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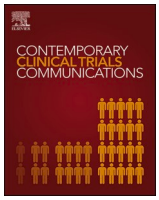

The ePark study protocol: A decentralized trial of individual video-assisted cognitive behavioural therapy for depressive disorder in Parkinson's disease

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1.2 million Europeans [1]. The prevalence of PD in people over 60 is about 1%, increasing to 4% in people 80 years and older [2]. Although PD is defined as a motor disorder, non-motor symptoms including neuropsychiatric symptoms such as depression and anxiety, are frequent and disabling, with a major impact on quality of life, caregiver burden and healthcare costs [3].

Current pharmacological treatments for PD neuropsychiatric symptoms, including depression, are often unsatisfactory for several reasons, including frequent adverse effects of medication, elevated risk of polypharmacy, and limited availability for non-pharmacological treatment options [4,5]. Previously published RCTs have demonstrated large effect sizes of face-to-face, telephone administered and online CBT for depressive symptoms in PD [6–8]. Despite strong evidence that cognitive behavioural therapy (CBT) is effective and cost-efficient in reducing depressive symptoms in PD, few patients are offered this treatment [3,6–10]. This is likely due in part to a shortage of CBT therapists at neurological outpatient clinics, particularly in rural areas, resulting in geographical differences in the availability of CBT treatment. This calls for the development of novel, evidence based online therapeutic strategies, which may significantly improve the lives of PD patients suffering from depressive symptoms.

1.1. Study aims and hypotheses

We will conduct a remote, randomized, delayed start trial, in order to.

I. Assess the effectiveness of online, video-assisted cognitive behavioural therapy (eCBT) for depressive symptoms in patients with PD.
II. Assess long-term outcomes, and predictors of long-term outcomes, of eCBT for depressive symptoms in PD.
III. Explore the impact and clinical correlates of eCBT working alliances in patients with PD.

For the first aim, we hypothesize that.

i. eCBT will reduce the self-reported severity of depressive symptoms in patients with PD, as compared to patients in a control group receiving treatment as usual (TAU).
ii. eCBT will reduce the observed severity of depressive symptoms in patients with PD, as compared to patients in a control group receiving TAU.
iii. eCBT will improve self-reported health related quality of life in patients with PD, as compared to patients in a control group receiving TAU.

For the second aim, we hypothesize.

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iv. Participants in group A (early eCBT) and group B (late eCBT) will have comparable depression scores 14 weeks following the eCBT intervention.
v. A poorer long-term treatment response to eCBT for depressive symptoms is predicted by more severe self-reported comorbid symptoms of anxiety and impulse control disorders at baseline.
vi. A better long-term treatment response to eCBT for depressive symptoms is associated with greater change in self-reported co-morbid symptoms of anxiety and impulse control disorders at the time of treatment completion.

For the third aim, we hypothesize.

vii. The quality of the therapeutic working alliance, as measured by patient self-report, as well as adherence levels, will significantly predict change in self-reported depression scores.
viii. Patients self-reported working alliance scores will significantly predict the acceptability of eCBT, as defined by patient reported experience measures.

2. Methods

2.1. Study setting

This study is a decentralized national trial, recruiting from both clinical settings (i.e. neurological clinics) and allowing for self-referral by PD patients from the general population. The project is organized by the Norwegian Centre for Movement Disorders, Stavanger University Hospital, Norway.

2.2. Study design

This study is an online, randomized, delayed start trial of the effectiveness of eCBT for PD patients with depressive symptoms. N = 120 PD patients with depressive symptoms will be recruited from outpatient clinics and via self-referral in Norway, and randomized into two arms: (A) immediate 10-weeks eCBT with concurrent TAU and (B) a delayed start (14 weeks) of eCBT with TAU alone. Patients will be assessed at baseline before allocation to a specific treatment arm, with follow-up evaluations after 14, 28 and 42 weeks. See Fig. 1 for the study flow.

