who performed assessments and analyses blinded to treatment allocation. Allocation of participants was made invisible for assessors in Castor EDC. Patients and therapists could not be masked, but were instructed not to talk about the treatment allocation with the assessors. The assessors kept track of what presumption they had about group allocation for every participant (intervention group, control group, or no idea).

Procedures

Measurements took place in the patients' homes at three time points: T0 measurement (baseline), T1 measurement at 8 weeks after baseline (primary endpoint), and T2 measurement at 32 weeks after baseline (secondary endpoint, only for the intervention group). If the patient was allocated to the intervention group, treatment started within a week. If the patient was allocated to the control group, treatment started after the second measurement (T1), as shown in the flowchart (Figure 1).

No T2 measurements took place for the control group. We decided not to include this, because in this trial, having insights into whether the effects of speech therapy would be maintained in the long term was only a secondary question, and we considered it more important to optimise our trial design for the primary research question that was focused on T1. To optimise compliance for the control group, we wanted to keep the waiting list brief, which motivated us to offer them the delayed treatment immediately after T1, instead of after T2.

Data were collected by three assessors. Questionnaires were completed online by the patient within three days after each visit. At the end of the baseline assessment, patients received an explanation on how the remote treatment would take place.

Intervention

The intervention was delivered by 20 speech therapists throughout the Netherlands. All therapists participated in the Dutch ParkinsonNet, which is a nationwide healthcare approach of regional multidisciplinary networks of healthcare professionals specialised in PD, aiming to provide high-quality care for patients with PD (18). Therapists were selected based on their experience and caseload (minimum of one new PD patient per month for a full treatment) to ensure treatment quality and to ascertain a stable inclusion. The treatment delivery was planned for a maximum period of 8 weeks. The exact number of sessions depended on the complexity of goals and capacity of the patient. Between T1 and T2, participants in the intervention group did not receive any further speech therapy (19). The PERSPECTIVE treatment approach combines three elements: (1) treatment delivery in the patient's home using telerehabilitation, as a replacement for in-house therapy; (2) personalised treatment approach; and (3) consistent use of a feedback-app for smartphone or tablet that delivers real-time visual feedback.

1. Highly experienced therapists who deliver online treatment

In addition to the initial three-day training course by the Dutch ParkinsonNet, the speech therapists participating in the study followed an extra two-day training during which they were informed about the study procedures and the PERSPECTIVE intervention protocol, including delivering online treatment. Delivery of the online treatment was done using a reliable, certified and secured online platform, which is easy to use without extra costs for patients (software provided by Zaurus B.V.). To guarantee compliance and treatment quality, participating speech therapists were supported during the study by a coach (one of two expert speech therapists). Coaching took place during a full treatment session in week 1, 3 and

5 for every patient via a group video call with the patient, the speech therapist and the coach, creating the opportunity to provide live detailed feedback to the patient and the speech therapist when needed.

2. Personalised treatment

The treatment is based on the Dutch Guidelines for Speech-Language Therapy in Parkinson's Disease (20) and the Pitch Limiting Voice treatment protocol (21). The techniques to improve intelligibility were personalised, based on the patient's individual treatment goal and ability to receive intensive treatment. The optimal treatment goal of PLVT is to independently speak intelligibly in all communication situations in order to regain social participation. PLVT is provided 3-4 times per week for 30 minutes, with a maximum treatment trajectory of 8 weeks. Patients also perform daily home-based exercises. If the goal of independently speaking intelligibly is not realistic for the patient, then optimal high-intensive treatment is still available, but a lower goal is set, namely speaking intelligibly with support from a caregiver or conversation partner. The treatment intensity, frequency, and goals were adjusted on a personal basis, based on the insights of the speech therapist.

Some patients might experience limitations such as cognitive decline or severe fatigue, making intensive treatment and the goal of independently speaking intelligibly not feasible. In these circumstanced, patients received less intensive treatment (1-2 times a week for 30 minutes), thereby accepting more modest treatment results compared to high intensive treatment. Also, if present, the caregiver was explicitly involved and, when necessary, instructed on how to support the patient in performing exercises or providing trained cues.

3. Support by feedback-app

To provide PD patients with specific feedback on how to improve their speech, we developed a dedicated app that delivers real-time visual feedback on speech loudness and pitch: the Voice Trainer (19). After the speech therapist sets frequency (Hz) and loudness (dB) levels, the Voice Trainer provides intuitive feedback using a circle on the screen of the device. If the circle is green and large, this means the speech is loud enough. Does it become red and small, the user speaks too softly. The placement of the circle reflects pitch: when the circle is placed up in the screen, the pitch is too high. Ideally, the circle is placed in the middle or slightly under the middle of the screen. The interface of the Voice Trainer is available in Supplement 1.

The app supports patients and therapists to practice and correctly maintain voice loudness and pitch, during exercises as well as beyond the therapy sessions. Using an online dashboard connected to the Voice Trainer of the patient, speech therapists were not only able to see how many times the Voice Trainer had been used by the patient, but also how well the patient performed regarding percentages of correct loudness and pitch. This allowed the speech therapist to keep track of the daily home exercises. To use the Voice Trainer and the online platform for video conferencing at the same time, patients needed two devices (preferably a smartphone and a tablet or computer) (16). Patients who did not have a supporting device for online therapy could loan a tablet during study participation.

Outcomes

Primary outcome measure

Our primary endpoint was quality of life using the summary index score of the Parkinson's Disease Questionnaire (PDQ-39) at 8 weeks follow-up (T1). The PDQ-39 is the most widely used PD-specific health-related quality of life questionnaire (22). A decrease of this score over time suggests improvement.

Secondary outcome measures (observer-rated)

Observer-rated secondary outcome measures were evaluation of speech and voice quality (speech tasks as described in the Radboud Dysarthria Assessment (23); maximum repetition rate, maximum phonation duration, maximum pitch range, maximum loudness level, and dysarthria severity) and Acoustic Voice Quality Index (24)), speech intelligibility (Dutch intelligibility test – sentence level (25)), and swallowing speed (maximum swallowing speed (26)).

Secondary outcome measures (patient-rated)

Patient-rated outcome measures were voice-related complaints (Voice Handicap Index (27)), Parkinson-specific speech-related complaints (Radboud Oral Motor inventory for Parkinson's disease (28)), mood and anxiety (Hospital Anxiety and Depression Scale (29)), and health-related quality of life (EuroQol-5D (30)). Outcome measures for caregivers were caregiver burden (Zarit caregiver Burden Interview Short Form (31)), and caregiver reported Parkinson-specific speech-related complaints (Radboud Oral Motor inventory for Parkinson's disease, adapted to caregiver).

Sample size

Based on a trial on the effectiveness of multidisciplinary care (32), we calculated the sample size based on our primary outcome with a conservative estimated PDQ-39 total score improvement of 2.5 points in the intervention group, and no difference in controls (assuming a shared SD of 5.8). This estimated improvement exceeds the minimally important difference of 1.6 points (33). A sample of 170 patients would be needed to show this expected difference. Allowing for 20% drop-out, we aimed to include a maximum of 215 patients.

Statistical methods

Descriptive statistics

Depending on whether the outcomes were normally distributed (based on visual inspection of Q-Q plots, the presence of outliers, and whether there is a clinically relevant difference between the mean and median), means and standard deviations (SD) or median and interquartile range and frequencies are used to describe the outcome, demographics and baseline variables.

Analysis of effectiveness

Based on our hypothesis and design, two comparisons were made: at the primary endpoint (T1), we compared the mean PDQ-39 between the intervention group and the control group. At the secondary

endpoint (T2), we identified the long-term effects of speech therapy in the intervention group after 24 weeks of follow-up. Statistical analyses were performed based on the intention-to-treat principle. For the primary endpoint, analyses of covariance (ANCOVA) was used with group allocation as fixed variable. Baseline values of the dependent variable, age at baseline, Hoehn & Yahr stage and disease duration served as covariates. For the PDQ-39 at T2, a paired sampled T-test was performed.

Additional analyses

To gain insights into the different domains of the PDQ-39, we conducted post-hoc analyses for the single index scores using ANCOVA in the same way as described above. To evaluate whether disease stage modified the intervention effect on our primary outcome, we conducted a post-hoc ANCOVA in the same way as described above. In this analysis, we studied the interaction effect between Hoehn & Yahr stage and group allocation. Lastly, we conducted a post-hoc sensitivity analysis (ANCOVA) using the stratification variables as covariates to verify robustness of the results.

Role of funding

The funders were not involved in the writing process of the manuscript, nor involved in any other aspect pertinent to the study.

Results

Between March 1, 2019, and March 27, 2021, 417 patients were screened for eligibility. Between March 3, 2020, and June 26, 2020, inclusion was paused because of the lockdown during the COVID-19 pandemic. Follow-up measurements took place until November 10, 2021. 214 patients were included, who were assigned randomly (1:1) to the intervention group (n=109, 51%) or the control group (n=105, 49%). For 136 participants, of whom 67.3% in the intervention group and 76.9% in the control group, assessors had no inkling in what group they were allocated. Their presumption was correct for 31.6% in the intervention group and 23.1% in the control group, and incorrect for 1 participant from the intervention group. This difference between the groups was not statistically significant (p=0.195, Fisher's Exact test). For 23 participants, no presumption was filled in due to drop-out (10) or human errors. For the 55 other participants, their presumption was incorrect for 2 participants, was correct for 32 in the intervention group and for 21 in the control group. Baseline characteristics were similar between both groups (Table 1). A total of 12 patients (6%) dropped out, of whom 10 dropped out between the T0 and T1 measurements, and two between the T1 and T2 measurements (Figure 1).

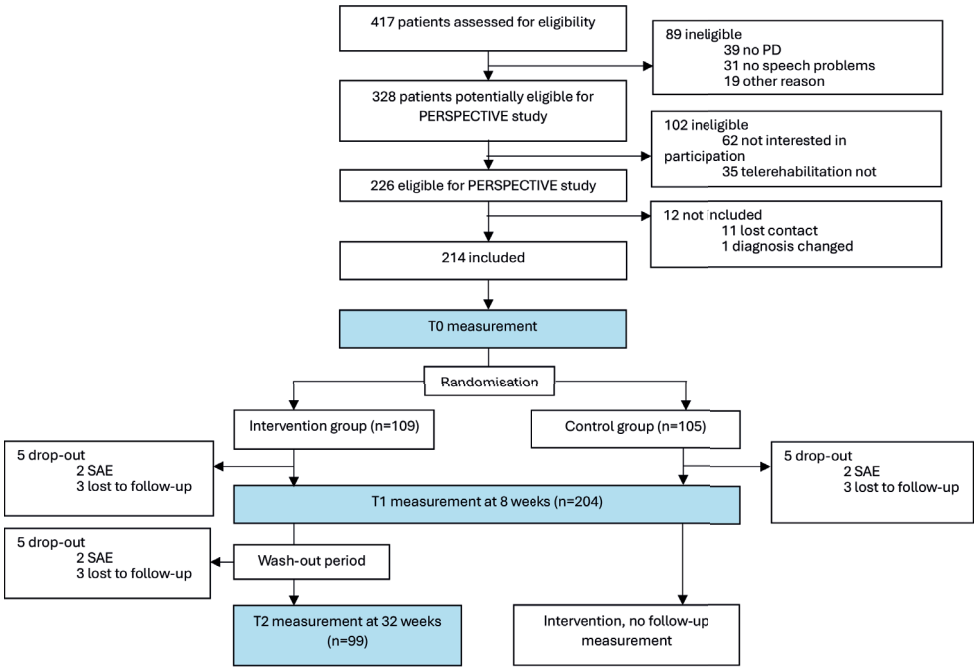


Figure 1. Trial profile

There were five serious adverse events (SAE) in the intervention group (5%) and five in the control group (5%), but these were judged not to be directly associated with the intervention or study procedures (verified by the medical ethical committee). During the study, the diagnosis changed from PD to atypical parkinsonism for one patient in the intervention group (1%) and four patients in the control group (4%). A total of twenty speech therapists participated, of whom five quit during the study for various reasons that were entirely unrelated to the study protocol itself (retirement, or a change of professional focus or job).

In Table 2 and 3, for every outcome measure it is reported how many participants completed the assessment. Most missing data are a result of the COVID-19 pandemic, when assessments had to be conducted online instead of at the patients' home. The 1:1 ratio between the intervention and control group stayed intact. Therefore, we did not impute the missing data.

Primary outcomes

At the primary endpoint of 8 weeks, the intervention group did not have a significantly improved health-related quality of life (summary index score of the PDQ-39) compared to the control group (p=0.056;

Figure 2a, Table 2). The estimated mean difference in PDQ-39 between the intervention group and the control group was -2.0 (95% CI -4.0 to 0.1), in favour of the intervention group. A post-hoc sensitivity analysis using stratification variables as covariates showed no notably differences in the summary index score of the PDQ-39 with an estimated difference of -2.0 (95% CI -4.0 to 0.4), p=0.054, demonstrating the robustness of our findings. Post-hoc analyses showed that out of the total of the eight single index scores of the PDQ-39, only the communication index score showed an improvement (p=0.011) in favour of the intervention group, with an estimated mean difference of -5.3 (95% CI -9.4 to -1.2) (see Appendix). Furthermore, post-hoc analyses showed no interaction effect of Hoehn & Yahr stage and group allocation on health-related quality of life (interaction effect = -.652, CI = -1.36 to 2.67, p-value = 0.524.), suggesting that disease stage did not affect the results much.

Secondary outcomes

For the secondary outcomes, significant benefits in favour of the intervention group were found for voice-related complaints (VHI) and severity of speech complaints as reported independently by both the patient (ROMP) and the caregiver (ROMP adapted to caregiver), see Table 2. There were no notably differences in the other secondary outcomes between both groups.

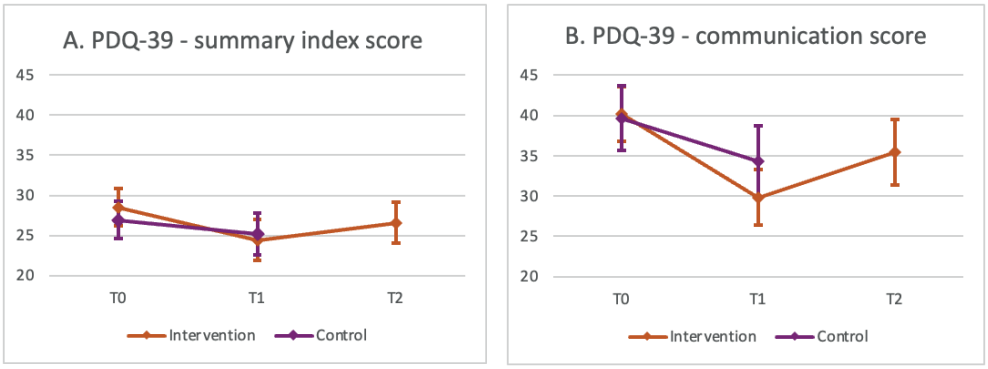


Figure 2. A. Primary analysis: the observed summary index score of the Parkinson's Disease Questionnaire 39 (PDQ-39) for the intervention and the control group (score 0-100). 95% confidence intervals are displayed. **B.** Post hoc analysis: the observed communication index score of the PDQ-39 for the intervention and the control group (score 0-100). 95% confidence intervals are displayed.

Table 1. Demographics and baseline characteristics.

	Intervention (n=109)	Control (n=105)
With participating caregiver	64	62
Age, in years (mean; SD)	67.4 (8.5)	68.9 (8.5)
Sex: women	32 (29.4%)	26 (24,8%)
Disease duration, in years (mean; SD)	8.1 (5.8)	7.5 (6.0)
Hoehn and Yahr stage (n; %)		
1	25 (22.9)	29 (27.6)
2	59 (54.1)	39 (37.1)
3	13 (11.9)	22 (21.0)
4	9 (8.3)	12 (11.4)
5	3 (2.8)	3 (2.9)
MDS-UPDRS		
I (mean; SD)	10.2 (5.5)	10.9 (5.8)
II (mean; SD)	13.6 (6.7)	13.9 (6.6)
III (mean; SD)	28.2 (10.9)	28.5 (12.5)
IV (median; IQR)	1.0 (0.0 - 6.0)	0.0 (0.0 - 5.0)
MMSE (median, IQR)	29.0 (27.0 - 30.0)	29.0 (27.0 - 30.0)
Word fluency (mean; SD)	22.02 (6.61)	21.96 (6.45)
Dysarthria severity (n; %)		
Minimal dysarthria	18 (16.5)	27 (25.7)
Light dysarthria	58 (53.2)	48 (45.7)
Moderate dysarthria	27 (24.8)	24 (22.9)
Severe dysarthria	5 (4.6)	6 (5.7)
Very severe dysarthria	1 (0.9)	0 (0.0)

Long-term follow-up measurement (32 weeks)

At the secondary endpoint (T2), we found a significant reduction in disease-related quality of life on summary index score of the PDQ-39 compared to T1, reflected in a higher score. A significant decline was also found for the ROMP Speech and for the ROMP adapted to the caregiver. For the objective speech-related outcomes, a significant improvement was found for maximum loudness level, maximum pitch range, and the maximum repetition rate of the syllable /ta/. Finally, a decline in caregiver burden was found with the Zarit caregiver Burden Interview Short form. There were no other significant differences at the secondary endpoint. An overview of all secondary outcomes can be found in Tables 2 and 3.

Table 2. Primary and secondary outcomes – subjective measures

Outcomes	T0		T1		T2		Estimated difference between intervention and control group at T1		Difference intervention group between T2 and T1	
							Mean (95% CI)	p value	Mean (95% CI)	p value
PDQ-39 (score 0-100) †	n		n		n					
Intervention	109	28.5 (12.4)	104	24.7 (13.2)	99	26.6 (12.8)	-2.0 (-4.0 to 0.1)	0.056	2.4 (0.8 to 4.0)	**0.004**
Control group	105	26.9 (12.2)	100	25.5 (13.1)	NA	NA				
ROMP (patient) †										
Speech (score 7-35)										
Intervention	109	18.0 (16.0 to 20.0)	104	15.0 (13.0 to 18.8)	99	16.0 (14.0 to 20.0)	-1.3 (-2.2 to -5.2)	**0.001**	1.4 (0.7 to 2.1)	**0.000**
Control group	105	18.0 (15.0 to 20.0)	100	16.0 (13.0 to 20.5)	NA	NA				
Swallowing (score 7-35)										
Intervention	109	11.0 (8.5 to 14.0)	104	10.0 (7.0 to 13.0)	99	10.0 (7.0 to 14.0)	-0.58 (-1.2 to 0.1)	0.073	0.3 (-0.3 to 0.9)	0.271
Control group	105	10.0 (8.0 to 13.0)	100	10.0 (8.0 to 13.5)	NA	NA				
Drooling (score 9-45)										
Intervention	109	14.5 (5.5)	104	13.9 (4.6)	99	14.43 (5.5)	-0.22 (-1.1 to 0.7)	0.682	0.44 (-0.2 to 1.1)	0.200
Control group	105	13.6 (4.8)	100	13.5 (4.8)	NA	NA				
VHI (score 0-120) † ¶										
Intervention	97	34.0 (24.5 to 44.0)	92	28.0 (18.0 to 41.8)	83	28.0 (18.0 to 45.0)	-4.9 (-8.0 to -1.8)	**0.002**	0.1 (-2.4 to 2.7)	0.912
Control group	94	33.0 (21.0 to 46.5)	87	31.0 (18.0 to 47.0)	NA	NA				
EQ-5D (score -0.33-1.0) ¶										
Intervention	99	0.78 (0.69 to 0.89)	93	0.81 (0.71 to 0.95)	85	0.78 (0.69 to 0.89)	0.01 (-0.27 to 0.05)	0.520	-0.02 (-0.05 to 0.02)	0.345
Control group	94	0.78 (0.69 to 0.86)	88	0.78 (0.68 to 0.89)	NA	NA				
HADS (score 0-21) † ¶										
Intervention	98	8.0 (5.0 to 15.0)	93	7.0 (4.0 to 13.0)	84	7.5 (4.0 to 13.0)	-0.6 (-1.7 to 0.6)	0.333	-0.5 (-1.4 to 0.4)	0.292
Control group	94	8.5 (4.0 to 14.0)	88	8.0 (3.3 to 13.0)	NA	NA				
ZBI-12 (score 0-48) † ¶										
Intervention	59	7.0 (3.0-14.0)	57	7.0 (3.0 to 14.0)	49	9.0 (6.0 to 15.0)	-0.7(-2.1 to 0.8)	0.354	1.8 (0.2 to 3.4)	**0.026**
Control group	61	7.0 (4.0-11.0)	59	7.0 (4.0 to 12.0)	NA	NA				

ROMP -Speech (caregiver) (score 7-35) † ¶										
Intervention	57	16.0 (14.0 to 20.0)	56	15.0 (11.6 to 18.4)	49	15.0 (12.0 to 19.5)	-2.1 (-3.3 to -1.0)	**<0.001**	0.81 (0.00 to 1.6)	**0.040**
Control group	61	16.0 (13.5 to 18.0)	59	16.0 (13.0 to 19.0)	NA	NA				

Data are median (IQR), or mean (SD). † Decrease in score over time suggests improvement. ‡ During the COVID-19 pandemic, a part of the T1 and T2 assessments had to be conducted online. Not all assessment could be conducted remotely, resulting in a lower n for marked outcomes ¶ Surveys sent online. Despite sending reminders, not all participants filled in the online surveys, resulting in a lower n for marked outcomes.

Abbreviations: PDQ-39 = Parkinson's Disease Questionnaire -39; ROMP = Radboud Oral Motor Inventory for Parkinson's Disease; VHI = Voice Handicap Index; EQ-5D = EuroQol-5 Dimension; HADS = Hospital Anxiety and Depression Scale; ZBI-12 = Zarit Caregiver Burden Interview short form; NA = not applicable.

Table 3. Secondary outcomes - objective measures

Outcomes	T0		T1		T2		Adjusted difference between intervention and control group at T1		Difference intervention group between T2 and T1	
							Mean (95% CI)	p value	Mean (95% CI)	p value
MRR /pa/ (syllables per second)										
Intervention	107	6.43 (1.02)	103	6.45 (1.02)	97	6.59 (1.01)	0.04 (-0.13 to 0.21)	0.650	0.09 (-0.11 to 0.30)	0.357
Control group	105	6.44 (1.12)	98	6.53 (0.94)	NA	NA				
MRR /ta/ (syllables per second)										
Intervention	108	6.00 (1.21)	103	6.04 (1.11)	97	6.25 (1.01)	-0.04 (-0.24 to 0.16)	0.712	0.17 (0.00 to 0.35)	**0.047**
Control group	105	6.07 (1.07)	98	6.18 (1.00)	NA	NA				
MRR /ka/ (syllables per second)										
Intervention	107	5.38 (1.1)	102	5.54 (1.02)	96	5.56 (1.09)	0.11 (-0.07 to 0.28)	0.222	0.05 (0.08 to 0.18)	0.481
Control group	104	5.49 (1.08)	98	5.61 (1.06)	NA	NA				
MRR /pataka/ (syllables per second)										
Intervention	108	6.15 (1.06)	103	6.22 (1.19)	97	6.27 (1.30)	0.07 (-0.14 to 0.27)	0.512	0.06 (-0.16 to 0.28)	0.596
Control group	105	5.99 (1.24)	97	6.04 (1.19)	NA	NA				
MPT (seconds)										
Intervention	108	18.5(14.0 to 24.9)	103	18.0 (14.1 to 23.9)	98	17.9 (13.8 to 23.5)	-0.3 (-1.7 to 1.2)	0.731	0.2 (-1.1 to 1.5)	0.714
Control group	105	15.7(12.0 to 22.1)	99	16.3 (12.8 to 23.5)	NA	NA				
MPR (semitones)										
Intervention	109	24.2 (6.2)	103	24.4 (6.9)	98	25.7 (6.3)	-4.0 (-1.8 to 1.0)	0.580	1.2 (0.1 to 2.3)	**0.031**
Control group	105	24.5 (6.6)	98	24.5 (6.9)	NA	NA				
MLL (dB) ‡										
Intervention	108	103.0 (9.2)	91	104.3 (8.2)	82	104.3 (8.9)	-1.1 (-2.4 to 0.2)	0.089	1.3 (0.1 to 2.4)	**0.029**
Control group	105	102.3 (9.0)	85	103.8 (7.8)	NA	NA				

AVQI (score 0-10) †‡										
Intervention	108	4.69 (1.28)	90	4.29 (1.15)	81	4.32 (1.28)	-1.00 (-0.40 to 0.21)	0.536	0.13 (-0.18 to 0.43)	0.406
Control group	105	4.84 (1.50)	85	4.53 (1.25)	NA	NA				
MSS (timed test) (ml/s) ‡										
Intervention	105	13.6 (7.7 to 18.1)	91	13.7 (8.3 to 20.4)	81	14.7(8.6 to 19.7)	0.6 (-0.6 to 1.8)	0.318	-0.6 (-1.7 to 0.5)	0.281
Control group	102	11.5 (7.8 to 16.5)	86	12.1 (7.7 to 15.8)	NA	NA				
DIT (percentage) ¶										
Intervention	108	98.3 (96.6 to 99.2)	99	98.4 (97.4 to 100)	96	98.3 (96.8 to 100)	2.1 (0.3 to 3.9)	**0.024**	-0.4 (-1.1 to 0.4)	0.320
Control group	104	98.3 (95.0 to 99.8)	96	98.3 (94.4 to 99.2)	NA	NA				

Data are median (IQR), or mean (SD). † Decrease in score over time suggests improvement. ‡ During the COVID-19 pandemic, a part of the T1 and T2 assessments had to be conducted online. Not all assessment could be conducted remotely, resulting in a lower n for marked outcomes. ¶ the percentage scores at baseline almost reached the maximum of 100% for all patients, making further improvement impossible. Abbreviations: PDQ-39 = Parkinson's Disease Questionnaire -39; MRR = maximum repetition rate; MPT = maximum phonation time; MPR = maximum pitch range; MLL = maximum loudness level; AVQI = acoustic voice quality index; MSS = maximum swallowing speed; DIT = Dutch intelligibility test (sentence level); NA = not applicable.

Discussion

We found that remotely delivered and personalised speech therapy (the PERSPECTIVE intervention) did not significantly improve disease-related quality of life in general. Immediately following treatment, quality of life was better in the treatment arm, with a difference that exceeded the hypothesised minimally clinically important difference of 1.6 points on the PDQ-39 (33), but this difference did not reach statistical significance. Although the study was not powered for post-hoc analyses, secondary analyses did suggest that remote speech therapy improved the communication sub-score of self-reported quality of life, but not any of the subdomains of the PDQ-39, suggesting a genuine effect driven by improvements in speech. Additional secondary analyses also showed an improvement in the self-reported severity of voice and speech complaints, as reported independently by both the patients and caregivers. Objectively measured speech outcomes did not differ significantly between both study arms. Of the observed improvements after speech therapy, only the VHI-score was retained at 6 months follow-up.

We opted for disease-related quality of life as an ambitious primary treatment goal, since we believe that the ultimate goal of any treatment for persons with PD should be to improve their quality of life. Our motivation to include quality of life as primary outcome came from the notion that speech is an important factor contributing to quality of life for persons with PD. At the same time, we do acknowledge that quality of life is a challenging outcome that is determined not just by speech but also by a wide variety of other domains, many of which are not targeted specifically by speech therapy. We also acknowledge that quality of life measurement tools such as the PDQ-39 lack discriminative validity, certainly when applied in a heterogenous PD population (as we did) where patient performance varies considerably over time, often for reasons unrelated to the study intervention. In that regard, measures of change in speech are arguably better outcomes as these offer proof-of-concept evidence for target engagement. Post-hoc analyses showed that the trend towards an improved general quality of life in the intervention group was driven by only one of the eight domains, namely the communication-related quality of life, which is in line with a genuine treatment effect. This improvement in the communication subdomain exceeded the minimally important difference of 4.2 for this domain. Although this is only a small part of the overall PDQ-39, being able to communicate independently is an important aspect of quality of life. The absence of change in other domains of the PDQ-39 after treatment actually, supports our hypothesis that speech therapy specifically improves communication and thereby quality of life.

Our findings are largely comparable to two smaller earlier studies. A noninferiority study comparing online speech therapy to face-to-face therapy found a significant improvement in the communication subdomain for PD patients who received online speech therapy, but no improvement in overall quality of life (13). Another RCT of speech therapy in PD also found an improvement in speech outcomes and communication effectiveness (8). Contrary to our trial, this latter study also noted an improvement in objective speech measurements. However, in both other studies, the intervention

was delivered at high intensity for all participants, whereas we personalised the treatment according to what participants could tolerate. Moreover, the objective speech measures used in this study (8) (sound pressure level during reading tasks and monologue) are hard to compare with the objective outcome measures in this trial (maximum performance tasks). This difference might explain the improvements of the objective speech measures in the study by Ramig and colleagues (8). An important advantage of the PERSPECTIVE study compared to other studies is the inclusion of participants with a broad range of disease severity, making this a more real-life intervention with greater external validity. Specifically, although we included overall more people in early disease stages, we also recruited 62 participants in Hoehn & Yahr stage III, IV and V, giving valuable information on this relatively underrepresented group in PD research. This broad inclusion was enabled by the remote delivery of the treatment, and also by the personalised nature of the intervention which was tailored to the abilities and treatment goals of each individual.

Based on earlier results of Ramig and colleagues, who found a retained improvement of a participant-reported Modified Communication Effectiveness Index (CETI-M) 6 months after speech therapy (8), we expected that the observed improvements of the self-rated secondary outcomes in our trial would also persist at long-term follow-up. However, this was only the case for the VHI and not for the ROMP speech. To enhance the validity of our findings, we included a real-life sample of patients with any degree of speech complaints, also including those with modest treatment goals and those who could not comply with highly intensive therapy because of less endurance, more cognitive problems, or greater dependency on caregivers. Although intensive treatment is considered as the optimal approach for persons with PD to regain speech intelligibility, realistically however, such an intensive treatment is not feasible for all patients. This could explain why in this trial, not all observed effects were retained at follow-up. As such, the results of this trial offer a realistic view on actual daily clinical practice, suggesting that some form of maintenance therapy is likely required. How to achieve such a retainment deserves further study.

An important aspect of our intervention was the fully remote delivery in the patient's own homes using telerehabilitation, making this treatment theoretically accessible to many people with PD around the world, provided they have a functioning internet connection. Occasional problems were reported with maintaining a stable internet connection, but telerehabilitation worked well for most participants. We appreciate that the experience may be less gratifying in other parts of the world where IT networks are less well developed. But overall, our findings do suggest that telerehabilitation offers an opportunity to make specialised and high-quality speech therapy accessible to more persons with PD, since the distance to a therapist is no longer a limitation. This may ultimately also improve the quality of care, because therapists will be able to increase their caseload and hence become progressively more experienced to treat a specific group of patients, while more patients are able to choose to be treated by a specialised therapist. Our experience in The Netherlands is that specialised treatment by allied health therapists treating a high case load is associated with better patient outcomes and lower cost (34, 35).

The remote element of our intervention will also be helpful in delivering a low intensity maintenance therapy to achieve a more long-term persistence of the therapeutic benefits.

We included two swallowing outcomes because pilot studies (36, 37) suggested that LSVT in PD may also improve swallowing and cough effectiveness, via activation of the laryngeal system. However, we found no difference in swallowing capacity, as measured by maximum swallowing speed, or swallowing complaints as measured by a validated PD specific questionnaire. One possible explanation is the relatively low severity of swallowing complaints at baseline, conceivably because we purposely included PD patients with speech complaints, but not necessarily those with dysphagia. Another explanation is that there is a large discrepancy between subjective prevalence of dysphagia (about one third) and objective prevalence of dysphagia in PD (57 – 80%) (38, 39) and therefore, our measurements are less sensitive to finding dysphagia. Whether intensive speech treatment may ameliorate swallowing remains to be studied in a large dedicated study combining a range of subjective and objective measures, performed in participants with clinically relevant dysphagia.

Several limitations of this study should be mentioned. First, our outcome measu0res presented several challenges. Besides the already mentioned lack of discriminative validity, quality of life as a primary outcome is also potentially affected by several confounding variables, and we were not able to measure all of them (e.g. medication status, sleep, or cognitive challenges). However, since participants were randomised at baseline, we assume that both study groups were comparable to each other, also for factors that we did not measure. Some outcome measures of speech may not have provided a realistic view of daily functioning, since they were assessed in a test situation. This applies in particular to the assessments of speech intelligibility and the maximum performance task. When participants know that their speech is being evaluated, the assessment itself may act as an incentive to speak more intelligibly or to perform better than without being supervised (40). Moreover, in daily life patients must rely more on cognitive functions, e.g. while maintaining a conversation with background noise. We did not assess speech intelligibility with these influencing factors. Future research could use more advanced techniques like intelligibility in the presence of background noise such as babbling (41) to create a more realistic communication environment. Moreover, maximum performance tasks and speech intelligibility are widely used and helpful dysarthria assessments (42), but may not be sufficiently sensitive in detecting changes in hypokinetic speech.

Second, since we compared the intervention group to a waiting list instead of a sham intervention, it is possible that the 'tender, loving care' effect could have influenced our results in a positive way (43). However, out of all the measurements that we conducted, only the speech related outcomes improved, suggesting that the intervention only showed an effect specifically on speech instead of on overall wellbeing. This effect is particularly visible in the outcomes of the subscales of the PDQ-39, where only the communication subscale improved. Also, anxiety and depression status as measured by the HADS

did not differ between and within study groups. This makes it less likely that a more global tender loving care effect influenced our results.

Third, a part of the data collection was conducted during the COVID-19 pandemic. Since the intervention was delivered via telemedicine, the pandemic did not hamper the continuation of online speech therapy, which is a strength. However, not all assessments could be completed since a part of them had to be conducted online instead of at the patients' home, resulting in missing data. Although we cannot completely rule out that the pandemic influenced our results, the circumstances regarding the COVID-19 pandemic did not differ for the intervention and control group as a result of the randomisation. Therefore, we expect that possible effects of the pandemic have the same size between both groups and no data were imputed. Furthermore, the safety measures did impact the assessment visits. Baseline home visits were delayed until the lockdown restrictions were lifted. To continue the study, part of the planned T1 and T2 visits had to be conducted online. This made it impossible to conduct some of the assessments, such as maximum loudness level, swallowing speed and the physical examination of the MDS-UPDRS. However, the latter was used only for baseline descriptive purposes, and these measurements were complete.

Furthermore, while participants were instructed not to disclose their group allocation, some participants accidentally revealed it to the assessor, thereby de-blinding the assessor. In addition, some participants spoke remarkably better at the follow-up assessment based on which the assessor might have guessed group allocation. There is a possibility that this influenced some of the results. However, the primary outcome (PDQ-39) is a questionnaire completed by the participant, hence this was not affected by the assessor's presumption. The presumptions may have had an effect on the outcomes that are sensitive to the assessor's influence (such as the maximum performance speech tasks), but we did not find any significant differences for these outcomes between the intervention and the control group, which would in fact suggest that the influence of the assessor was negligible.

Lastly, as in most other studies in PD (44), a relatively low proportion of women participated in our study (27%, which is less than the proportion of women in the Dutch PD population, estimated to be 42% (45)). Other studies of speech therapy in PD had a similar recruitment issue (5). We have no specific reason to believe that the remote speech therapy benefited men and women differently, yet every effort must be made to make speech therapy accessible to everyone with PD, both in research and daily care. More work is also needed to better understand how speech therapy should be optimally personalised for people with PD.

Contributions

B.R. Bloem, N.M. de Vries, and J.G. Kalf conceived the study and initiated the study design. J.J.L. Maas performed the study and analysed the results together with J. In 't Hout. J.J.L. Maas accessed and verified the data. All authors contributed to the final manuscript.

Data Sharing

We will make aggregated and anonymised data available in a validated database. Access to the data is restricted, meaning that researchers who are interested in re-use of the data are asked to contact the central contact person for permission. Approval is given after a signed agreement. Data will be available beginning 1 year after publication.

Declaration of Interest

J.J.L. Maas has nothing to declare. N.M. de Vries reports grants from the Netherlands Organisation for Health Research and Development (ZonMw), Michael J Fox Foundation, and Verily Life Sciences, has received a travel stipend to visit the World Parkinson Congress, serves in the advisory board of the Royal Dutch Society for Physical Therapy, and serves as the associate editor of the Journal of Parkinson's disease. J. IntHout has nothing to declare. B.R. Bloem serves as the co-Editor in Chief for the Journal of Parkinson's disease, serves on the editorial board of Practical Neurology and Digital Biomarkers, serves on the executive scientific advisory board of the Michael J fox Foundation for Parkinson Research, serves as officer (Secretary) of the Movement Disorder Society, has received fees from serving on the scientific advisory board for the Critical Path Institute, Gyenno Science, MedRhythms, UCB, Kyowa Kirin and Zambon (paid to the Institute), has received fees for speaking at conferences from AbbVie, Bial, Biogen, GE Healthcare, Oruen, Roche, UCB and Zambon (paid to the institution), and has received research support from Biogen, Cure Parkinson's, Davis Phinney Foundation, Edmond J. Safra Foundation, Fred Foundation, Gatsby Foundation, Hersenstichting Nederland, Horizon 2020, IRLAB Therapeutics, Maag Lever Darm Stichting, Michael J Fox Foundation, Ministry of Agriculture, Ministry of Economic Affairs & Climate Policy, Ministry of Health, Welfare and Sport, Netherlands Organization for Scientific Research (ZonMw), Nothing Impossible, Parkinson Vereniging, Parkinson's Foundation, Parkinson's UK, Stichting Alkemade-Keuls, Stichting Parkinson NL, Stichting Woelse Waard, Health~Holland / Topsector Life Sciences and Health, UCB, Verily Life Sciences, Roche and Zambon. J.G. Kalf has received grants from the Michael J Fox Foundation, Michel Keijzerfonds, Ataxie Vereniging Nederland, and from the Netherlands Organisation for Health Research and Development (ZonMw) (all paid to the institution), has received a fee for lecturing for the International Parkinson & Movement Disorders Society, has received a travel stipend to visit the World Parkinson Congress, and has served as councillor of the board for the Dysphagia Research Society (2021-2022).

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Appendix 1 – Post hoc analyses

Table 1. Post hoc analyses: estimated mean index scores of the Parkinson's Disease Questionnaire 39. Outcomes are not adjusted for multiple testing

Parkinson's Disease Questionnaire 39 domain	T1 index scores intervention group	T1 index scores control group	Estimated difference between intervention and control group at T1, mean (95% CI)	P value
Mobility	25.3	26.3	-1.0 (-4.1 to 2.1)	0.518
Activities of daily living	30.7	33.7	-3.0 (-6.2 to 0.2)	0.067
Emotional wellbeing	22.4	23.1	-0.8 (-3.8 to 2.2)	0.617
Stigma	13.9	13.6	0.33 (-3.1 to 3.8)	0.850
Social support	15.0	18.4	3.4 (-7.2 to 0.47)	0.085
Cognition	28.5	27.5	1.08 (-1.9 to 4.1)	0.478
Communication	29.4	34.7	-5.3 (-9.4 to -1.2)	**0.011**
Bodily discomfort	30.9	34.4	-3.5 (-7.9 to 1.0)	0.124
Total score	23.8	25.9	-2.0 (-4.0 to 0.1)	0.056

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PART II

Development and usability of a speech intervention tool in Parkinson's disease



Chapter 4

The Voice Trainer: development and usability evaluation of an application for improving speech in Parkinson's disease

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Submitted

Abstract

Background: Most persons with Parkinson's disease (PD) experience speech problems in the course of the disease. Speech in PD can be improved through exercise and by providing patients with feedback on vocal production.

Objectives: To evaluate the use and usability of an application (Voice Trainer) for providing visual feedback for persons with PD to improve their speech.

Methods: 81 persons with PD, participating in a trial evaluating the effectiveness of speech therapy, were asked to fill out two questionnaires about the use and usability of this app with the System Usability Scale (SUS), and a questionnaire developed for evaluating use of the app, the Voice Trainer Questionnaire (VTQ).

Results: Participants judged the usability of the Voice Trainer with a median SUS score of 78.8, indicating above average satisfaction. Of those who continued using the app (45%), 92.3% would recommend the app to other persons with PD. Of the participants discontinuing its use, (55%), 81.3% would recommend it to others. There were various reasons for (dis)continuing its use.

Conclusions: The vast majority of patients are satisfied with the usability of the app and had positive experiences while using it. Although the app is well-received amongst patients, individual variability in needs and wishes regarding its use should be taken into account in therapy.

Introduction

Parkinson's disease (PD) is a fast-growing progressive neurological disorder, affecting both motor and nonmotor symptoms (1). Motor symptoms are characterised by bradykinesia (i.e. slowness of movement) combined with either rest-tremor, rigidity, or both (1). These symptoms are also reflected in speech (hypokinetic-rigid dysarthria), leading to mumbling and a soft, hoarse voice, which can be accompanied by a higher voice pitch (2). When left untreated, this results in a reduced speech intelligibility in up to 70% of people with PD which affects social interaction and quality of life (3).