2.3. Recruitment procedures

A recruitment and information website will be established for the study. As well as being a recruitment portal, this website will also contain instructions on how to complete online self-report measures, and how to use the videoconference system "Join.nhn.no". The study will recruit participants in collaboration with 1) neurological clinics in all four health regions of Norway, and 2) the national user organization for people with PD in Norway (Norwegian PD Association, NPDA). The role of collaborating clinics and the NPDA is to raise awareness of the study, to inform potential participants and direct them to the bespoke study web-page. Neither the clinics nor NPDA will be required to perform any assessment of potential participants.

Potential study participants will be directed to the study website, where they will be informed about the design and goals of the study. Those visiting the website will be informed that participation is voluntary, and that they have the right to withdraw from the study at any time without the risk of repercussions or prejudice. Participants interested in joining the study are then guided to an online platform (on the TSD-platform, see details later in the protocol) to read and sign an informed consent form. After signing an informed consent form, all participants will complete an online screening procedure, consisting of a short, structured questionnaire, and self-report measures for depression and anxiety. The screening procedure includes the following: a) Screening form addressing demographic information, medical history and current symptoms, and subjective cognitive complaints; and b) Hospital Anxiety and Depression Scale (HADS). A score of >7 on HADS depression items (HADS-D) will be considered a positive screening for depression [11]. This cut-off is in line with previous studies using HADS with PD [12]. After completion of the screening procedure, participants meeting the central *a priori* inclusion criteria (see section 2.4) will be invited to a second screening after one to two weeks. Patients will also be informed that they may use the time until the second screening session to reflect on whether they want to participate in the study.

During the second screening process, participants will undergo a more comprehensive evaluation of their medical history, medication use, clinical status, cognitive functioning, and severity of neuropsychiatric symptoms. This screening will be performed by a trained study nurse over "Join.nhn.no". After the second screening, patient records will be evaluated by an interdisciplinary team (nurse and senior consultant clinical psychologist) against the criteria for major depressive disorder (MDD). The diagnosis of MDD will be assessed using the provisional diagnostic criteria for depression in PD and the MDD criteria from the Diagnostic and Statistical Manual for Mental Disorders, 5th edition [13,14]. Participants will be considered for inclusion in the study according to the core inclusion and exclusion criteria (see 2.4 study eligibility criteria). Included patients will be trained in the use of the TSD-platform while completing a set of self-report measures as part of their baseline assessment. Excluded patients will be referred on to appropriate treatment services near their area of living. For all included participants, information will passed on to the treating neurologist and general practitioner, detailing the aims of the study, information of diagnostic assessments of PD, and information of medication limitations during the trial.

2.4. Study eligibility criteria

2.4.1. Core inclusion criteria

- Signed written electronic consent
- Confirmed PD clinical diagnosis based on self-report
- A verified diagnosis of depressive disorder, according to adjusted DSM-5 criteria [14].
- Aged 35-85
- Currently using levodopa or a dopamine agonist
- Stable frequency, dosage and use of levodopa, dopamine agonists and antidepressants or other psychopharmacological medication for at least 6 weeks
- Internet access from a computer or tablet.

2.4.2. Core exclusion criteria

- Cognitive impairment as defined by MoCA Blind version scores of <18
- Suicidal thoughts with plan and intent (based on clinical interview)
- Medically unstable
- Currently receiving psychotherapeutic treatment, or in psychotherapy within the last 2 months before inclusion
- History of bipolar or psychotic disorders
- Does not speak Norwegian
- A history of neurosurgery (such as deep brain stimulation)
- No familiarity and/or access to a computer or tablet with camera, or limited internet access

2.5. Sample size and feasibility

A priori power calculations was performed using G*Power 3.1.9.2 [15,16]. Power analysis is based on power calculation for *t*-test, and it serves as a lower bound estimate of power as it applies as long as each patient has at least two measurements. Multiple observations per subject will increase the power and eliminate the impact of possible missing

observations. The study is powered to identify a mean difference in HADS-D score of 1.98 points, with $\alpha = 0.05$, power set to 80%, and a predicted effect size of Cohen's $d = 0.80$. Based on these calculations, the required number of participants is 84 (42 per group). Including N = 60 participants per group will allow for up to 30% dropout from the study, while retaining sufficient statistical power. Based on the large effect sizes observed in other RCTs investigating CBT for depression in PD [6–8], we expect the effect size to be larger and the drop out to be lower (≈10%). Participants whom decide to leave the study prematurely will not be replaced by new participants, and their data will be included in the main analysis according to an intention-to-treat principle.