People with PD can overcome their hypokinetic speech with the instruction to speak louder (4-6). When doing so, the whole motor speech system is activated (voice production, breathing effectiveness during speech and augmented articulation movements), immediately improving the speech intelligibility. This physiological mechanism has been demonstrated by multiple studies and is successfully incorporated by exercise-based treatment approaches for many years (7-9). To achieve the skill to independently overcome hypokinetic speech and to integrate this technique into normal speech and conversation, daily exercises are required. To (re)gain control of a (new) motor skill, feedback during exercising is vital (10). This is particularly true for people with PD, due to impaired monitoring of motor performances including self-produced speech (11). External sensory cues (e.g. auditory, visual) can facilitate motor initiation and can help people with PD to draw attention to the task aimed. Verbal feedback by a therapist or the conversation partner is helpful, but may also be annoying, in particular during conversation; it can disrupt the communication flow and may induce feelings of irritation.

Because feedback on speech production ideally should be real-time, we sought a solution to provide wearable real-time visual feedback during speech. This makes individuals with PD less dependent on their conversation partner to speak intelligibly. Since the smartphone is a feasible device to deliver feedback (12), this resulted in an app: the Voice Trainer. The app delivers real-time visual feedback on both loudness and pitch and is designed in accordance with the Pitch Limiting Voice Treatment (PLVT) (9). This approach encourages persons with PD to speak 'loud and low' to compensate for hypokinetic speech: enhanced loudness improves voice quality and articulation, whereas a lower pitch helps prevent vocal strain (9). While the app was originally developed for hypokinetic-rigid dysarthria, the feedback on loudness and pitch can also be helpful for other groups, such as people with transgender-related voice problems, individuals in voice-demanding professions, or people with ataxic dysarthria, for whom the added value of the Voice Trainer has already been demonstrated (13). In addition, though the instructions are only in Dutch or in English (depending on the pre-set language of the device), the functioning of the Voice Trainer is language-independent.

We used the Voice Trainer as an integrated part of our intervention that we researched in the PERSPECTIVE study (14). In this paper, we first describe the Voice Trainer, including its web-based dashboard, and present results of our investigation on how people with Parkinson's disease experience the Voice Trainer

regarding the use and usability. Our hypothesis is that people with PD find the Voice Trainer to be user friendly and generally experience an improvement of speech using the app. However, we also expect a variability in individual experiences and satisfaction.

Description of the applications

Description of the Voice Trainer

The Voice Trainer is a single payment app that can be downloaded from the regular app stores for iOS and Android operating systems. The core feature is providing real-time feedback on loudness and pitch when the user is speaking. The application accesses the microphone of the device to measure the sound pressure level in decibel (dB) and sound frequency in hertz (Hz). The software generates a data point every 100 milliseconds (ms) of speech, capturing information on pitch, loudness, and time of use. A dot responds to this information, providing the user visual feedback representing the average over 700 ms of speech (see Figure 1). To prevent ambient noise from influencing the performance of the app, sounds must be louder than a silence threshold of 40 dB to be displayed.

When opening the app, there are two buttons: 'Start' and 'Settings' (Figure 1). When clicking on 'Start', a dot is displayed on the screen, showing both loudness and pitch. The size of the dot grows larger when the loudness increases. When the speech is loud enough, the dot is green and large, but when the loudness is lower than the pre-set level (explained in the next paragraph), the dot turns red and small. To reflect pitch, the dot stays in the middle of the screen when the pitch is between the minimum- and maximum pre-set Hz-level; when the dot stays at the top of the screen the pitch of the speaker's voice is too high, and when the dot is at the bottom of the screen the pitch is too low (see Figure 1). The button 'Settings' shows all functionalities and a detailed explanation is reported in Appendix A.

It is vital for functional feedback that the levels of optimal loudness and pitch are chosen individually to react to the speaker's targeted voice. The target loudness level and pitch range can be set with the buttons 'loudness' and 'frequency' . Loudness only needs a minimal level, where we chose 52 or 55 dB as a realistic starting point for speech production reflected on the Voice Trainer. Loudness level can be adjusted in steps of 3 dB.

Pitch is set by choosing a frequency range: as a start, for men a minimum of 100 Hz and a maximum of 150 Hz (minimal range of 50 Hz), for women a minimum of 170 Hz and a maximum of 230 Hz (minimal range of 60 Hz). Pitch settings can be adjusted in steps of 10 Hz. Because the app only provides feedback, obviously the first goal during speech treatment is to regain the optimal voice quality in terms of loudness and pitch. Then the speech therapist sets the limits in the app, in such way that the dot provides the intended feedback. Initially, the feedback can be set with tolerant limits (easy to achieve a green dot in the middle), later in treatment the feedback can be set with stricter limits.

The loudness and pitch displayed on the screen is influenced by the technical quality of the device and the distance between the speaker and the device. Therefore, the advice is to keep the speaker-device distance consistent but with a maximum of one arm length (about 30 cm), and to only use one device per individual for practicing with the Voice Trainer.

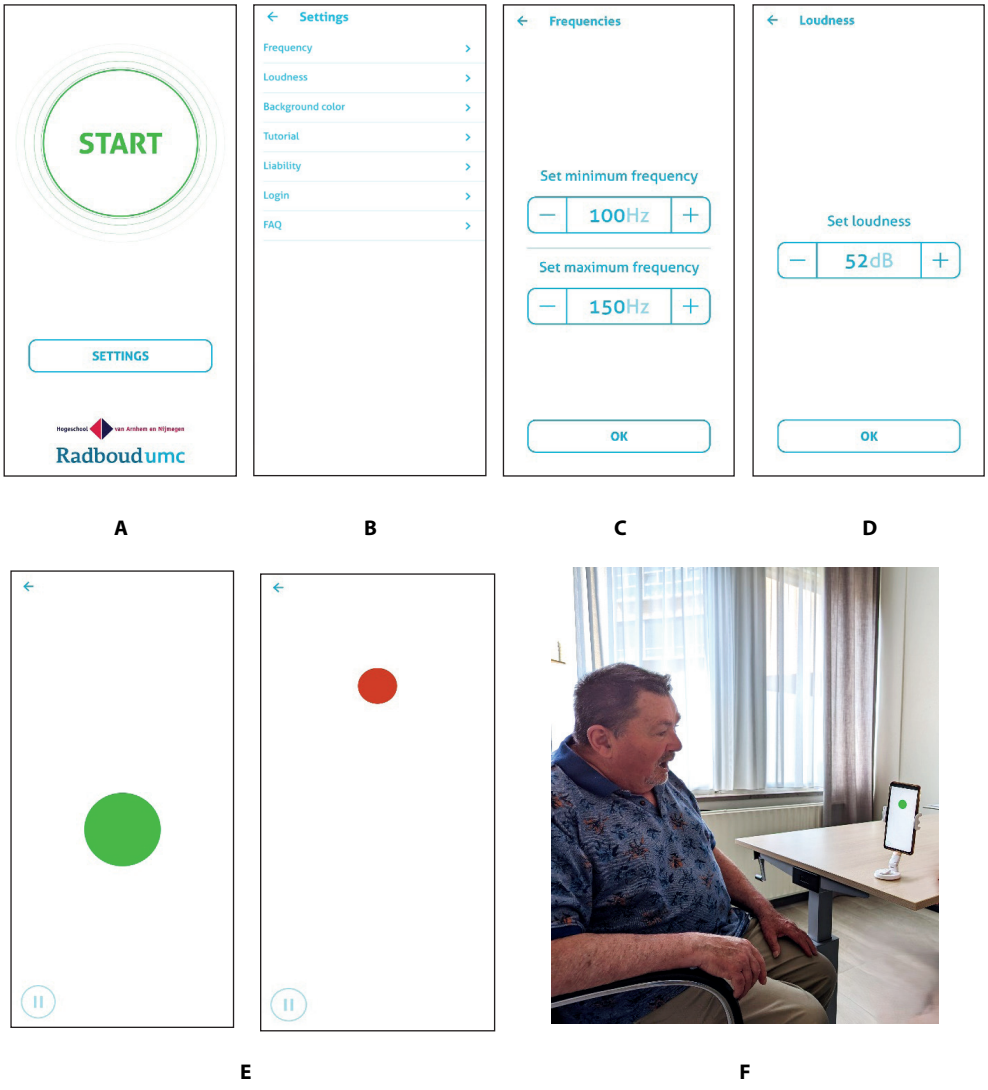


Figure 1. Interface of the Voice Trainer.
A. Home screen. **B.** Settings overview. **C.** Setting the frequency range (Hz). **D.** Setting the minimum loudness level (dB). **E.** Visual feedback on pitch and loudness: when the circle is large and green, it means the speech is loud enough; red and small means speaking too softly. The placement of the circle reflects pitch: when the circle moves upwards in the screen, the pitch is too high. Ideally, the circle is placed in the middle of the screen to support intelligible speech. **F.** Person with PD using the Voice Trainer.

In short, the Voice Trainer provides real-time visual feedback on pitch and loudness. The essential features for exercise training are that the settings can be adjusted to individual targets, and that the feedback is clear and easily interpretable for the user.

While visual feedback apps for speech, such as digital decibel meters or pitch tracking applications, are not new, to our knowledge the Voice Trainer is the only app to combine all above mentioned features.

Another important characteristic of the Voice Trainer is its compatibility for both face-to-face therapy and telerehabilitation, as demonstrated in the PERSPECTIVE study (14). As such, the Voice Trainer aligns with the increasing use of telerehabilitation, facilitating access to specialised care, reducing travel burden, and potentially lowering healthcare costs and waiting lists (15).

Description of the Voice Trainer Dashboard

During treatment, the speech and voice exercises with the Voice Trainer are used in a controlled setting, i.e. persons with PD who use the app on their own device are instructed by their speech therapist how to use the app. However, it remains unseen to what extent persons with PD exercise at home and utilise the new learned skills outside of the therapeutic setting. To further improve the impact of training with the app, a web-based dashboard (from now on called Dashboard) was developed, providing the option for speech therapists to link the Dashboard to the Voice Trainer of their clients (from now on referred to as 'users'), enabling extra functionalities (see Appendix A). To make a connection between the Dashboard and the Voice Trainer, the speech therapist adds a new user to the Dashboard. The user receives an email with credentials to log in to the Voice Trainer. When done, the Voice Trainer of the user is connected to the Dashboard of the speech therapist.

The Dashboard provides three extra functionalities. First, the speech therapist has the option to add extra speech profiles to the user's Voice Trainer. Speech profiles are relevant when the user wishes to use the Voice Trainer in another conversational situations, for example when talking with background noise, or when needing to speak louder in a group or during driving. These situations require different pitch and loudness levels compared to having a one-to-one conversation in a silent room. When extra speech profiles are added, the user can easily switch between different situations, making the Voice Trainer react in an adequate way to the user's speech.

Second, using the Dashboard the speech therapist can send notifications (push messages) to the user's device at prescheduled times, in order to remind the user to the much-needed moments to practice. The user itself can disable the function to receive notifications at all times.

Third, if the user gave permission for this, the speech therapist can see a graphic performance overview of the user in the Dashboard (Figure 2). This provides valuable insights in both the user's compliance and improvement over time and enables precise evaluation of the user's performance outside of the

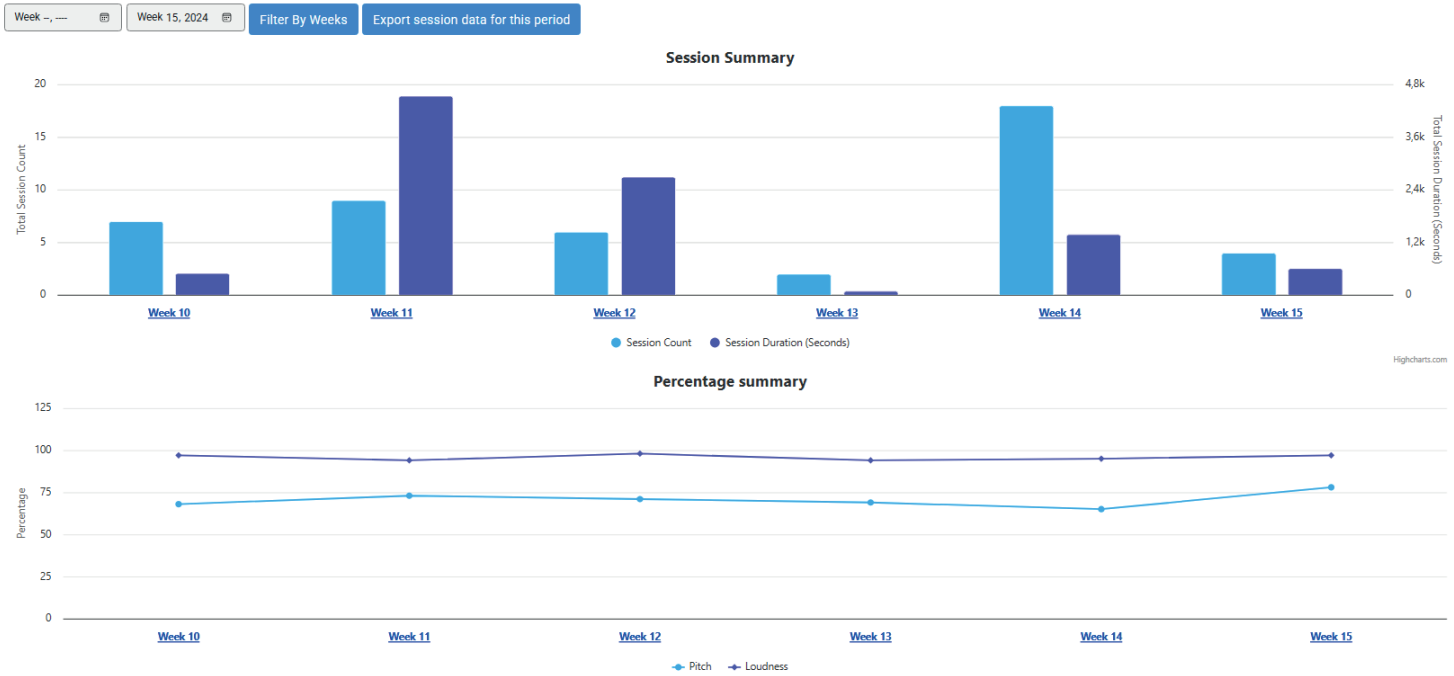


Figure 2. Dashboard overview of one user's performance in six weeks. In the upper half, an overview of the session summary is displayed, providing information about the number of practice sessions and the average length of the moments practiced. In the lower half, the session summary is displayed, in which the percentages of correct pitch and loudness level are separately displayed. These percentages are best reliably in situations in which the patient is in a quiet environment and mainly speaks for him- or herself.

therapeutic setting. The performance overview is also visible for users in the Voice Trainer on their own device. The user can disable the possibility to share this data with his therapist in his Voice Trainer any time.

Methods

Participants

To evaluate the experiences of patients regarding the use and usability of the Voice Trainer, participants of the PERSPECTIVE study (14), a trial investigating the effectiveness of remote speech therapy in PD, were approached by telephone to fill out additional questionnaires about the Voice Trainer. Participants were treated with the Pitch Limiting Voice Treatment (PLVT, (9)) including the use of the Voice Trainer, a treatment program consisting of three online half-our sessions per week for a maximum of 8 weeks. Similar to other speech therapy programs like Lee Silverman Voice Treatment (LSVT) (16) or Speak Out! (17), PLVT aims to overcome hypokinetic speech by training loudness and more energetic speech. Only participants in the intervention group (and thus who had received speech therapy) were selected, to make it possible to send questionnaires directly after finishing the treatment program (T1) and at six months (T2), since only the intervention group received a long-term follow-up. Between T1 and T2, participants did not receive speech therapy, but the use of the Voice Trainer was still allowed. In brief, inclusion criteria were: being diagnosed with idiopathic PD and having the ability to receive online treatment for speech problems. For further study details, we refer to the PERSPECTIVE study protocol (18). Participants signed informed consent at baseline, and the study was approved by the medical ethical committee of Arnhem-Nijmegen (NL67867.091.18).

Demographic data

Demographic data were obtained at baseline measurement of the PERSPECTIVE study and consisted of age, sex, disease duration, disease severity and MDS-UPDRS scores.

Questionnaires

Two questionnaires were used to evaluate the use of the Voice Trainer: an unofficial Dutch translation of the validated System Usability Scale (SUS) (19) and the Voice Trainer questionnaire (VTQ), an ad hoc questionnaire to evaluate the experiences of the Voice Trainer.

The SUS is a frequently used questionnaire for examining the usability of new systems and tools. The SUS consists of 10 items scored on a scale from 1 (strongly disagree) to 5 (strongly agree). It provides a global view of subjective assessments of usability, including factors such as the need for support, training, and complexity. We adjusted the SUS by replacing the words 'the system' with 'the Voice Trainer' in every item, stating the actual product name appears not to influence the SUS scores (20). Besides, two additional questions were added: one about how the participant rates the Voice Trainer on a scale

of 1-10, and another asking for arguments regarding the given rating. The adjusted SUS can be found in Appendix B.

The VTQ was developed in consultation with two patient researchers who after careful discussion agreed on the final version. The goal of the VTQ was to find out whether the participants continued using the Voice Trainer after finishing the speech therapy, how frequently and in which situations they used it, or from those who to find out the reason for discontinuing using the Voice Trainer. Furthermore, participant's opinions on the Voice Trainer were examined. Caregivers were allowed to assist the participants in completing the VTQ (Appendix C).

The SUS and VTQ were sent to participants using Castor EDC (21), a validated electronic data management platform. The SUS was sent to participants who had just finished speech therapy (T1) and to participants who completely finished the RCT, 24 weeks after treatment (T2). The VTQ was only sent out to T2 participants, since this questionnaire evaluates long-term use of the Voice Trainer. As the T1-group was not asked to fill out the VTQ, an extra question was added to the SUS for them about whether participants intended to use the Voice Trainer after therapy.

Data analysis

Depending on whether the outcomes are normally distributed, means and standard deviations or median and interquartile range and frequencies was used to describe demographics and outcomes.

The SUS was scored by calculating the score of every original item and multiplying the sum of those item scores by 2.5 to obtain the overall value. Positive items were scored by the scale position (1 to 5) minus 1, and negative items are scored by 5 minus the scale position (19). The mean or median SUS score was interpreted using the Sauro and Lewis Curved Grading Scale in which a score of 68 is considered an average experience and 80 indicates a good experience (22). The rating of the added Voice Trainer question was reported using descriptive statistics, including percentages. The percentages of multiple answer questions were based on the number of people that answered the question. Therefore, the sum of the percentages could be above 100%. The answers to open questions were corrected on typing errors and spelling mistakes, making sure the content of answers was not changed. Data was exported from Castor EDC, and RStudio (23) was used for data analysis.

Results

Eighty-one participants were approached and asked to fill in the SUS and/or the VTQ. Of these patients, 74 (91.4%) responded to the SUS and 63 (77.8%) responded to the VTQ (Figure 3). The demographics of the 65 patients who fully completed the SUS and/or the VTQ are reported (Table 1). No significant

differences were found between the group of patients who fully completed the questionnaires and those who did not (based on sex, age, disease duration, and Hoehn and Yahr stage).

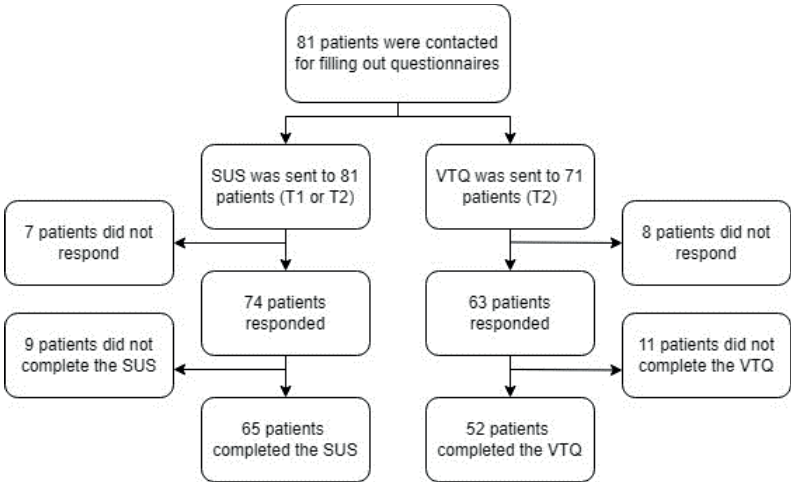


Figure 3. Flowchart of questionnaires sent. SUS = System Usability Scale; VTQ = Voice Trainer Questionnaire

Table 1. Demographics and baseline characteristics of participants

	N = 65
Age (mean; SD)	67 (8.1)
Sex: men	45 (69.2%)
Disease duration in years (median; IQR)	6 (4.0-10.0)
Hoehn and Yahr stage	
1	14 (21.5%)
2	38 (58.5%)
3	8 (12.3%)
4	4 (6.2%)
5	1 (1.5%)
MDS-UPDRS	
I (mean; SD)	9.5 (5.44)
II (mean; SD)	12.8 (6.24)
III (mean; SD)	28.2 (12.08)
IV (median; IQR)	1 (0.0-6.0)

Abbreviations: MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; SD = standard deviation; IQR = interquartile range.

System Usability Scale

The median SUS-score was 78.8 (IQR = 67.5-84.4), which corresponds with a high acceptability score and can be interpretated as a 'good' to 'excellent' rating (24). Participants scored the Voice Trainer with a median score of 8 on a scale of 1-10 (IQR = 6-8, Figure 4). Participants who scored an 8 or higher (n = 42), mentioned the Voice Trainer was easy to use and did a good job providing feedback about their speech. Some reported answers of patients who gave a score of 5 or lower (n = 16) are: preferring feedback from a person rather than an application; inability to use the Voice Trainer since their phone was too outdated; or use of the Voice Trainer did not suit them because using it took too much effort. An overview of all answers can be found in Appendix D.

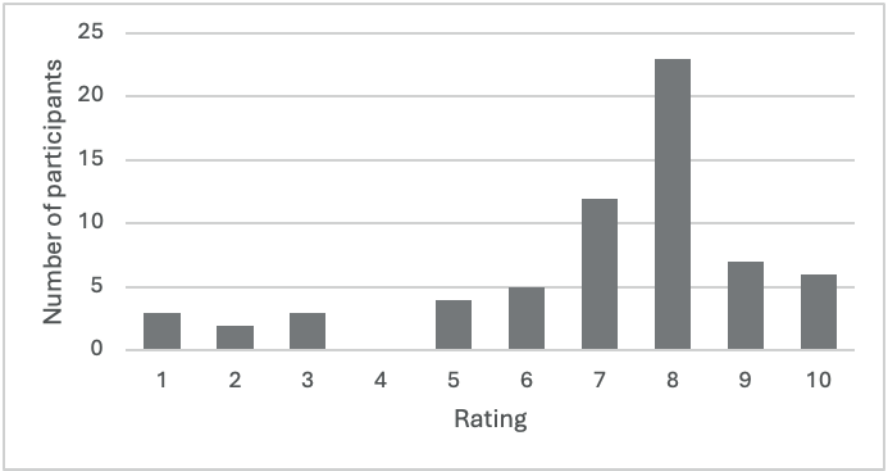


Figure 4. Ratings of the Voice Trainer. 1 is the lowest possible rating, 10 the highest possible rating.

Voice Trainer questionnaire

Forty-five participants (71.4%) completed the VTQ on their own, 14 (22.2%) with their partner and 12 (6.4%) did not report whether they were assisted in filling out the VTQ. No significant differences were found between the group of participants who continued using the Voice Trainer and the group that did not (based on sex, age, disease duration, and Hoehn and Yahr stage).

Use of the Voice Trainer

Twenty-six participants (44.8%) continued using the Voice Trainer after the treatment program and 32 (55.2%) participants stopped using the Voice Trainer. Among the group of participants who continued using the Voice Trainer, the majority (65.4%) mentioned that their partner (spouse or care provider) played a supporting role in the use of the Voice Trainer. In contrast, among the group of participants who discontinued using the Voice Trainer, most participants (68.8%) reported that their partner did not play a role (Appendix E). Of the participants continuing using the app, most reported monthly (38.5%)

or weekly (34.6%) usage of the Voice Trainer and they had various reasons for using the application: the majority (57.7%) used the Voice Trainer to improve their voice when it sounded weak or hoarse. Others (46.2%) used the Voice Trainer during individual practice sessions, while 23.1% used the application to work on goals previously discussed with the speech therapist. One participant reported using the Voice Trainer whenever they remembered to do so, and another used the Voice Trainer during conversational situations, such as one-to-one conversations with acquaintances or discussions in a domestic setting.

Among the 26 participants who continued using the Voice Trainer, only one used more than one speech profile (3.8%), 16 participants used only one speech profile (61.5%), and eight persons were not familiar with speech profiles at all (30.8%). Furthermore, 7.7% of the participants used the performance overview to enhance their speech proficiency, while 11.5% consulted the performance overview without taking any further action, and 34.6% indicated never viewing the performance overview. 38.5% of the participants were not familiar with the performance overview (Appendix E).

Reasons for discontinuing using the Voice Trainer

Participants who discontinued using the Voice Trainer did so immediately after completing the treatment (50.0%), one month after completing the treatment (31.3%), one to three months after completing the treatment (12.5%), or more than three months after completing the treatment (6.3%). The primary reason for discontinuing was that participants forgot to use it (46.9%). Additionally, 25% indicated they no longer needed the Voice Trainer, and 25% found it too much effort. Some participants felt uncomfortable when others observed them using the Voice Trainer (9.4%), and others no longer knew how to practice independently with the Voice Trainer (6.3%). Other reasons for discontinuing using the Voice Trainer could be found in Appendix F. When asked what would help them to use the Voice Trainer again, the answers varied. Some people mentioned that they need someone to stimulate them to use it (33.3%), others need fixed practice moments (16.7%) or a maintenance plan (15.6%), and some did not want to continue using the Voice Trainer (41.7%). In Appendix F an overview of all answers can be found. Remarkably, half of the patients who discontinued using the Voice Trainer reported intending to start using the application again after filling out the VTQ.

Reactions from social environment

Among those who continued using the Voice Trainer, 30.8% received positive reactions regarding use of the Voice Trainer from their social environment. Due to these reactions, participants felt comfortable using the application. 15.4% of the same group mentioned that their social environment did not care whether they used the Voice Trainer. One person reported that his social environment considered the use of the Voice Trainer unnecessary, and another person that his social environment had to get used to it. Furthermore, a substantial part of this group (42.3%) did not know how their social environment felt about the use of the Voice Trainer. This percentage was lower among the participants who discontinued using the Voice Trainer (31.3%). In that group, a third (37.5%) received positive reactions from their social environment and another third (37.5%) mentioned that their social environment did not care. Of the

latter group, 2 participants (6.3%) reported that their social environment considered the use of the Voice Trainer unnecessary, and another 2 (6.3%) that their social environment had to get used to it. Overall, these reactions seemed to have little influence on the participants in both groups. In Appendix E, an overview of all answers can be found.

Reminders of the Voice Trainer

Among those who continued using the Voice Trainer, 88.5% stated that they never received reminders for using the app. Comparably, in the group who discontinued using the application, this was 81.3%. In both groups, there was one person who received reminders. Two participants (7.7%) among those who continued using the Voice Trainer had received reminders in the past, but not anymore, compared to 5 (15.6%) in the group of participants who discontinued using the Voice Trainer. In both groups – those who continued using the Voice Trainer and those who did not – approximately half (52.4% and 53.8% respectively) believed that reminders would not have assisted them in using the Voice Trainer.

Recommending the Voice Trainer

Of participants who continued using the Voice Trainer, 24 persons (92.3%) stated they would recommend the Voice Trainer to other persons with PD, for reasons such as it supports them in speaking clearly, or it increased self-confidence during speech. Also 81.2% of the participants who discontinued using the Voice Trainer would recommend the application, as they consider it a useful tool. However, the others (18.8%) would not recommend the application, because they thought its effect is too small, they experienced technical issues, or they did not like to use it.

With an overall median of 7 (IQR= 5-8), most participants think the Voice Trainer contributed to their improvement of speech. Some patients mentioned that the Voice Trainer helped them speak louder and lower (at their optimal pitch), while others indicated they only had experienced minimal results. An overview of all answers can be found in Appendix G.

Suggestions for improvement

In the final question of the VTQ, we inquired whether the participants had any suggestions or other comments on the Voice Trainer. Fourteen different responses were added. The only comment that was given more than once was the disappointment that contact with the speech therapist was discontinued after treatment. An overview of all suggestions can be found in Appendix F.

Discussion

This study examining the use and usability of the Voice Trainer among individuals with PD and hypokinetic-rigid dysarthria showed that overall, participants are satisfied with the app in terms of

usability, praising its user-friendliness and the feedback it provides about their voice. Moreover, most participants rated the contribution of the Voice Trainer to their speech quality as satisfactory.

Besides these positive experiences, we also found that there is individual variability in experiences and needs regarding using the Voice Trainer. Some participants encountered technical issues, preferred feedback from a person over an app, or it took them too much effort to use it. These findings emphasise the importance of tailoring treatment and app use to individual needs, preferences, and motivational factors in order to optimise transfer of the new-learned skills to daily life.

Although the usability score of the app could be interpreted as 'good' to 'excellent', more than half of the participants discontinued using the app after speech therapy. The main reasons mentioned are forgetting to use it, perceiving it as no longer necessary, or finding its use too effortful. Importantly, because of the design of the study the contact with the speech therapist was discontinued after therapy, which does not reflect typical clinical practice. This absence of follow-up may likely have contributed to reduced app engagement.

Loss of initiative is a common complaint in persons with PD (25), meaning that external stimulation and the use of reminders is relevant for maintaining intelligible speech. This is demonstrated here by the finding that half of the participants who stopped using the Voice Trainer after therapy mentioned that they were planning to use the Voice Trainer again after filling out the VTQ, suggesting that the questionnaire itself may have served as a reminder. Additionally, more than one third of the participants who continued using the app after speech therapy mentioned that the reminder notifications would stimulate them to keep using the Voice Trainer. Remarkably, the majority of participants stated that they did not receive app notifications to practice their speech. The cause of this remains unclear: it could be due to speech therapists not activating these reminders, patients disabling them, or technical malfunctions. Altogether, this highlights the essence of optimising the use of reminders to support speech quality outside the therapeutic setting, as is recommended in all other speech treatment programs for PD as well (5, 17). Furthermore, partner involvement could be a stimulator to use the app, since the majority of those participants who continued using the Voice Trainer mentioned that their partner played a role in using the app (in contrast to the participants who stopped using the app). This underpins the involvement of care partners in speech therapy.

Regarding personalised feedback, Riggare et al. (2021) emphasised that digital health could reach its full potential when persons with PD receive personalised feedback based on their own data (26). The Voice Trainer meets the need of patients' perspective by offering real-time visual feedback and performance overviews. Although persons with PD have the possibility to view their own performances, results of the VTQ showed limited use and knowledge of the performance overview. The same applies to the functionality of adding several speech profiles for using the Voice Trainer in different conversational situations. This highlights the importance of enhancing education and implementation of these

functions in future use of the Voice Trainer for both speech therapists and persons with PD, so that the Voice Trainer and its Dashboard can be used to its full potential.

Limitations

This study has several limitations. First, all participants were individuals who had been enrolled in a randomised controlled trial on online speech therapy. Therefore, we cannot rule out that there was a selection bias of individuals who were already willing to and comfortable with the use of technology for receiving treatment. Nevertheless, we believe that results of the questionnaires provide the first valuable insights in use and usability of the Voice Trainer and represent a wide range of persons with PD, since persons in all disease stages were included.

Another limitation of this study is its design which was limited by the original trial design: after completing speech therapy no further contact was possible between the speech therapist and the patient. Usually it is more common for speech therapists to maintain contact with their clients for evaluation, support or refresher sessions. As such, the results may underestimate the use and usability of the app compared to usual practice.

Furthermore, not all 109 participants in the intervention group were invited to fill out additional questionnaires about their experiences with the Voice Trainer. This was because the evaluation of the Voice Trainer's use was added later to the study protocol. Nevertheless, we consider the subgroup that received these questionnaires sufficiently large to provide a first representative insight into the use and usability of the Voice Trainer.

Finally, it is important to note that we did not collect information on the use of the Voice Trainer from the perspective of the speech therapists. Therefore, the results from the patient questionnaires should be interpreted with caution. As self-reported data may be subject to recall bias, participants may have underreported their use of the Voice Trainer, potentially leading to an underestimation of actual app engagement. Additionally, when participants reported not receiving reminders, it remains unclear whether this was due to a technical malfunction, the therapist's decision not to send them, or participants overlooking or disabling notifications. Future studies could address these limitations by incorporating therapist-reported information, allowing for a more comprehensive assessment of app use and adherence.

Beyond these limitations, the findings of this study also have implications for further research and clinical practice. Future studies should explore the role of care partners in supporting the use of the Voice Trainer. In this study, partner involvement appeared to be associated with continued app use, suggesting that actively engaging partners in speech therapy and app-based practice may enhance adherence and long-term maintenance of speech outcomes. Exploring how partners can be effectively involved, for example through education or shared use of the app, may be a valuable direction for future work.

The Voice Trainer demonstrates strong usability and potential for monitoring speech in PD. While generally well-received amongst persons with PD, individual variability in needs and wishes regarding its use must be considered in speech therapy, justifying further and more detailed research.

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Appendix A – Voice Trainer functionalities

All the app functionalities are listed below.
Note that functionalities that are marked with an asterisk are only available when the user is logged in his Voice Trainer and thus a connection is made between the Voice Trainer and the Dashboard of the speech therapist.

Home screen

Start: When pressing the Start button, the dot will appear. The app provides feedback about pitch and loudness level of the user's voice.
Pause button*: When practicing with the Voice Trainer, the pause button can be used when the person with PD is not talking. The sound analysis will be paused, preventing the app to register the voice of the conversation partner, which may affect the performance overview.
Speech profiles*: When created by the speech therapist, different speech profiles for various conversational situations can be selected.
Settings: For viewing or adjusting various settings.
Contact therapist*: when the 'Contact therapist' button is pressed, a request for help will be emailed to the speech therapist. The request will only be sent when the person with PD first confirms he would like to send a help request. The speech therapist can disable this button using the Dashboard.

Settings

Frequency: Minimum and maximum pitch settings can be adjusted in steps of 10 hertz. The dot will move between the maximum pitch (top of the screen) and minimum pitch (bottom of the screen).
Loudness: The loudness level can be adjusted in steps of 3 decibel. While practicing, the dot will become green when reaching or overcoming this loudness threshold, and will become red when the captured sound is under this threshold.
Background color: The background color can be set in black or white.
Performance overview*: The performance overview is displayed per day. Users can see how many times the Voice Trainer is used and the total amount of time it is used for that day. For every session, percentage of correct pitch and loudness level are displayed.
Show pause button*: Users have the option to enable or disable the pause button while using the Voice Trainer. When activated, this button freezes the dot on the screen, pausing the measurement of pitch and loudness until resumed. This feature is particularly helpful when the user is not speaking, ensuring a more accurate and reliable performance review since ambient noise or other voices are ignored.
Share data with therapist*: Users can select whether they want to share their performance data with their therapist.
Receive reminders*: Users can select whether they want to receive practice reminders at set times of the day, if they have not used the Voice Trainer yet at that time.
Tutorial: Users can swipe through a brief tutorial about how to use the Voice Trainer.

Liability: Liability information can be found here.
Login: Enables the user to log in or log out, using his email address and password.
Change password*: When logged in, the password can be changed here.
FAQ: Refers to a page with frequently asked questions.

Appendix B – Adjusted System Usability Scale

	Strongly disagree				Strongly agree
1. I think that I would like to use this product frequently.	1	2	3	4	5
2. I found the product unneccessarily complex.	1	2	3	4	5
3. I thought the Voice Trainer was easy to use.	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use the Voice Trainer.	1	2	3	4	5
5. I found the various function in the Voice Trainer were well integrated.	1	2	3	4	5
6. I thought there was too much inconsistency in the Voice Trainer.	1	2	3	4	5
7. I imagine that most people would learn to use the Voice Trainer very quickly.	1	2	3	4	5
8. I found the Voice Trainer very awkward to use.	1	2	3	4	5
9. I felt very confident using the Voice Trainer.	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with the Voice Trainer.	1	2	3	4	5
11. How would you rate the Voice Trainer on a scale of 1 to 10?	1	2	3	4	5	6	7	8	9	10
12. Please explain your rating here.	[open-ended question]				

<u>This question is exclusively for participants at T1:</u>

13. Have you made a maintenance plan with your speech therapist regarding your use of the Voice Trainer after the treatment program?

- o Yes, a maintenance plan is made and I am planning to continue using the Voice Trainer
- o Yes, a maintenance plan is made, but I am not planning to continue using the Voice Trainer
- o No, we did not make a maintenance plan, but I am planning to continue using the Voice Trainer
- o No, we did not make a maintenance plan and I am not planning to continue using the Voice Trainer

Appendix C – Voice Trainer Questionnaire

Introduction

You have participated in the PERSPECTIVE study, a research study on the effectiveness of online speech therapy. You have received treatments via video calls and you have also used the Voice Trainer (the app on your phone). We are curious about your opinion and experiences with the Voice Trainer. We would also like to know whether you still use the Voice Trainer after the treatment program. With your answers we will gain more insight into your experiences with the Voice Trainer and know how we can better use it in speech therapy treatment. Therefore, there are no right or wrong answers.

You may complete this questionnaire on your own, but we recommend doing it together with your close one(s). This is because together you will have a better understanding of your use of the Voice Trainer.

It takes about 10-15 minutes to complete the questionnaire.

Questions

Questions completed by all participants:

1. By whom will the questionnaire be completed?

- Myself
- My close one (for example, spouse or caregiver)
- Together

2. What is (or has been) your close one's role in your use of the Voice Trainer?

- My close one sets up the Voice Trainer for me so that I can use it independently afterwards.
- My close one reminds me to look at the Voice Trainer to adjust my speech.
- My close one sets up the Voice Trainer for me and reminds me to look at the Voice Trainer to adjust my speech.
- My close one has not played a (major) role in my use of the Voice Trainer.
- Other:

3. Have you made a maintenance plan/agreements with your speech therapist regarding your use of the Voice Trainer after the treatment program?

- Yes, a maintenance plan has been made and I am using the Voice Trainer. (*Participant goes to question 4)*
- Yes, a maintenance plan has been made, but I do not use the Voice Trainer (anymore). *(Participant goes to question 14)*
- No, no maintenance plan has been made, but I do use the Voice Trainer. (*Participant continues to question 4)*
- No, no maintenance plan has been made and I am not using the Voice Trainer (anymore). (*Participant continues to question 14)*

Questions for those participants who answered "Yes, a maintenance plan was created and I use the Voice Trainer" or "No, a maintenance plan was not created, but I do use the Voice Trainer" in question 3:

4. In what situations do you use the Voice Trainer? (*multiple answers possible*)

- If my voice sounds soft or hoarse, to get my voice right again (*participant goes to question 5)*
- At times when I am working on the same speech goal I also worked on with the speech therapist (*participant goes to question 5*)
- At times when I am practicing independently (*participant goes to question 5*)
- At times when I am practicing, together with my partner (*participant goes to question 5*)
- In conversational situations (*participant continues to question 4.1*)
- Other: (*participant continues to question 5*)

4.1. In what kind of conversational situations do you use the Voice Trainer? (multiple answers possible)

- During meetings/work situations
- During group conversations
- During one-to-one conversations
- During conversations with acquaintances
- During conversations with strangers
- During conversations at home
- During conversations outside the home
- During telephone conversations

5. How often do you use the Voice Trainer?

- Daily
- Weekly
- Monthly
- Other:

6. How do others in your environment react to the fact that you use the Voice Trainer? *(Multiple answers possible)*

- Others react positively, because they notice the Voice Trainer helps me. *(Participant goes to question 6.1)*
- Others have to get used to the fact that I use the Voice Trainer (*Participants goes to question 6.1)*
- Others feel uncomfortable when I use the Voice Trainer *(Participant goes to question 6.1)*
- Others find it unnecessary that I use the Voice Trainer *(Participant goes to question 6.1)*
- It does not matter to others whether I use the Voice Trainer or not *(Participant goes to question 6.1)*
- I do not know what others think about my use of the Voice Trainer. (*Participant goes to question* 7)
- Other: (*Participant goes to question 6.1*)

6.1 How do you feel about these reactions from your environment?

- I like these responses and therefore feel comfortable using the Voice Trainer.