There is an estimated 7000 patients with PD in Norway, of whom about 3500 are members of the patient organization the Norwegian PD Association. With a conservative frequency of 30%, depressive symptoms would affect approximately >2000 Norwegian PD patients in general, and >1000 of the members of the Norwegian PD Association. While access to computers and adequate internet bandwidth is largely ubiquitous in a Norwegian setting, familiarity with online platforms and video-conferencing could still limit recruitment for this study. However, a recent nationwide survey using similar data-gathering tools demonstrated that a large proportion of the PD community manages to use the technologies employed in this study [17]. Thus recruitment of N = 120 participants for this study is thus considered feasible.

2.6. Randomization, allocation concealment and blinding

After completion of the baseline examination, participants will be randomly assigned to either Arm A (CBT followed by TAU) or Arm B (TAU followed by CBT) using a randomized block design with 20 blocks of six participants. For participants randomized to arm A, the eCBT intervention will be initiated in short succession of the baseline visit, with 10 treatment sessions to be conducted over the next 13 weeks. The allocation key will also be stored on an access restricted research server, only accessible by key personnel.

Due to the nature of the intervention, neither patients nor therapists can be blinded to the intervention or treatment allocation. However, all video-based assessments will be performed by study personnel blinded to the treatment allocation, in order to limit the risk of bias. Participants will not be allowed to share this information during the follow up visits. During the start of each assessment, the study personel will remind the participant that they should not share whether they have received the intervention or not. Study personnel schedule assessments with the participants independently of the clinical personnel.

2.7. Interventions

After the blinded baseline assessment, participants are randomized into two arms:

Arm A: Immediate start group (see Fig. 1). Those randomized into the immediate start group will receive eCBT followed by TAU. The eCBT treatment manual (see Table 1 for a short summary of the session structure) is an adjusted version of previously published treatment manuals for neuropsychiatric symptoms in PD, to be tailored to the preferences and needs for each participant. This manual encompasses modules from manuals for both depression in PD and anxiety in PD [6,9]. Out of the nine modules in the manual, 5 are considered "core modules", while 4 can be offered depending on the patients