- I don't like these responses and don't always feel comfortable using the Voice Trainer.
- I don't like these responses, but it does not influence my use of the Voice Trainer.
- These reactions do little to me; it does not affect my Voice Trainer use.
- Other:

7. Voice TrainerThe speech therapist can send you notifications as a reminder to practice with the Voice Trainer. Do you receive these notifications?
- Yes, I receive these reminder notifications. *(Participant goes to question 7.1)*
- No, I do not receive these reminder notifications and I have never received them in the past. *(Participant goes to question 7.2)*
- No, I do not receive these reminder notifications, but I used to receive them in the past. *(Participant goes to question 7.1)*

7.1 Do you need these reminder notifications as a motivation to start practicing?
- Yes, these reminder notifications motivate me to use the Voice Trainer (more often).
- No, I do not need these reminder notifications to use the Voice Trainer (more often).
- Other:

7.2 Would these notifications motivate you to practice (more often)?
- I think the reminders would help me use the Voice Trainer more often.
- I don't think the reminders would help me use the Voice Trainer more often/I wouldn't want to receive the reminders either.
- Other:

8. The speech therapist can set different speech profiles for you. This allows you to use the Voice Trainer in different situations (for example, at work or in the car). Do you use different speech profiles in the Voice Trainer?
- Yes, I use different speech profiles.
- No, the speech therapist set different speech profiles, but I only use one.
- No,I only have one speech profile.
- I do not know what speech profiles are.
- Other:

9. In the performance overview of the Voice Trainer, you can see if you have spoken loud and low enough. Do you use this performance overview?
- Yes, I look at my performance overview to improve my speech in a more targeted way.
- I look at my performance overview, but I do not use the feedback.
- No, I never look at my performance overview.
- I do not know what a performance overview is.
- Other:

10. Would you recommend the Voice Trainer to other people with Parkinson's disease?

- Yes (*Participant goes to question 10.1)*
- No (*Participant goes to question 10.2*)

10.1 Why would you recommend the Voice Trainer to other people with Parkinson's disease?

- [open-ended question]

10.2 Why would you not recommend the Voice Trainer to other people with Parkinson's disease?

- [open-ended question]

11. To what extent has the Voice Trainer contributed to an improvement of speech, on a scale from 1-10?

- [Slider from 1-10]

12. Could you explain your rating on the previous question?

- [open-ended question]

13. Do you have any other comments or points for improvement regarding the functionalities of the Voice Trainer?

- [open-ended question]

Questions for participants who answered to question 3 either 'Yes, a maintenance plan has been made, but I do not use the Voice Trainer (anymore)' or 'No, no maintenance plan has been made and I am not using the Voice Trainer (anymore)':

14. How long did you continue using the Voice Trainer after the treatment program?
- I did not use the Voice Trainer after the treatment program.
- I did not use the Voice Trainer for more than one month after the treatment program.
- I used the Voice Trainer for one to three months after the treatment program.
- I used the Voice Trainer for more than three months after the treatment program.

15. What is the reason you have stopped using the Voice Trainer? *(multiple answers possible)*
- I do not need the Voice Trainer anymore *(Participant goes to question 16)*
- I find it too much effort using the Voice Trainer *(Participant goes to question 15.1)*
- I do not like that others see that I am using the Voice Trainer. *(Participant goes to question 15.1)*
- I forget to use the Voice Trainer *(Participant goes to question 15.1)*
- I don't know (anymore) how to practice with the Voice Trainer by myself *(Participant goes to question 15.1)*
- I deleted the Voice Trainer / I cannot find the Voice Trainer on my phone *(Participant goes to question 15.1)*
- Other: (*Participant goes to question* 15.1)

15.1 What would help you to start using the Voice Trainer again? *(multiple answers possible)*
- It would help me to practice at set times, which I determine myself or in consultation with my close ones or speech therapist
- Someone would have to encourage me to practice
- A maintenance plan from the speech therapist with how I should use it
- I have no desire to use the Voice Trainer again
- Other:

16. How do others in your environment react to the fact that you use the Voice Trainer? *(Multiple answers possible)*
- Others react positively, because they notice the Voice Trainer helps me. *(Participant goes to question 16.1)*
- Others have to get used to the fact that I use the Voice Trainer (*Participants goes to question 16.1)*
- Others feel uncomfortable when I use the Voice Trainer *(Participant goes to question 16.1)*
- Others find it unnecessary that I use the Voice Trainer *(Participant goes to question 16.1)*
- It does not matter to others whether I use the Voice Trainer or not *(Participant goes to question 16.1)*
- I do not know what others think about my use of the Voice Trainer. (*Participant goes to question* 17)
- Other: (*Participant goes to question 16.1*)

16.1 How do you feel about these reactions from your environment?
- I like these responses and therefore feel comfortable using the Voice Trainer.

- I don't like these responses and don't always feel comfortable using the Voice Trainer.
- I don't like these responses, but it does not influence my use of the Voice Trainer.
- These reactions do little to me; it does not affect my Voice Trainer use.
- Other:

Voice Trainer

17. The speech therapist can send you notifications as a reminder to practice with the Voice Trainer. Do you receive these notifications?

- Yes, I receive these reminder notifications. *(Participant goes to question 17.1)*
- No, I do not receive these reminder notifications and I have never received them in the past. *(Participant goes to question 17.2)*
- No, I do not receive these reminder notifications, but I used to receive them in the past. *(Participant goes to question 17.1)*

17.1 Do you need these reminder notifications as a motivation to start practicing?

- Yes, these reminder notifications motivate me to use the Voice Trainer (more often).
- No, I do not need these reminder notifications to use the Voice Trainer (more often).
- Other:

17.2. Would these notifications motivate you to practice (more often)?

- I think the reminders would help me use the Voice Trainer more often.
- I don't think the reminders would help me use the Voice Trainer more often/I wouldn't want to receive the reminders either.
- Other:

18. Do you now plan to resume using the Voice Trainer?

- Yes
- No

19. Would you recommend the Voice Trainer to other people with Parkinson's disease?

- Yes (*participant goes to question 19.1*)
- No (*participant goes to question 19.2*)

19.1 Why would you recommend the Voice Trainer to other people with Parkinson's disease?

- [open-ended question]

19.2 Why would you not recommend the Voice Trainer to other people with Parkinson's disease?

- [open-ended question]

20. To what extent has the Voice Trainer contributed to an improvement of speech, on a scale from 1-10?
- [Slider from 1-10]

21. Could you explain your rating on the previous question?
- [open-ended question]

22. Do you have any other comments or points for improvement regarding the functionalities of the Voice Trainer?
- [open-ended question]

End

Thank you very much for completing the questionnaire! Your answers will help us to better understand your experiences with the Voice Trainer and how we can improve its use in speech therapy.

Appendix D – Explanations on ratings on the Voice Trainer

Answers to the question: 'How would you rate the Voice Trainer on a scale of 1 to 10?'

Score	Explanation
10	Is easy to use, invites you to keep using so you can keep training your voice when needed
10	Does exactly what it needs to do and it is not complicated
10	It is a good concept.
10	Pleasant to work with. Gives good insight where I stand with my voice
10	Simple app, little impact on your concentration
10	
9	Based on intuition. I never give a 10.
9	I find it a useful tool. You can practice well with it. It is clearly visible when you use your voice incorrectly
9	Simple app. Does what it is supposed to do.
9	Learning through play, it is like a computer game from one of the first phases of the electrical grid
9	Useful app, which has helped me well and (occasionally) still helps me
9	To me, the Voice Trainer is a good and clear tool.
9	After the right pitch was set for me together with the speech therapist, using it was very simple.
9	Works well, you just have to know the how and what
9	The Voice Trainer is really easy to use
8	Good to handle, easy to use
8	?????
8	Useful app, easy to use
8	After explanations from both staff members, it spoke for itself. It helps you with the use of language, the power you speak with and to regain control when you lose it.
8	Easy to use.
8	Convenient to use.
8	It shows me well how I use my voice.
8	It works well.
8	The Voice Trainer is very user friendly. However there is a device on the table that can be distracting. So it may be an invasion of your privacy. So you would have to explain to those who are with you what the Voice Trainer is for.
8	If one really wants to exercise at home, then this voice trainer is an accessible stimulating tool that is easy to use
8	Once started, it goes by itself.
8	After setting up, the system is clear and easy to use
8	Intuitive to use
8	It requires some skills to use it
8	I could handle it with ease
8	It is very simple to learn and easy
8	Works simply.

8 The dot "forces" you to speak low and clearly

8 The Voice Trainer is a great addition to online speech therapy. In a simple way, you get feedback on how you use your voice.

8 Clear user convenience and clearly explained

8 The Voice Trainer is pleasant and easy to use

8 Convenient tool

8 No problems when using it

8 Convenient and easy to use, but you have to know where you can find the various functions/settings. A short explanation is sufficient

8 Pleasant and easy to control and practice your voice

8 User-friendly tool

8 User-friendly

7 The app reacts very slowly and the dot often jumps up or down. It does not accurately reflect voice pitch. This is distracting while doing exercises.

7 I have it on my phone, and using it simultaneously with a phone call does not work and that is a pity, I would like to use it in the car while calling.

7 As I experienced it

7 Can still make some improvements. The interface is old-fashioned and a good UX designer can modernise it quite a bit

7 I obviously don't know all the possibilities yet

7 The setup in online contact with the speech therapist took a while to figure it out, but for own training it was fine

7 Because I find it a good addition to existing methods

7 Sometimes it was unclear that the program was not logged in to my personal profile

7 Its use is easy, it is harder to install

7 Convenient app, also while using Zaurus [program for video conferencing]

7 Adjusting the voice and raising and lowering my pitch sounded weird to me and unusual

7 It is easy to use when properly adjusted

7 I was already familiar with the Voice Trainer because I already had it installed on my phone

7 I found it simple

7 Instinctive

6 No.

6 I did find the trainer useful, but as the sessions progressed I began to use the trainer less and less. Why I did that, I don't know.

6 Does not add much to reminding myself to talk low, loud and slowly

6 It does not measure fatigue

6 Voice Trainer is good in its use. The problem is to continue using it. Regular stimulation is desirable here.

6 Because it was asked to me.

5 Benefit is not clear

5 The reaction of the cursor is delayed

5 No, not directly

5 I need an incentive to use it. You have to keep thinking about it yourself now.

5	The Voice Trainer is not inviting to use it a lot
5	Because I can't handle the questions well
4	Cumbersome
3	I don't feel that the voice trainer has contributed to my speech therapy
3	No
3	For my husband, it was totally unsuitable. His voice is hoarse and falters constantly. Takes too much effort
3	Technically there were many hitches, which adversely affected using it
2	I'd rather deal with a person than a device
2	I have not been able to use it because my iPhone was too old and it could not be installed
1	-
1	For me, the voice trainer did not work. I was too much "on" to use it properly
1	I don't have a smartphone and cannot use the Voice Trainer

Appendix E - Results of Voice Trainer Questionnaire

Table 1. Answers of participants who continued using the Voice Trainer

Question	Answer options	Participants who continued using the Voice Trainer
		Total N=26
What is (or has been) your close one's role in your use of the Voice Trainer?	My close one sets up the Voice Trainer for me so that I can use it independently afterwards.	3 (11.5%)
	My close one reminds me to look at the Voice Trainer to adjust my speech.	4 (15.4%)
	My close one sets up the Voice Trainer for me and reminds me to look at the Voice Trainer to adjust my speech.	17 (65.4%)
	My close one has not played a (major) role in my use of the Voice Trainer.	2 (7.7%)
	Other	1 (3.9%)
In what situations do you use the Voice Trainer? *(multiple answers possible*)*	If my voice sounds soft or hoarse, to get my voice right again	15 (57.7%)
	At times when I am working on the same speech goal I also worked on with the speech therapist	6 (23.1%)
	At times when I am practicing independently	12 (46.2%)
	At times when I am practicing, together with my partner	-
	In conversational situations	1 (3.9%)
	Other	1 (3.9%)
In what kind of conversational situations do you use the Voice Trainer? *(multiple answers possible*)*	#of participants who received this question	N= 1
	During meetings/work situations	-
	During group conversations	-
	During one-to-one conversations	1 (100%)
	During conversations with acquaintances	1 (100%)
	During conversations with strangers	-
	During conversations at home	1 (100%)
	During conversations outside the home	-
	During telephone conversations	-
How often do you use the Voice Trainer?	Daily	4 (15.4%)
	Weekly	9 (34.6%)
	Monthly	10 (38.5%)
	Other	3 (11.5%)

How do others in your environment react to the fact that you use the Voice Trainer? *(Multiple answers possible*)*	Others react positively, because they notice the Voice Trainer helps me.	8 (30.8%)
	Others have to get used to the fact that I use the Voice Trainer	1 (3.9%)
	Others feel uncomfortable when I use the Voice Trainer	-
	Others find it unnecessary that I use the Voice Trainer	1 (3.9%)
	It does not matter to others whether I use the Voice Trainer or not	4 (15.4%)
	I do not know what others think about my use of the Voice Trainer	11 (42.3%)
	Other	4 (15.4%)
How do you feel about these reactions from your environment? *If previous answer was: 'I do not know what others think about my use of the Voice Trainer,' this question was not asked.*	#of participants who received this question	N= 15
	I like these responses and therefore feel comfortable using the Voice Trainer.	9 (60.0%)
	I don't like these responses and don't always feel comfortable using the Voice Trainer.	-
	I don't like these responses, but it does not influence my use of the Voice Trainer.	-
	These reactions do little to me; it does not affect my Voice Trainer use.	5 (33.3%)
	Other:	1 (6.7%)

Question	Answer options	Patients who continued using the Voice Trainer Total N=26
The speech therapist can send you notifications as a reminder to practice with the Voice Trainer. Do you receive these notifications?	Yes, I receive these reminder notifications	1 (3.9%)
	No, I do not receive these reminder notifications and I have never received them in the past.	23 (88.5%)
	No, I do not receive these reminder notifications, but I used to receive them in the past.	2 (7.7%)
Do you need these reminder notifications as a motivation to start practicing? (1) *If previous answer was: 'No, I do not receive these reminder notifications, but I used to receive them in the past,' this question was not asked.*	# of participants who received this question	N=3
	Yes, these reminder notifications motivate me to use the Voice Trainer (more often).	1 (33.3%)
	No, I do not need these reminder notifications to use the Voice Trainer (more often).	1 (33.3%)
	Other	1 (33.3%)
Would these notifications motivate you to practice (more often)? (2) *Only asked when previous answer was 'No, I do not receive these reminder notifications and I have never received them in the past'*	# of participants who received this question	N=21
	I think the reminders would help me use the Voice Trainer more often.	8 (38.1%)
	I don't think the reminders would help me use the Voice Trainer more often/I wouldn't want to receive the reminders either.	11 (52.4%)
	Other	2 (9.5%)
The speech therapist can set different speech profiles for you. This allows you to use the Voice Trainer in different situations (for example, at work or in the car). Do you use different speech profiles in the Voice Trainer?	Yes, I use different speech profiles.	1 (3.9%)
	No, the speech therapist set different speech profiles, but I only use one.	-
	No, I only have one speech profile.	16 (61.5%)
	I do not know what speech profiles are.	8 (30.8%)
	Other	-
In the performance overview of the Voice Trainer, you can see if you have spoken loud and low enough. Do you use this performance overview?	Yes, I look at my performance overview to improve my speech in a more targeted way.	2 (7.7%)
	I look at my performance overview, but I do not use the feedback.	3 (11.5%)
	No, I never look at my performance overview.	9 (34.6%)
	I do not know what a performance overview is.	10 (38.5%)
	Other:	1 (4.9%)
Would you recommend the Voice Trainer to other people with Parkinson's disease?	Yes	24 (92.3%)
	No	2 (7.7%)

Table 2. Answers of participants who stopped using the Voice Trainer

Question	Answer options	Patients who stopped using the Voice Trainer Total N=32
What is (or has been) your close one's role in your use of the Voice Trainer?	My close one sets up the Voice Trainer for me so that I can use it independently afterwards.	2 (6.3%)
	My close one reminds me to look at the Voice Trainer to adjust my speech.	5 (15.6%)
	My close one sets up the Voice Trainer for me and reminds me to look at the Voice Trainer to adjust my speech.	-
	My close one has not played a (major) role in my use of the Voice Trainer.	22 (68.8%)
	Other	3 (9.4%)
How long did you continue using the Voice Trainer after the treatment program?	I did not use the Voice Trainer after the treatment program.	16 (50.0%)
	I did not use the Voice Trainer for more than one month after the treatment program.	10 (31.3%)
	I used the Voice Trainer for one to three months after the treatment program.	4 (12.5%)
	I used the Voice Trainer for more than three months after the treatment program.	2 (6.3%)
What is the reason you have stopped using the Voice Trainer? *(multiple answers possible*)*	I do not need the Voice Trainer anymore	8 (25.0%)
	I find it too much effort using the Voice Trainer	8 (25.0%)
	I do not like that others see that I am using the Voice Trainer.	3 (9.4%)
	I forget to use the Voice Trainer	15 (46.9%)
	I don't know (anymore) how to practice with the Voice Trainer by myself	2 (6.3%)
	I deleted the Voice Trainer / I cannot find the Voice Trainer on my phone	2 (6.3%)
	Other	4 (12.5%)
What would help you to start using the Voice Trainer again? *(multiple answers possible*)* *Not asked if previous answer was 'I do not need the Voice Trainer anymore'.*	# of patients who received this question	N=24
	It would help me to practice at set times, which I determine myself or in consultation with my close ones or speech therapist	4 (16.7%)
	Someone would have to encourage me to practice	8 (33.3%)
	A maintenance plan from the speech therapist with how I should use it	-
	I have no desire to use the Voice Trainer again	10 (41.7%)
	Other	2 (8.3%)

How do others in your environment react to the fact that you use the Voice Trainer? (*Multiple answers possible*)*	Others react positively, because they notice the Voice Trainer helps me.	12 (37.5%)
	Others have to get used to the fact that I use the Voice Trainer	2 (6.3%)
	Others feel uncomfortable when I use the Voice Trainer	2 (6.3%)
	Others find it unnecessary that I use the Voice Trainer	-
	It does not matter to others whether I use the Voice Trainer or not	12 (37.5%)
	I do not know what others think about my use of the Voice Trainer	10 (31.3%)
	Other	1 (3.1%)

Question	Answer options	Patients who stopped using the Voice Trainer Answer options N=32
How do you feel about these reactions from your environment? *If previous answer was: 'I do not know what others think about my use of the Voice Trainer', this question was not asked.*	#of participants who received this question	N=22
	I like these responses and therefore feel comfortable using the Voice Trainer.	9 (40.9%)
	I don't like these responses and don't always feel comfortable using the Voice Trainer.	2 (9.1%)
	I don't like these responses, but it does not influence my use of the Voice Trainer.	1 (4.6%)
	These reactions do little to me; it does not affect my Voice Trainer use.	9 (40.9%)
	Other	1 (4.6%)
The speech therapist can send you notifications as a reminder to practice with the Voice Trainer. Do you receive these notifications?	Yes, I receive these reminder notifications	1 (3.1%)
	No, I do not receive these reminder notifications and I have never received them in the past.	26 (81.3%)
	No, I do not receive these reminder notifications, but I used to receive them in the past.	5 (15.6%)
Do you need these reminder notifications as a motivation to start practicing? (1) *If previous answer was: 'No, I do not receive these reminder notifications, but I used to receive them in the past', this question was not asked.*	# of participants who received this question	N=6
	Yes, these reminder notifications motivate me to use the Voice Trainer (more often).	3 (50.0%)
	No, I do not need these reminder notifications to use the Voice Trainer (more often).	3 (50.0%)
	Other	-
Would these notifications motivate you to practice (more often)? (2) *Only asked when previous answer was 'No, I do not receive these reminder notifications and I have never received them in the past'*	# of participants who received this question	N=26
	I think the reminders would help me use the Voice Trainer more often.	8 (30.8%)
	I don't think the reminders would help me use the Voice Trainer more often/I wouldn't want to receive the reminders either.	14 (53.8%)
	Other	4 (15.4%)
Do you now plan to resume using the Voice Trainer?	Yes	16 (50.0%)
	No	14 (43,8%)
	N.a.	2 (6,2%)
Would you recommend the Voice Trainer to other people with Parkinson's disease?	Yes	26 (81.3%)
	No	6 (18.8%)

Appendix F - Comments to answer options 'other' and open-ended questions in the VTQ

	Patients who continued using the Voice Trainer		Patients who stopped using the Voice Trainer	
Question	**Maintenance plan**	**No maintenance plan**	**Maintenance plan**	**No maintenance plan**
What is (or has been) your close one's role in your use of the Voice Trainer?	-	- We talk about all kinds of things, and then my wife notices when I have to be reminded of my speech - My close one has no role in my use of the Voice Trainer	-	- My close one was a good conversation partner to practice my speech using the Voice Trainer - Sounding board for my speech quality. - I did not use the Voice Trainer. Even without Voice Trainer I could receive speech therapy easily using the PC and do the exercises
In what situations do you use the Voice Trainer?	-	- When I think of it		
How often do you use the Voice Trainer?	- When I hear or notice that I need it and my wife's phone is nearby and available. Unfortunately we installed the Voice Trainer on my wife's phone	- I actually use the Voice Trainer too little - Use is marginal, but still mesmerizing.		
How do others in your environment react to the fact that you use the Voice Trainer?	- I only use the Voice Trainer to practice my voice at home. Then there is no-one around usually.	-I use it in company of others. - I don't bother others with it. I practice in the morning when my partner has his own activities. However, he is positive about using the Voice Trainer. - Others never thought it was an issue when I was practicing. As said before, I now use it too little – but I believe others would applaud it if I used the Voice Trainer more often	-	- I have not used it.
How do you feel about these reactions from your environment?	-	- N.a.	-	- N.a.

Do you need these reminder notifications as a motivation to start practicing? (1)	-	- Because I have never received these reminder notifications (I have never asked for it), it is hard to answer this question.	-	
Would these notifications motivate you to practice (more often)? (2)	- I think of it myself, I don't need a reminder.	- I don't use it that much anymore. - I still practice with the old version of the Voice Trainer	-	- If I get guidance on how to use it, yes. - I wouldn't know if it would motivate me if I were reminded. I have thought about using the Voice Trainer once, or several times, but I don't know if I will do it or not and this is actually an answer to the next question - So far I had no need to use the Voice Trainer, now that things are getting worse, I do want to use it again, but it is not installed on my new phone yet. - For now I don't need it. I pay attention if I am intelligible and so far that has been the case.
In the performance overview of the Voice Trainer, you can see if you have spoken loud and low enough. Do you use this performance overview?	-	- I can't remember this, but I will look for it ánd use it.	-	-

What is the reason you have stopped using the Voice Trainer?	-	- In therapy, it turned out that I was trying so hard that it wasn't working for me. Because we had online appointments, the speech therapist used the app and that worked, because then I couldn't see it. - At the end of my treatment trajectory I had a substantial adjustment in my medication. Things were going so well at that point, that I felt I no longer needed the Voice Trainer. In all honesty, I have to say that things are not going as well at the moment, so I do need to start practicing more with the Voice Trainer again. - I have not been able to use it (see above) - Because of the trial, I was not allowed to have speech therapy for 6 months. Therefore I did not use the Voice Trainer to see if that had any influence. Now that I have had the last measurement, I do intend to use the Voice Trainer.
What would help you to start using the Voice Trainer again?	- I speak a lot for work. I'm having fun with it again, because I get to speak limitlessly low and loud. I also come across stronger then. That reward is better than a green dot!	- I have to purchase a new phone. Because of the Parkinson's, I have trouble handling it.

Why would you recommend the Voice Trainer to other people with Parkinson's disease? *(Only asked to participants who answered 'yes' to the question 'Would you recommend the Voice Trainer to others?')*	- improvement of speech - it helps you to use your voice better - you can practice independently and 'to measure is to know'	- specifically to practice voice loudness, I had a lot of benefit from it during intensive speech therapy. - Because it works well and it can help them too - Only when I encounter PD patients (with speech problems), I would definitely recommend it. - It helps you to speak well and clearly - It gives you more confidence to engage in a conversation when people understand you better. You don't want to end up in social isolation. - Supports speech training - It helps to train your voice and feel more confident - Improve intelligibility - Because it's a good way to check your speech from time to time. - It helps to practice speaking loud, low, and slow - Speaking better and more clearly gives confidence - Because its proven to be positive. - You are clearly engaged with your voice. More alert with speaking. - Start practicing early - A tool to activate your voice. I use it as a warm up in the morning. - Because it works - For me it is the way to get rid of my hoarse voice. - The Voice Trainer is good to use.	- handy and simple tool - Use it or lose it! - Better intelligible	- To get the chance to learn to speak intelligibly. - Useful if they are difficult to understand. - You can always try. - Can work well for some. - Initially, I did use the Voice Trainer successfully and I experienced that as positive. - It helps me pay better attention to the voice - Because it helps them to have a conversation better - Because it gives more insight of your speaking ability - any devices that contribute to better functioning are welcome - I think this app does help improve my voice. I honestly have to say that after my contact with the speech therapist I forgot to use it anymore. - Because it can help. - Useful tool they can benefit from - Unintelligible disappears or diminishes. - Quality of your voice volume visible! - It helps with awareness of how your voice works. - With Parkinson's, overdue maintenance quickly becomes difficult to catch up with. This is certainly the case with the voice, and I want to warn about that. - The Voice Trainer is a useful tool for discovering how to use your voice. Each person can decide for himself or herself after a longer period of time whether use is desirable. - Improving speech - Because I know it helps - Because it is an easy way to improve your speech - You become aware of the use of your voice - More quality of life

Why would you not recommend the Voice Trainer to other people with Parkinson's disease? *(Only asked to participants who answered 'no' to the question 'Would you recommend the Voice Trainer to others?')*		- I don't feel that it contributes a lot.	- It did not help me much	- Effect is too small. - I find it terrible - By my own [sentence is cut off] - Because of problems handling my PC. These problems are PC-related. - No contact with other Parkinson's patients.
Do you have any other comments or points for improvement regarding the functionalities of the Voice Trainer?	-in a conversation, the other person also has input. The other person's voice influences the measurements	- every speech therapist should have the Voice Trainer in the package for Parkinson's - continue on this path SURE!!! - cell phones are becoming more and more extensive and so will become more of a function in all kinds of areas. Also in the field of speech. Maybe in the future there can be an app on every phone with the capabilities that the Voice Trainer has to offer. Also people without PD could speak more clearly and may be helped with a Voice Trainer. - It sometimes responds (too) slowly, or gets stuck while up or down. I would like to be able to see how long I've practiced while practicing, and how long I practiced afterwards. I would like the option of an audible signal during practice! That could indicate when I am speaking too high/low, with margins to be adjusted. Then you don't have to look all the time. - Too bad there is no more follow-up from the speech therapist. - There is little challenge - No suggestions, I don't use the Voice Trainer optimally I notice from the questionnaire. Too bad the new version of the Voice Trainer could not be installed on my mobile phone. But I consistently use the old version as a warm-up for my voice.	-	- Show the overviews of performance (data) over time on the Voice Trainer as well. Then you can see for yourself how your voice develops and if necessary anticipate to it. - The app is quite affected by ambient noise. Perhaps it would be possible to implement some form of noise canceling. - It's been too long, as I look back now - Contact with the trainer to periodically evaluate and train again. For example once every 4 or 6 weeks!!! Now I don't do anything about it anymore. That is a pity. - A good overview with on the market available PC 's and phones that have large keys and are not bothered by tremors in the fingers is a good start - Useful tool - Would not know

Appendix G – Elaboration on to what extent the Voice Trainer improved speech

Answers to the question: 'To what extent has the Voice Trainer contributed to an improvement of speech?'

Score	Explanation
9	I practiced too little
8	It helps you to speak loud and low
8	Because it helps me and also others
8	The quality of my voice and voice volume became visible for me
8	It has made me more aware that I need to speak more clearly, but it still is a moment. Improving completely is unfortunately not possible. Because of the Parkinson's, I sometimes have cramps in my face and mouth and then I really have difficulty speaking. Hence the 8.
8	I don't always realise/hear if I speak too high or too fast. The VT helps with that. Also shows if I speak too softly or articulate too little.
8	It helped me well.
8	The loud-and-low rule is very important
8	Better control
8	I have become aware of how I use my voice and how I can improve it.
8	I managed to "move" better in conversations
8	Made a lot of progress
8	See above
8	Because now you know that you have to do your breathing in a calm and controlled way.
8	I learn how to use my voice better.
8	[Missing]
8	I use the Voice Trainer to maintain my voice
8	I think the Voice Trainer is an important addition to the online speech therapy program.
8	It's a pleasant way to practice your voice. It was also nice to practice with the speech therapist.
7	Because I worked with a speech therapist who used the Voice Trainer, it worked for me (at that time). In the delusion of everyday, I barely use the Voice Trainer. I don't allow myself enough time. Now that you are confronting me with it, I want to push myself a little more.
7	It has not given much improvement
7	It really improves speech
7	This app does help, it's nice to see the results of your pronunciation. But the most important thing is still the exercises you do with your voice (with the speech therapist).
7	It can help but I don't know if it is the solution to every speech problem
7	Because it's never perfect, but usually tells me if I need to speak more clearly
7	Clarity
7	Exercising (with Voice Trainer) definitely has an effect. But my medication/supplementation was also adjusted during the time I was using the Voice Trainer and that also had an effect.
7	You get motivated
7	In a conversation, the other person also has input. The other person's voice influences the measurements.

7	No
7	See previous answer
7	The Voice Trainer was a good tool.
7	I think my speech has improved
6	Despite the problems with the Voice Trainer, I did benefit from the speech therapy.
6	I want to, but forget it, because of the large amount of activities/treatment I have to think about as a result of Parkinson's
6	You pay better attention to speaking with others
6	Fatigue remains an important element
6	[Missing]
6	In my opinion and according to those around me, my voice has not deteriorated since I have been using the Voice Trainer (for about four to five years now).
5	[Missing]
5	-
5	[Missing]
5	Due to issues related to moving house, I didn't get to practice with the Voice Trainer enough
5	The therapist had much more influence
5	I have not used the Voice Trainer in conversations. Only for practicing.
5	[Missing]
4	I can easily reach the set points
3	I would like to have more frequent contact with someone who helps me.
3	Because I didn't like it.
2	Barely any results.
2	I haven't used it anymore.
2	I try too hard, and I am too competitive
1	For me no improvement
1	See previous answer
1	I have had good guidance, but without the Voice Trainer

PART III

Summary and general discussion



Chapter 5

English summary

English summary

Parkinson's disease (PD) leads to communication problems because of a reduced intelligibility of speech, caused by hypokinetic dysarthria. This occurs in up to 90% of people with PD during the course of the disease, impacting social interaction and quality of life. Highly intensive treatment seems beneficial to improve speech, but this is not feasible for every person with PD. Before the work completed as part of this thesis, there was limited knowledge as to how speech therapy impacts quality of life and verbal communication in people with PD, specifically in a heterogeneous population including people who are not able to adhere to highly intensive treatment. Furthermore, little was known about the use of technology in speech therapy, the use of which is now increasing, as it provides new opportunities to treat persons with PD in a more efficient way. A real-time feedback app for speech in PD is already widely used in the Netherlands, but its use and usability had thus far not been evaluated.

The aims of my thesis were:

1. To study the effectiveness of remote personalised speech therapy in persons with PD, irrespective of disease stage;
2. To evaluate how persons with PD experience a real-time visual feedback app regarding its use (e.g. frequency and manner of use) and usability.

In **Part I** of this thesis, I described the design and conducted a randomised controlled trial to examine the effectiveness of personalised, remotely delivered speech therapy in people with PD, also including individuals who were unable to follow intensive in-person treatment. In **Part II,** I evaluated the use and usability of a visual feedback app that supports speech intelligibility in people with PD. In this chapter, I summarise the contents of this thesis.

Part I: Effectiveness of personalised, remotely delivered speech therapy in people with PD

Evidence for the efficacy of speech therapy in PD is growing, but more work remains needed to explore its full potential. In **Chapter 2** I describe the design of a randomised controlled trial (RCT) to evaluate the effectiveness of our personalised and home-based (remote) parkinson-specific speech therapy (Pitch Limiting Voice Treatment: PLVT) on quality of life and speech outcomes for people with PD who have a reduced intelligibility of speech. The intervention is supported by a dedicated speech training app, the Voice Trainer. I expected this approach to improve speech intelligibility and quality of life in persons with PD. I performed a large single blinded RCT (the PERSPECTIVE study), comparing 8 weeks of personalised remote speech therapy to delayed intervention (waiting list design). Participants were assigned randomly (1:1) to the intervention group or control group. Measurements took place at baseline and after 8 weeks (both groups, T1), and after 32 weeks (intervention group only, T2). The aim was that participants were treated remotely by a highly experienced speech therapist (speech therapist) being trained by and actively involved in the Dutch ParkinsonNet). The primary outcome was disease-related quality of life at T1, assessed with the Parkinson's Disease Questionnaire 39 (PDQ-39).

In **Chapter 3**, I describe the results of this study. Data were analysed using analysis of covariance based on the intention-to-treat principle. Between March 1, 2019, and March 27, 2021, 214 patients were enrolled in the intervention group (n=109) or control group (n=105). At T1, the adjusted mean difference in PDQ-39 was -2.0 in favour of the intervention group (95% CI -4.0 to 0.1; p=0.056), which was statistically not significant. The intervention group did score significantly better on the communication index score of the PDQ-39 (post hoc analysis), with an adjusted mean difference of -5.3 (95% CI -9.4 to -1.2; p=0.011), also exceeding the minimally important difference of 4.2 for this domain. We found no between-group differences on any other PDQ-39 domain. T2 measurements showed a significant deterioration of the PDQ-39 compared to T1 measurements with a difference of 2.40 (95% CI 0.77 to 4.02; p=0.004). In conclusion, I found that remote speech therapy did not improve overall quality of life, although I did observe a modest, non-significant benefit in favour of the intervention arm at T1. I opted for disease-related quality of life as an ambitious primary treatment goal, realising that this is a challenging outcome that includes a wide variety of domains, many of which are not targeted specifically by speech therapy. Post-hoc analyses showed that the trend towards an improved general quality of life in the intervention group was driven by only one of these domains, namely the communication-related quality of life, which is in line with a genuine treatment effect. Although this is only a small part of the overall PDQ-39, being able to communicate independently is an important aspect of quality of life. None of the other domains of the PDQ-39 changed after treatment, which supports my hypothesis that speech therapy specifically improves communication and thereby quality of life. However, the results did not sustain at follow-up measurement after 32 weeks. This implicates the importance of some form of maintenance speech therapy at the long-term.

Part II: Usability evaluation of an application for improving speech in people with PD

Most persons with PD experience speech problems, which is called hypokinetic dysarthria. Their speech can be improved by learning to speak louder to overcome their soft voice, while keeping the vocal pitch low enough for a natural voice. Receiving specific feedback on pitch and loudness during these exercises is deemed to be very helpful. In **Chapter 4**, I described the Voice Trainer, an application that provides visual feedback to people while exercising their speech. I also described its accompanying dashboard, a web-based program that allows speech therapists to remotely monitor their patients' speech performance. In addition, I evaluated the use and usability of the Voice Trainer in people with PD. Eighty-one participants from the trial described in Chapter 3 were asked to fill out two questionnaires on the use and usability of the app: the System Usability Scale (SUS) (scored on a range of 0 indicating low usability to 100 indicating high usability), and a questionnaire developed for evaluating use of the app, the Voice Trainer Questionnaire (VTQ). Participants judged the usability of the Voice Trainer with a median SUS score of 78.8, indicating above average satisfaction. Of those who continued using the app (45%), 92.3% would recommend the app to other persons with PD. Of the participants discontinuing its use (55%), 81.3% would recommend it to others. There were various reasons for (dis)continuing its use, e.g. as not needing it anymore to improve speech, but also forgetting to use it. Most participants were satisfied with the usability of the app and had positive experiences using it. Although the app was well-

received amongst persons with PD, I found that there is individual variability in experiences and needs regarding its use, e.g. some participants experienced technical issues, preferred feedback from a person over an app, or it took them too much effort to use it. These findings emphasise that an individual treatment approach is required to meet the person's needs and to provide optimal personalised speech therapy to transfer the newly learned skills to daily life. The fact that more than half of the participants stopped using the app may partially explain the loss of treatment effect during follow-up as described in **Chapter 3**, again emphasizing the need of adequate maintenance after treatment.



Chapter 6

General discussion

General discussion

Being able to speak intelligibly is essential for effective verbal communication. However, in persons with PD speech becomes increasingly impaired. Speech therapy can help individuals with PD to improve their communication abilities and regain confidence during social interactions [2, 3]. The use of technology, such as video consultations or smartphone applications, could enhance speech therapy by enabling remote delivery by an expert and thereby providing real-time feedback on speech. In this thesis, I studied the effectiveness of remotely delivered speech therapy for people with PD in the PERSPECTIVE study. In addition, I evaluated the use and usability of a feedback application to support speech intelligibility. Overall, my results showed that personalised speech therapy improved communication-related quality of life in PD, but also that most treatment effects washed out 6 months after ending therapy. Furthermore, I found that a real-time visual feedback app to improve speech was generally well received by persons with PD, but its use in speech therapy requires a personalised approach. In this chapter, I will discuss several considerations to place the main findings into a broader context and reflect on future directions.

Personalised approach in speech therapy

It is widely recognised that PD manifests in as many different ways as there are individuals living with this disease [4]. Each person experiences a unique combination of motor, cognitive, and communicative challenges within the context of their personal life. Consequently, personalisation of therapy is widely recognised as essential in the treatment of people with PD [5-7]. The work presented in this thesis further confirms that speech therapy for PD is no exception to this generic rule, and that this intervention should be personalised on multiple levels, including treatment frequency, treatment goals, and treatment content.

Treatment frequency

Ideally, people with PD receive high-intensity treatment to improve their speech in an efficient way. However, some persons with PD are not able to adhere to such programs for understandable reasons such as cognitive impairments or fatigue [8]. Importantly, this does not imply that speech therapy is not useful for these individuals. Instead, therapy intensity should be adapted to what is realistically feasible. In **Chapter 3**, I therefore included participants across all disease stages, representing a broad range of cognitive and physical capacities. This allowed me to examine whether a personalised approach, meaning high-intensive when feasible (three to four times per week), but with a lower frequency when necessary, would still show meaningful improvements. Despite variability in treatment goals and intensity, the results demonstrated that – at the group level – this personalised approach led to improvements in communication-related quality of life and in patient- and caregiver-reported outcomes.

Treatment goals

Personalisation is also important when formulating treatment goals. The ultimate aim of speech therapy is to support individuals in speaking intelligibly and independently in everyday communicative

situations. However, for some individuals the cognitive load required to maintain intelligible speech without external cues is too high, especially in more advanced disease stages. For these individuals, adjusted goals may be more realistic and functional. For example, speaking intelligibly after receiving a verbal cue ("repeat that with a loud voice"), rather than maintaining loudness independently at all times. Such cueing strategies must be practiced with the conversation partners by the speech and language therapist (hereafter referred to as speech therapist) to ensure that they remain effective and are transferable to daily life. Speaking louder is therefore not a goal in itself: it is a means to enhance intelligibility and improve social participation. Treatment goals should always be tailored to the individual's abilities, needs, and communicative environments, as an integral part of person-centered care [7]. As the field increasingly recognises that improved speech performance is only meaningful when it supports real-life communication, treatment goals are now more explicitly linked to broader participation outcomes.

In recent years, there has been increasing attention for communicative participation as an ultimate treatment outcome and an integral part of quality of life, also in PD [9]. Communicative participation refers to a person's ability to take part in real-world communicative situations that are meaningful to them [9, 10], such as ordering a coffee, giving a speech at a wedding, or reading to their grandchildren. This construct is gaining importance in the field, reflecting a shift from focusing on speech impairment or functional skills toward evaluating whether therapy enables individuals to engage in their social roles [11-13]. Communicative participation is also actively embedded as an outcome of interest on the Research Agenda of the Dutch Association of Speech and Language Therapists (NVLF) [14], outlining the national research priorities and development goals for our profession in the Netherlands.

Treatment content

The importance of personalisation also emerged from the findings in **Chapter 4**, in which I examined the use and usability of the Voice Trainer application. Although most participants reported positive experiences, there was substantial individual variability in how, when, and why they used the Voice Trainer. Differences were observed in the types of situations in which the Voice Trainer was applied, the frequency of use, preferences regarding reminder notifications, and whether the Voice Trainer worked for the participants or not. These findings highlight that the decision to use the Voice Trainer should be made collaboratively with each individual with PD, taking into account their personal preferences, daily routines, and communicative needs. For example, for persons who are able to remind themselves to speak loudly and at a natural pitch, occasional use of the app to calibrate their voice may be sufficient. For others who rely more heavily on external feedback, the app can be used more frequently during conversations. This applies not only during active therapy ,but also for home practice and for maintaining speech improvements after therapy has ended.

Both speech therapy and the use of digital tools such as the Voice Trainer and its dashboard are therefore no 'one-size-fits-all' solutions. While group-level results provide valuable insights into what generally

works, optimal outcomes require a personalised approach. Although speech therapists can often elicit improved speech performance during therapy sessions, the true challenge lies in helping individuals transfer these improvements to everyday communication. For instance, a person who speaks clearly during speech therapy sessions, may still struggle to apply this when making a phone call or when talking to his or her spouse. This person may benefit from practicing these specific situations or may need support from a communication partner who can provide timely cues to speak louder. Achieving a successful transfer of speaking skills to daily life requires not only disease-specific expertise from the speech therapist, but also a deep understanding of the individual's motivation, personal circumstances, and the involvement of communication partners.

The importance of maintenance therapy

One of the questions raising from this thesis is, to what extent (when, how and how frequently) maintenance therapy should be provided. From the results of **Chapter 3**, I conclude that at the group level, most of the beneficial effects of speech therapy have been washed out at the time of the follow-up measurement, 24 weeks after ending the treatment. This could be as a result of disease progression, although a previous study has shown long-lasting results after intensive speech therapy in persons with PD [15]. This indicates that long-lasting effects are possible, at least for persons who can adhere to highly intensive treatment. Another explanation – and perhaps a more feasible one – is that some form of low-dose maintenance treatment is required to sustain the acquired improvements. How much maintenance therapy should be shaped and implemented requires further study.

Furthermore, I learned from the results described in **Chapter 4** that, for unknown reasons, most participants did not make agreements as part of a maintenance plan with their speech therapist. This might be a missed opportunity to make specific agreements to maintain results in the long term. It shows the importance for speech therapists to provide clear instructions to their patient on how to maintain their speech after ending treatment, e.g. by continuing daily exercises. However, even with a clear maintenance plan, reduced initiative, lack of motivation, fatigue, or apathy in PD [16, 17] may impede the continuation of keeping the skill of speaking intelligible by speech exercises when there is no therapist to regularly monitor one's speech. At the same time, research on treatment adherence in PD pinpoints several facilitators, including education, social engagement, a strong therapeutic relationship, feedback on performance, and social reinforcement [18]. This underscores the responsibility of therapists to integrate these facilitators into their treatment approach and to work with the persons with PD to develop a maintenance plan that maximises the likelihood of sustained practice.

It is also important to acknowledge that speech is only one of the many domains that can potentially be affected by PD. And it is a progressive disease, meaning that new challenges inevitably appear over time. People with PD must therefore constantly manage many different and also new challenges, which may lead them to prioritise other activities over daily speech exercises. Partners or other significant individuals can play a role in supporting and motivating the person with PD to practice and maintain

his or her speech. Although caregiver engagement is important for people with PD [19], in terms of caregiver burden it is not always realistic nor fair to expect them to carry the responsibility of regular practice. For these reasons, regularly check-ups induced by the speech therapist should be considered to monitor progress, identify early signs of decline, and intervene when resuming therapy is needed.

When and how often these check-ups should be conducted, remains unknown. Although there are no studies about the optimal treatment frequency or time intervals for maintenance follow-up visits in speech therapy in PD, a meta-analysis about timing, frequency and durability of physical therapy in PD can shed some light here [20]. Most physical therapeutic regimen ranged from 2 to 12 weeks and was performed either twice of three times weekly, with session duration from 30 to 60 minutes. This largely corresponds to speech therapy interventions. Follow-up appointments ranged from 17 days to 18 months and showed varying maintenance of treatment effects. Therefore, also in physical therapy the ideal moment for maintenance follow-up remains largely unknown [20]. Our national guideline on allied health treatment in PD [21] recommends Pitch Limiting Voice Treatment for three to four times per week during four to eight weeks when this is feasible for the person with PD. Overall, regular appointments for speech maintenance are already common care: the SPEAK OUT! program prescribes indefinitely ongoing group sessions every week [22], and Lee Silverman Voice Treatment (LSVT) LOUD prescribes every day 10-15 minute exercises [15]. In addition, it is likely that there is individual variability to what extent a maintenance plan is needed. Some people in the early stages of PD and mild dysarthria may be able to continue practicing independently for a longer period without the support of a speech therapist, whereas others require earlier or more intensive guidance and regular evaluations to maintain their speech abilities. Future research is required to find out to what extent and for whom maintenance therapy is needed.

The potential of telerehabilitation in PD

Before the start of the PERSPECTIVE study, the use of online delivered speech therapy had already been shown to be feasible in PD, and to be non-inferior to face-to-face therapy [23, 24]. For this reason, I chose to deliver online speech therapy in this trial, making use of its advantages: improved access to specialised treatment, and reduction of travel burden and time. Although evaluating feasibility was not the primary aim of this thesis, the intervention demonstrated that online therapy worked very well for the vast majority of the participants, regardless of age and disease stage. In fact, online delivered therapy was vital for continuing speech therapy during the COVID-19 pandemic, when in-person visits were not possible.

Part of the online intervention in this study was delivered using a feedback app by the participant (the Voice Trainer) and its accompanying dashboard, which enabled speech therapists to remotely monitor vocal performance outside the therapeutic setting. At first, combining online therapy with a second screen showing real-time feedback brought practical challenges, particularly in making the feedback visual to both the speech therapist and the person with PD. This was resolved by positioning the Voice

Trainer in front of the camera of the device used for the video call, allowing the speech therapist to view the feedback directly and the person with PD to see it indirectly via the screen. In general, a brief explanation and one-time demonstration for this setup was sufficient for persons with PD or their caregivers to apply this setup independently.

One of the aims of this thesis was to evaluate how persons with PD experienced the Voice Trainer in terms of use and usability. Although working with the app requires an individual approach, most participants reported positive experiences. These findings show that telemedicine for managing speech problems in persons with PD can involve more than just video consultations: telemonitoring, allowing speech therapists to remotely view speech performance, can also be successfully integrated into treatment. Altogether, these results confirm that telerehabilitation has great potential in speech therapy in individuals with PD, particularly in supporting intelligible speech.

The significance of PD-specific expertise in allied health care above generic health care has been highlighted in several studies, also in the field of speech and language therapy [2, 25, 26]. Consequently, online delivered therapy is crucial for improving access to specialised care, especially for individuals living in rural areas. Combined with previous evidence [23, 24, 27], my findings show that high-quality, specialised speech therapy can be delivered effectively regardless of the physical location of the speech therapist, thereby expanding patients' options for selecting a therapist when they prefer online treatment.

Lastly, based on American and Dutch studies and statistics showing a decline of telemedicine video consultations after the COVID-19 pandemic [28-30], it is likely that the use of online speech therapy has also declined. This raises the question whether speech therapists may be missing opportunities to provide intensive and efficient treatment to persons with PD needing specialised speech therapy. Future research should therefore on optimizing online treatment for speech therapy in PD.

Future outlook

Although I already mentioned some ideas for future research earlier, I would like to highlight several other future directions and clinical implications in this paragraph.

Because of the positive results of speech therapy with the PERSPECTIVE approach (i.e. personalised, remote, with individual coaching of speech therapists, and use of the Voice Trainer and Dashboard), it would be a waste to not further implement these elements and make them accessible for speech therapists who would like to broaden the scope of their PD care. In fact, an implementation program has already started in 2024 to further implement two elements: 1. individual online coaching for speech therapists to hone their speech therapy skills; and 2. the Voice Trainer Dashboard to monitor performance of the individual PD outside therapeutic setting, and the ability to send them reminder notifications [31].

Making these elements available to speech therapists will hopefully contribute to more efficient, high-quality, and accessible PD-specific speech therapy, improving care for persons with PD.

Furthermore, this thesis has shown several possibilities and the potential of the use of telerehabilitation in PD. What is not discussed yet, is the potential of upcoming technologies like artificial intelligence (AI) and speech recognition in the field of speech and language therapy in PD. At this moment, we are entering a new era with upcoming applications of AI in health care, also in the field of PD [32, 33]. In fact, it is already possible with AI to differentiate persons with PD from healthy controls by analysing their speech [34, 35]. Using AI enables new opportunities for the support of diagnostic tools, by example using automatic speech recognition for early detection, for the differential diagnosis (separating PD from the various forms of atypical parkinsonism), for measuring treatment responses, or for measuring disease progression. In the future, possibilities for AI in assessment and treatment of speech in PD should be explored to make individuals with PD benefit even more from accurate diagnosis and effective treatment. For instance, AI models could analyse speech characteristics for early disease detection, differential diagnosis, or disease progression, and could provide real-time feedback or personalised training recommendations during speech exercises.

In conclusion

Telerehabilitation and upcoming technologies have great potential in the field of speech therapy and PD. Although remotely delivered speech therapy accompanied by a real-time feedback app shows an improvement of communication-related quality of life, a personalised approach should always be warranted, since there is no 'one size fits all'. Above all, improving the lives of persons with PD should always be the guiding principle from both the clinical care and research perspective.

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Chapter 7

Nederlandse samenvatting

Nederlandse samenvatting

De ziekte van Parkinson (PD) leidt tot communicatieproblemen door een verminderde spraakverstaanbaarheid, veroorzaakt door een hypokinetische dysartrie. Dit komt voor bij tot wel 90% van de mensen met PD gedurende het ziekteverloop en heeft een negatieve invloed op sociale interactie en kwaliteit van leven. Hoog-intensieve behandeling lijkt effectief om de spraak te verbeteren, maar is niet voor iedere persoon met PD haalbaar. Voorafgaand aan de studies uit dit proefschrift, was er beperkte kennis over de invloed van logopedische behandeling op kwaliteit van leven en verbale communicatie bij mensen met PD, met name in een heterogene populatie, waaronder ook mensen die niet in staat zijn om intensieve behandeling te volgen. Daarnaast was er weinig bekend over het gebruik van technologie in de logopedie, terwijl dit gebruik toeneemt doordat het nieuwe mogelijkheden biedt om mensen met PD efficiënter te behandelen. Een app met real-time feedback op spraak wordt al veel gebruikt in Nederland, maar het gebruik en de gebruiksvriendelijkheid waren tot nu toe niet geëvalueerd.

De doelen van dit proefschrift waren:

1. Het onderzoeken van de effectiviteit van gepersonaliseerde online logopedie bij mensen met PD, ongeacht het ziektestadium;
2. Het evalueren hoe mensen met PD een app met real-time visuele feedback ervaren, met betrekking tot hun gebruik (bijvoorbeeld frequentie en manier van gebruik) en de gebruiksvriendelijkheid.

In deel I van dit proefschrift beschrijf ik het ontwerp en de uitvoering van een gerandomiseerde gecontroleerde studie (RCT) om de effectiviteit van gepersonaliseerde online logopedie te onderzoeken bij mensen met PD, inclusief mensen die geen intensieve face-to-face behandeling kunnen volgen. In deel II evalueer ik het gebruik en de gebruiksvriendelijkheid van een visuele feedback-app die de verstaanbaarheid van spraak bij mensen met PD ondersteunt. In dit hoofdstuk geef ik een overzicht van de inhoud van het proefschrift.

Deel I: Effectiviteit van gepersonaliseerde logopedie op afstand bij mensen met PD

Het bewijs voor de effectiviteit van logopedie bij PD groeit, maar er is nog aanvullend onderzoek nodig om het volledige potentieel te verkennen. In **hoofdstuk 2** beschrijf ik het design van een RCT om de effectiviteit te evalueren van gepersonaliseerde, op afstand aangeboden (online) parkinsonspecifieke logopedie (middels de Pitch Limiting Voice Treatment: PLVT) op kwaliteit van leven en spraakuitkomsten bij mensen met PD met een verminderde spraakverstaanbaarheid. De interventie wordt ondersteund door een speciale feedback-app, de Voice Trainer. Ik verwachtte dat deze aanpak de spraakverstaanbaarheid en de kwaliteit van leven zou verbeteren.

Ik voerde een grote single-blinded gerandomiseerde studie uit (de PERSPECTIVE-studie), waarin 8 weken gepersonaliseerde online logopedie werd vergeleken met uitgestelde behandeling

(wachtlijstdesign). Deelnemers werden willekeurig (1:1) toegewezen aan de interventiegroep of de controlegroep. De metingen vonden plaats bij aanvang en na 8 weken (beide groepen, T1) en na 32 weken (alleen interventiegroep, T2). Het doel was dat deelnemers online behandeld werden door zeer ervaren logopedisten die getraind zijn binnen én actief betrokken zijn bij ParkinsonNet. De primaire uitkomstmaat was ziekte-specifieke kwaliteit van leven op T1, gemeten met de Parkinson's Disease Questionnaire-39 (PDQ-39).

In **hoofdstuk 3** beschrijf ik de resultaten van deze studie. De data werden geanalyseerd met behulp van analyse van covariantie volgens het intention-to-treat principe. Tussen 1 maart 2019 en 27 maart 2021 werden 214 patiënten geïncludeerd in de interventiegroep (n=109) of controlegroep (n=105). Op T1 was het aangepaste gemiddelde verschil in PDQ-39 -2,0 in het voordeel van de interventiegroep (95% BI -4,0 tot 0,1; p=0,056), wat statistisch niet significant was. De interventiegroep scoorde wel significant beter op het communicatie-domein van de PDQ-39 (post-hoc analyse), met een gecorrigeerd gemiddeld verschil van -5,3 (95% BI -9,4 tot -1,2; p=0,011), wat ook groter was dan het minimaal klinisch relevante verschil van 4,2 voor dit domein. Er werden geen verschillen gevonden tussen de groepen op de andere domeinen van de PDQ-39.

De metingen op T2 lieten een significante verslechtering zien van de PDQ-39 ten opzichte van T1, met een verschil van 2,40 (95% BI 0,77 tot 4,02; p=0,004). Concluderend bleek logopedie op afstand geen verbetering te geven in de algehele kwaliteit van leven, hoewel er op T1 wel een bescheiden, niet-significant voordeel werd gezien voor de interventiegroep. Ik koos ziekte-specifieke kwaliteit van leven als ambitieuze primaire uitkomstmaat, wetende dat dit een complexe maat is met meerdere domeinen die niet allemaal direct door logopedie worden beïnvloed. Post-hoc analyses lieten zien dat de trend naar verbetering vooral werd verklaard door het communicatie-domein, wat past bij een daadwerkelijk behandeleffect. Hoewel dit slechts een onderdeel van de totale PDQ-39 betreft, is zelfstandig kunnen communiceren een belangrijk aspect van kwaliteit van leven. De andere domeinen veranderden niet, wat mijn hypothese ondersteunt dat logopedie specifiek communicatie verbetert en daarmee (deels) kwaliteit van leven beïnvloedt. De effecten waren echter niet behouden bij de follow-up na 32 weken, wat het belang onderstreept van onderhoudsbehandeling op de lange termijn.

Deel II: Evaluatie van de gebruiksvriendelijkheid van een app voor spraakverbetering bij mensen met PD

De meeste mensen met PD ervaren spraakproblemen, veroorzaakt door een hypokinetische dysartrie. Hun spraak kan verbeteren door te leren om luider te spreken om hun zachte stemgeluid te compenseren, terwijl de toonhoogte laag genoeg blijft voor een natuurlijk klinkende stem. Specifieke feedback op luidheid en toonhoogte tijdens oefeningen wordt als zeer waardevol beschouwd.

In **hoofdstuk 4** beschrijf ik de Voice Trainer, een applicatie die visuele feedback geeft tijdens het oefenen van spraak. Daarnaast beschrijf ik het bijbehorende dashboard, een web-based programma

waarmee logopedisten op afstand de spraakprestaties van patiënten kunnen monitoren. Ook evalueer ik het gebruik en de gebruiksvriendelijkheid van de Voice Trainer bij mensen met PD.

Eenentachtig deelnemers uit de studie (beschreven in **hoofdstuk 3**) vulden twee vragenlijsten in: de System Usability Scale (SUS) (score 0–100, waarbij een hogere score staat voor betere gebruiksvriendelijkheid) en de Voice Trainer Questionnaire (VTQ), ontwikkeld om het gebruik van de app te evalueren. De mediane SUS-score was 78,8, wat wijst op een bovengemiddelde gebruiksvriendelijkheid. Van de deelnemers die de app bleven gebruiken (45%), zou 92,3% deze aanbevelen aan anderen met PD. Van de deelnemers die stopten met gebruik (55%), zou 81,3% de app eveneens aanbevelen.

Er waren verschillende redenen om het gebruik voort te zetten of te stoppen, zoals het niet meer nodig hebben van de app of hem vergeten te gebruiken. De meeste deelnemers waren tevreden over de gebruiksvriendelijkheid en hadden positieve ervaringen. Tegelijkertijd bleek er variatie te zijn in ervaringen en behoeften, bijvoorbeeld door technische problemen, voorkeur voor persoonlijke feedback boven een app, of de inspanning die het kostte om de app te gebruiken.

Deze bevindingen benadrukken het belang van een individuele aanpak van de behandeling, afgestemd op de behoeften van de mens met parkinson, om optimale gepersonaliseerde logopedie te bieden en de transfer naar het dagelijks leven te bevorderen. Dat meer dan de helft van de deelnemers stopte met het gebruik van de app kan mogelijk deels verklaren waarom het behandelingseffect na verloop van tijd afnam (zoals beschreven in **hoofdstuk 3**). Dit onderstreept opnieuw het belang van adequate nazorg en onderhoudsbehandeling.



Appendices

A1. Research data management

A2. Dankwoord

A3. About the author

A4. Portfolio

A5. Donders Graduate School for Cognitive Neuroscience

A1. Description of the Research Data Management

Ethics and Privacy

This thesis is based on the results of research involving human participants. The research presented in this thesis was conducted in accordance with the principles of the Declaration of Helsinki and the ICH-GCP guidelines (Good Clinical Practice).

The study was approved by the medical ethics committee (CMO Arnhem Nijmegen; 2018-4858; file number: NL67867.091.18). Informed consent was obtained from participants to collect and process their data for this research project. Optionally consent was obtained for sharing and reuse of the (pseudonymised) data for future research.

The privacy of the participants in these studies was warranted by the use of pseudonymisation. The pseudonymisation key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymisation key was stored separately from the research data.

This research was funded by a grant from the Michael J Fox Foundation. The funder has no involvement in the study design, outcomes, and publishing of this work. Radboud University Medical Center is the owner of the data.

Data collection and storage

Data was collected from the department of Neurology of the Radboud University Medical Center in Nijmegen. All study data was collected and stored in a secured data management system (Castor EDC). All data described in this thesis are securely stored at the server of the Neurology department at the Radboud University Medical Center and only accessible for members of the research team. Source documentation on paper is archived (GCP compliant) and stored in cabinets at the Radboud University Medical Center. All study documents will be archived for fifteen years.

Data sharing according to the FAIR principles

Findable and Accessible

The studies in Chapter 2 and Chapter 3 are published open access. Chapter 4 is submitted for publication and currently under review. The data from Chapter 3 will be published with restricted access and will only include participants who granted additional permission for their data to be reused in future research. This data will be published in the Radboud Data Repository (DOI: 10.34973/g55d-hn65).

Interoperable and Reusable

The data shown in this thesis are adequately documented for interpretation and to be reusable for further research and analysis. Quantitative data were stored using SPSS Statistics Data Documents, which can be opened with SPSS or Microsoft Office Excel. Qualitative data were stored using .csv and .doc formats.

A2. Dankwoord

Het schrijven van een proefschrift is een reis die je nooit alleen aflegt. Zonder de steun van vele mensen om mijn heen, was dit boekje er niet geweest. Daarom wil ik graag via deze weg iedereen bedanken die op wat voor manier dan ook heeft bijgedragen.

Allereerst was dit onderzoek niet mogelijk geweest zonder de inzet van alle **mensen met parkinson en hun naasten,** die bereid waren om deel te nemen aan het onderzoek. De online logopedische behandelingen, het werken met de Voice trainer, de onderzoeksmetingen thuis: het vraagt moed om dit avontuur aan te gaan, zeker voor degenen met minder technische vaardigheden. Zonder jullie inzet en motivatie hadden we nooit de kennis gekregen die we nu hebben. Daarom een speciale dank naar jullie!

Dan mijn promotor Prof. dr. Bas Bloem. **Bas**, jouw eeuwige optimisme, passie voor betere parkinsonzorg, en snelle denkwerk zijn een grote motivator en inspiratiebron. Bedankt dat ik onder jouw vleugels een mooie start mocht maken met mijn carrière als parkinsononderzoeker.

Mijn co-promotoren dr. Nienke de Vries en dr. Hanneke Kalf. **Nienke,** jouw nuchterheid, relativeringsvermogen en 'dit regelen we wel'-mentaliteit waren altijd een fijne aanvulling in onze Perspective-overleggen. Geen vraag was te gek of te moeilijk. Bedankt dat ik altijd op jou kon terugvallen bij methodologische kwesties en uitdagingen. **Hanneke**, vanaf het begin was jij een ware mentrix die mij als wetenschappelijk onderzoeker, parkinsonlogopedist en docent begeleidde vanuit jouw enorme kennis en ervaring. Jouw oog voor detail en motivatie om altijd de beste kwaliteit te leveren houden mij scherp. Ondertussen zijn we een echt team. Bedankt voor jouw vertrouwen in mij.

Het opzetten van onderzoek en het uitvoeren van 500 metingen bij mensen met parkinson door heel Nederland is een grote klus. Daarom ben ik blij dat onderzoeksassessoren Carmen en Lisa mij daar ontzettend goed bij hebben geholpen. **Carmen**, wat hebben we samen veel gebrainstormd, gepuzzeld met systemen en dossiers (ik zet het wel in de Cast-or!), maar bovenal ook veel plezier gehad. Jouw enthousiasme was aanstekelijk. **Lisa**, met jouw oog voor precisie en harde werk vormden we een goed team, ook al werkten we vaak op afstand van elkaar. Dank je wel voor het mooie werk dat we samen hebben neergezet!

Ook wil ik alle **logopedisten** bedanken die hebben bijgedragen aan het Perspective-onderzoek. Het vraagt nieuwsgierigheid en een onbevangen inzet om binnen de setting van wetenschappelijk onderzoek online behandelingen te geven, een online dashboard te gebruiken, én daarbij ook nog eens gecoacht te worden. Dankzij jullie bereidwilligheid hebben we de meerwaarde van ons mooie vakgebied kunnen aantonen.

Selma en **Bert**, jullie kennis, expertise en coachingskwaliteiten kwamen zeer goed van pas tijdens het onderzoek. Door jullie hebben de logopedisten hun behandeling naar een hoger niveau kunnen tillen en is daarmee het zaadje gepland voor implementatieonderzoek voor individuele online coaching van logopedisten.

Lilian, Lisa en **Madelon**, jullie bijdragen aan dit proefschrift is van grote waarde geweest. De hulp met de dataverzameling, de analyses, en het samen sparren over de resultaten heeft me enorm geholpen. Daarnaast was het ook heel fijn om met jullie samen te werken en jullie te zien groeien als student.

Een bijzondere dank gaat ook uit naar patiëntonderzoekers **Marina** en **Martin**. Zij hebben zich gedurende de opzet en de uitvoering van de studie ingezet om mee te denken vanuit het perspectief van mensen met parkinson. Hoewel ze het einde van de studie niet hebben mogen meemaken, hebben zij met hun inzet bijgedragen aan een toekomst met meer kennis en inzichten voor hun lotgenoten.

Joanna, wat was ik blij met jou als mijn statisticus met wie ik kon sparren en op wie ik kon terugvallen met al mijn statistische en SPSS-vragen. Jouw hulp was onmisbaar bij het analyseren van de resultaten en bij het schrijven van de rebuttals.

Anne-Claire en **Brenda,** als gemotiveerde parkinsonlogopedisten zijn jullie inzet en ervaring ontzettend waardevol, zowel tijdens onderzoeksprojecten als bij het implementeren van ideeën en het geven van onderwijs. Daarnaast is het altijd fijn om met jullie samen te werken. Betere ambassadeurs voor goede logopedie bij parkinson kan ik me niet wensen!

Op het expertisecentrum voor parkinson en bewegingsstoornissen werken we met veel mensen op een afdeling. Inmiddels voelt dit als één grote familie. In het bijzonder wil ik graag **Danique, Ana, Tamine, Angelika, Stacha, Anouk, Lotte, Jolien, Pauline, Amber, Robin, Amir, Willanka, Thomas, Kevin, Kars, Erik, Nienke, Jules, Helena, Debbie, Anouk, Ilse, Marjan, Dagmar** en **Bart** bedanken voor de gezellige activiteiten, borrels, lunchwandelingen, feestjes, bandoptredens en koffiemomenten, die het werk extra leuk maakten.

Ook een speciale dank aan **Sabine**. Samen een kamer delen in Nice is niet een gebruikelijke manier om elkaar voor het eerst te ontmoeten, maar vanaf het begin hadden we een goede klik. Jouw onvermoeibare enthousiasme en energie, de hardekern-activiteiten, etentjes en wandeling- en fietstochten maakten het werken tot een feestje.

Ook mijn collega's van het **ParkinsonNet-team**: Anja, Marten, Florence, Anne-Marie, Anneli, Annika, Anoek, Colin, Hendriëtte, Ellen, Herma, Ingrid, Irma, Karin, Maarten, Marieke, Marlies, Maxime, Milou, Renate, Sanne, Seher, Stef, Wilfred, en Annelien wil ik graag bedanken. Ook al weet niet iedereen wat ik precies uitspookte als ik aan mijn onderzoek werkte, de gezelligheid, collegialiteit en koffiemomenten

waren altijd aanwezig. De overgang van onderzoek naar ParkinsonNet voelde daardoor als een warm bad.

Een studie met technologie vraagt ook om technische ondersteuning. Daarom ook een hartelijke dank voor **Paul**, **Bart,** en **Pieter**, die met hun kennis, inzicht en vooral probleem-oplossend vermogen een onmisbare rol hebben gespeeld bij het meedenken de programma's voor online behandelingen, de Voice trainer en het dashboard.

Mijn oud-collega's bij **Liemerije** en **Communicatiecentrum Taalstroom:** bedankt voor de samenwerking en praktijkervaring die ik kon opdoen als logopedist in de (parkinson)zorg. Een waardevolle en onmisbare aanvulling op mijn onderzoeks- en onderwijswerkzaamheden.

Mijn bachelor- en mastergenootjes, maar bovenal vriendinnen **Karleen** en **Ines.** Jullie begrepen wat er allemaal komt kijken bij het uitvoeren van logopedisch wetenschappelijk onderzoek. Ik zie ons nog tijdens onze master een dissertatie bijwonen. 'Pfoe, dat ga ik nóóit doen!' was onze reactie. Maar het bloed kruipt waar het niet gaan kan. Bedankt voor de support, de gezellige koffiemomenten en de (ondertussen iets minder actieve) activiteiten!

Mijn vriendinnen **Aniek, Puk, Marieke** en **Marijn**. We go way back: jullie volgen mijn pad al sinds de basis- of middelbare school en hebben alles vanaf de zijlijn meegekregen. Alle bijklets-lunches/borrels/vriendinnenweekenden zijn een welkome afwisseling geweest naast het werk- en gezinsleven. Bedankt dat jullie er altijd voor mij waren en zijn, in goede en slechte tijden.

Lieve **Alex,** jij hebt de opstart van mijn onderzoek intensief meegemaakt. Bedankt dat je er voor mij was. Ik heb veel waardering voor en ook veel geleerd van je onvermoeibare doorzettingsvermogen om je dromen waar te maken.

Aan **Wim, Marion, Ymke, David** en **Lewis**: wat ben ik blij met jullie als schoonfamilie en de warmte en betrokkenheid die ik vanaf het eerste moment heb gevoeld. Dank jullie wel!

Job, met jouw nuchterheid en grapjes is het altijd lachen. Ondanks onze uiteenlopende werelden ben ik dankbaar voor de momenten die we samen hebben.

Lieve **pap** en **mam,** ik kan me nog herinneren dat pap me als kind ooit uitlegde wat je na de middelbare school kunt gaan doen: doorstuderen, doctorandus worden, en - als je dan zelf nieuwe dingen zou gaan onderzoeken - zelfs een doctortitel kunnen behalen. Dit klonk toen als zo iets 'einsteinerigs' dat ik nooit had kunnen bedenken dat dit mijn pad zou worden. Mam, een speciale dank ook aan jou, voor het thuis altijd klaarstaan voor ons en de vele uren liefdevolle zorg die wij en Loua hebben mogen ontvangen.

Pap en mam, bedankt voor de warme en liefdevolle basis die jullie mij hebben gegeven, en voor het vertrouwen dat jullie altijd in me hebben gehad.

Lieve **Loua**, alle werkzorgen zijn snel te relativeren als ik jou zie. Wat geniet ik van jouw grapjes, lachjes en gekke plannetjes. En wat ben ik dankbaar om jou te zien opgroeien en trots om jouw mama te mogen zijn. Ik hou van je!

Aan jou, lieve **Luc**: je hebt als collega, goede vriend en later ook als partner mijn promotietraject van begin tot eind mogen volgen. Jij hebt me als geen ander gezien en gecoacht, zowel inhoudelijk als persoonlijk. Samen hebben we veel meegemaakt en kijk eens waar we nu staan: beide (bijna) gepromoveerd, een fijn nestje, maar bovenal een prachtige dochter en nog een kleintje op komst. Wat ben gelukkig met jou en trots op ons, en ik kan niet wachten op alles wat nog gaat komen. Ik hou van je.

A3. About the author

Janna Maas was born on January 6th 1995 in Cuijk, the Netherlands. After graduating from secondary school (Gymnasium, Merletcollege in Cuijk), she began her Bachelor's degree in Speech and Language Therapy at the HAN University of Applied Sciences in Nijmegen. Following her graduation in 2016, she pursued a Master's degree in Speech and Language Pathology at the Radboud University, Nijmegen. She graduated cum laude in 2018, with her Master's thesis focusing on speech problems in Duchenne muscular dystrophy. During her Master's, she simultaneously worked as a speech and language therapist at Zorgcentra de Betuwe.

Driven by a strong interest in neurological disorders, Janna started her PhD trajectory in 2018 at the Department of Neurology of the Radboud University Medical Center, under supervision of Prof. dr. Bas Bloem, dr. Hanneke Kalf and dr. Nienke de Vries. Her doctoral research focused on evaluating the effectiveness of speech therapy in Parkinson's disease and exploring how use of a visual feedback app can enhance speech treatment. During her PhD, Janna has presented her work at several national and international conferences.

Alongside her work as a doctoral researcher, Janna worked as a speech and language therapist in both primary care and secondary care settings. She currently works as a speech therapist at Radboudumc. She has also lectured in the Master's program in Speech and Language Pathology at Radboud University.

Since 2022, Janna has been working as an expert speech therapist at ParkinsonNet, and from 2023 also as a regional advisor within this organization. Since 2024, she has contributed to the IMPRESS project, implementing online coaching and the Voice trainer dashboard among Dutch speech and language therapists working with people with Parkinson's disease and/or ataxia.

Janna lives together with Luc Evers and their daughter Loua in Lent.

A4. Portfolio

Department: Neurology
PhD Supervisor(s): **Prof. B.R. Bloem**
PhD Co-supervisor(s): **Dr. J.G. Kalf, dr. N.M. de Vries**

Training activities	Hours
Courses	
- DGS – GS Introduction Day (2018)	7
- RU – Management voor Promovendi (2018)	56
- RU – Analytic Storytelling (2019)	28
- Research Integrity Course (2019)	7
- RU - Presentation Skills (2019)	42
- Radboudumc – eBROK course (2019)	42
- DGS – Graduate School Day (2019)	7
- RU – Advanced Conversation (2019)	42
- DGS – Scientific Integrity Course (2019)	7
- Becoming a facilitator for peer coaching (2020)	14
- Statistiek voor Promovendi met SPSS (2020)	60
- RU – Effective Writing Strategies	84
- DGS – Graduate School Day (2021)	7
- RU – Education in a Nutshell (2021)	28
- RU – Mindfulness Based Stress Reduction (2021)	45
- RU – Design and Illustration (2022)	26
- DGS – Graduate School Day (2022)	7
- EMWO – eBROK re-registration (2023)	5
- Spies&Spreken Presentatietraining (2023)	8
Seminars	
- Dag van de Logopediewetenschap - Logoscientia (2021) (design of the PERSPECTIVE study, oral presentation)	
- NVLF Webinar (2024) (integrated guideline for allied healthcare in Parkinson's disease, oral presentation)	
Conferences and congresses	
- International Congress of Parkinson's Disease and Movement Disorders 2019, Nice, France (design of the PERSPECTIVE study, poster presentation)	
- ParkinsonNet congres, 2023, Nieuwegein (atypical parkinsonism, oral presentation)	
- International Congress of Parkinson's Disease and Movement Disorders 2023, Copenhagen, Denmark (results of the PERSPECTIVE study, poster presentation)	
- ParkinsonNet congres, 2024, Nieuwegein (Voice trainer, oral presentation)	
- Parkinson Symposium, 2025, 's-Hertogenbosch (speech therapy in Parkinson's disease, oral presentation)	
- ParkinsonNet congres, 2025, online (cognitive communication disorders in Parkinson's disease, oral presentation)	
- NVLF Congress, 2025, online, (feedback apps in speech therapy, oral presentation)	
- NVLF Congress, 2025, online, (Masterclass Parkinson's disease, oral presentation)	

Other

- Parkinson Café, 2020, Ede (PERSPECTIVE study, oral presentation)
- Yoppers Café, 2023, Roosendaal (Speech therapy in Parkinson's disease, oral presentation)
- Parkinson Weekend, 2023, Nijmegen (online speech therapy in Parkinson's disease, pitch)
- Parkinson Weekend, 2023, Nijmegen (non-pharmacological interventions in Parkinson's disease, oral presentation)
- Meet the author, Logoscientia, 2025, (results of PERSPECTIVE study, oral presentation)

Teaching activities

Lecturing

- Radboud University, Supervising bachelor thesis (2021-2022)
- Radboud University, Research methods in speech- and language pathology (2021-2022)
- ParkinsonNet, Basisscholing logopedie (2022 – 2026)
- Han University of Applied Sciences, Master Neurorevalidatie en Innovatie, guest lecture 'Kennis opdoen over richtlijnontwikkeling en beslisondersteuning in de praktijk' (2024)

Supervision of internships

- Master thesis: The process evaluation of the use and implementation of the Voice trainer in Parkinson's disease patients. Lilian Manning (biomedical science), 2022
- Master thesis: Ervaring van patiënten met de ziekte van Parkinson met online logopedie en het gebruik van de Voice trainer. Madelon ten Boom (speech and language pathology), 2023

Total	**522**

A5. Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 750 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit: http://www.ru.nl/donders/graduate-school/phd/

A6. Dissertations of the Center of Expertise for Parkinson & Movement Disorders

Parkinson's disease

- Jasper Visser. The basal ganglia and postural control. Radboud University Nijmegen, June 17, 2008.
- Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, May 27, 2009.
- Wilson Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, October 7, 2009.
- Samyra Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, April 29, 2010.
- Lars Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, November 29, 2010.
- Maarten Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, November 29, 2010.
- Rick Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, May 24, 2011.
- Ilona Bruinsma. Amyloidogenic proteins in Alzheimer's and Parkinson's disease. Interaction with chaperones and inflammation. Radboud University Nijmegen, September 21, 2011.
- Charlotte Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, December 6, 2011.
- Hanneke Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, December 22, 2011.
- Anke Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, June 4, 2012.
- Yvette Grimbergen. Falls in Parkinson's Disease and Huntington's Disease. Leiden University Medical Center, October 23, 2012.
- Bart van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, November 22, 2012.
- Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, February 13, 2013.
- Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, March 6, 2013.
- Arlène Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, March 6, 2013.
- Tjitske Boonstra. The contribution of each leg to bipedal balance control. University of Twente, June 6, 2013.

- Marjolein van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, January 20, 2014.
- Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, May 21, 2014.
- Marjolein Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, June 27, 2014.
- Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, February 13, 2015.
- Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, June 23, 2015.
- Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, September 25, 2015.
- Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, December 1, 2015.
- Carolien Strouwen. Pathophysiology of Freezing in Parkinson's Disease. KU Leuven, December 16, 2015.
- Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, February 11, 2016.
- Merel van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, April 13, 2016.
- Arno Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, June 2, 2016.
- Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patiënt. Radboud University Nijmegen, June 15, 2017.
- Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, September 1, 2017.
- Digna de Kam. Postural instability in people with chronic stroke and Parkinson's disease: dynamic perspectives Radboud University Nijmegen, October 4, 2017.
- Freek Nieuwhof. The complexity of walking: Cognitive control of gait in aging and Parkinson's disease Radboud University Nijmegen, October 27, 2017.
- Koen Klemann. A molecular window into Parkinson's disease. Radboud University Nijmegen, November 3, 2017.
- Jeroen Venhovens. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. Radboud University Nijmegen, March 20, 2018.
- Claudia Barthel. Moving beyond: freezing of gait in Parkinson's disease. Radboud University Nijmegen, April 4, 2018.
- Esther Bekkers. Freezing and postural control in Parkinson's disease. KU Leuven, May 15, 2018.
- Erik te Woerd. Feeling the beat: The neurophysiology of cueing in Parkinson's disease. Radboud University Nijmegen, January 18, 2019.

- Ana Silva de Lima. Quantifying Parkinson's disease: the use of technology for objective assessment of motor symptoms. Radboud University Nijmegen, March 26, 2019.
- Monique Timmer. Neurocognitive mechanisms underlying depression in Parkinson's disease. Radboud University Nijmegen, April 16, 2019.
- Sabine Janssen. Virtual visual cues: vice or virtue? University of Twente, March 11, 2020.
- Anna Santaella Tortós-Sala. Tackling Parkinson's disease: a proteomic approach to biomarkers and regenerative therapy. Radboud University Nijmegen, October 22, 2020.
- Nicolien van der Kolk. Towards a prescription for exercise for persons with Parkinson's disease. Radboud University Nijmegen, October 30, 2020.
- Michiel Dirkx. Neural mechanisms of Parkinson's tremor. Radboud University Nijmegen, November 22, 2020.
- Sjors van de Weijer. Digital technology-enabled home health care: Gamification in online cognitive therapies for Parkinson's disease. Maastricht University, September 1, 2021.
- Taina Macherini Marques. Discriminating Parkinsonian Disorders. Radboud University Nijmegen, September 9, 2021.
- Danny Hommel. Impairment and disability in late-stage parkinsonism. Radboud University Nijmegen, September 27, 2021.
- Floris Vlaanderen. Towards seamless and sustainable care for Parkinson's disease. Radboud University Nijmegen, October 27, 2021.
- Rui Araújo. The art of clinical neurology. Radboud University Nijmegen, March 7, 2022.
- Sara Riggare. Personal science in Parkinson's disease. Radboud University Nijmegen, March 25, 2022.
- Tamine Teixeira da Costa Capato. Clinical assessment and management of balance impairments in Parkinson's disease. Radboud University Nijmegen, June 29, 2022.
- Herma Lennaerts - Kats. Palliative care for people with Parkinson's disease and their family caregivers. Radboud University Nijmegen, July 6, 2022.
- Carlijn Borm. Vision in Parkinson's disease: more than meets the eye. Radboud University Nijmegen, February 22, 2023.
- Heidemarie Zach. Parkinson's Tremor: Effects of dopamine and cognitive Load. Radboud University Nijmegen, February 27, 2023.
- Anouke van Rumund. Differential Diagnosis in Early Stage Parkinsonism. Radboud University Nijmegen, June 8, 2023.
- Lieneke van den Heuvel. Towards personalized decision making in Parkinson's disease. Radboud University Nijmegen, August 24, 2023.
- Anouk Tosserams. PEARL-PD: Personalized Gait Rehabilitation in Parkinson's Disease. Radboud University Nijmegen, December 14, 2023.
- Helena Cockx. The nature of freezing of gait: investigating its neurophysiological and cardiovascular underpinning with wearable technology. Radboud University Nijmegen, February 23, 2024.
- Sonal Sengupta. Influence of hyperreflexive responding on motor behavior in Parkinson's Disease. Radboud University Nijmegen, March 11, 2024.

- Martin Johansson. How Cerebral Plasticity Shapes Motor Progression in Parkinson's Disease: A Longitudinal Neuroimaging Study. Radboud University Nijmegen, March 20, 2024.
- Josefa Domingos. Community Based Exercise in Parkinson's Disease. Radboud University Nijmegen, March 21, 2024.
- Anoek van der Heide. Psychological stress and Parkinson's disease: underlying mechanisms and focused interventions. Radboud University Nijmegen, April 3, 2024.
- Luc Evers. Stepping out of the clinic: towards objective, real-life monitoring of Parkinson's disease. Radboud University Nijmegen, June 19, 2024.
- Angelika Geerlings. Personalized care management in Parkinson's disease: One size does not fit all. Radboud University Nijmegen, October 7, 2024.
- Jorryt Tichelaar. Role of Neuroinflammation in Progressive Basal Ganglia Dysfunction in Parkinson's Disease. Radboud University Nijmegen, October 31, 2024.
- Robin van den Bergh. Telemedicine and remote monitoring for people with Parkinson's disease. Radboud University Nijmegen, December 9, 2024.
- Frouke Nijhuis. Decision-making for advanced therapies in Parkinson's disease. It takes a shared choreography. Radboud University Nijmegen, January 23, 2025.
- Sabine Schootemeijer. Promoting physical activity in Parkinson's disease. Towards scalable interventions. Radboud University Nijmegen, April 11, 2025.
- Amir Talebi. Leveraging big data to improve care for people with Parkinson's disease. Radboud University Nijmegen, May 26, 2025.
- Thieme Stappe. Through the learning lens: On innovation towards integrated and person-centered Parkinson's care. Radboud University Nijmegen, August 28, 2025.
- Veerle van de Wetering-van Dongen. Respiratory issues screened and explored in Parkinson's disease. Radboud University Nijmegen, November 3, 2025.
- Amber van Stam. Head-up tilt sleeping in Parkinson disease and multiple system atrophy. Radboud University Nijmegen, February 2, 2026.

Non-Parkinsonian disorders of movement

- Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellar ataxias. Radboud University Nijmegen, April 5, 2012.
- Susanne de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, December 20, 2013.
- Cathérine Delnooz. Unravelling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, January 7, 2014.
- Megan Herbert. Facing Uncertain Diagnosis: The Use of CSF Biomarkers for the Differential Diagnosis of Neurodegenerative Diseases. Radboud University Nijmegen, July 8, 2014.
- Ella Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias. Radboud University Nijmegen, June 29, 2016.
- Britt Hoffland. Investigating the role of the cerebellum in idiopathic focal dystonia. Radboud University Nijmegen, March 22, 2018.
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