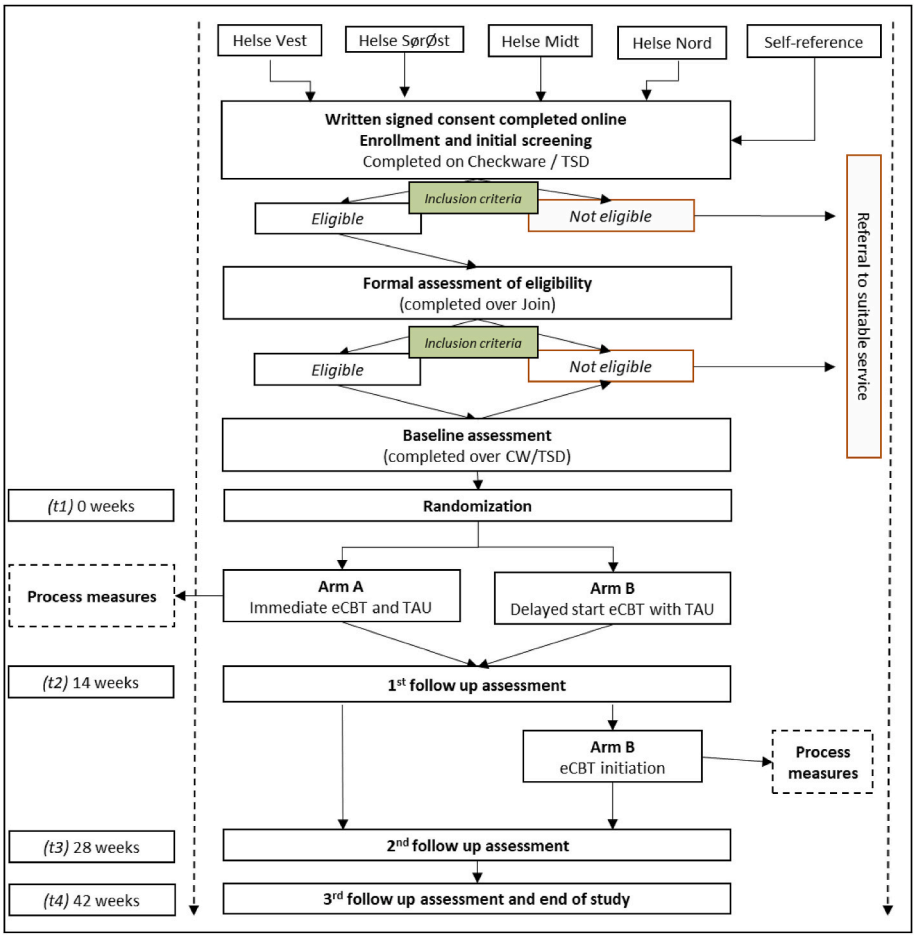

Fig. 1. Flow chart of crossover trial.

Table 1
Summary of the cognitive behavioural therapy sessions.

Session	Core modules	Aim	Estimated duration
1	x	Introduction, psychoeducation and motivational enhancement.	75–90 min
2	x	Symptom monitoring and cognitive restructuring.	60 min
3–7		Behavioural activation, exposure, relaxation techniques and imaginal exposure, worry control.	60 min
8–9	x	Problem-solving, addressing executive functioning, self-management.	60 min
10	x	Review, relapse prevention planning.	60 min

* Module refers to the module in the treatment protocol.

individual needs, allowing for Individualization of the treatment course. The participant may include partners or caregivers in the treatment. The treatment is scheduled to be completed within 13 weeks, with a maximum of ten sessions during this period. Following each eCBT session, the participant will be asked to complete a short survey evaluating session acceptability and relevance, as well as the therapeutic alliance.

Arm B: Delayed start group. Those randomized to the waiting list control arm of the study will receive TAU and wait 14 weeks before receiving the intervention. TAU will include ongoing review by the patient's primary care physician, neurologist and PD nurse. TAU does not preclude clinically indicated adjustments to medication or specialist referrals, but physicians are asked to keep medication constant if possible. After the 14 week assessment, patients will start receiving eCBT, following the same procedures described for the immediate start group.

All therapists administering CBT are trained clinical psychologists at specialist or PhD-level. Before initiation of the treatment, each CBT-therapist will undergo individual training to ensure manual adherence, fidelity and quality. During the course of the trial, each therapist will receive regular supervision from an external CBT supervisor in order to ensure continued adherence to the manual and fidelity to a CBT methodology. Supervision will be based on audio recorded therapy sessions (with consent from participants) and session records provided by the CBT-therapists, and rated using the Cognitive Therapy Adherence and Competence Scale.

Treatment adherence is monitored closely during the trial. At the beginning of each session the therapist will evaluate homework from the previous session with the patient. As a global measure of compliance, the therapist will assign a qualification of 'no', 'partial' or 'good adherence' to how the patient dealt with their homework assignment. In addition, all sessions considered core sessions need to be attended (five sessions). Missed appointments will be rescheduled where possible within the 14-week timeframe. The number of, and reason for missed optional sessions is also recorded. Participants who have not completed the five core sessions will be defined as non-completers. All costs associated with participation in this study is covered by the study.

2.8. Measures

Eligible, consenting participants will complete the baseline examination schedule over "Join.nhn.no", and receive instructions on how to use the videoconference call system. The baseline evaluation includes a clinical evaluation and cognitive assessment, performed by trained study nurses blinded for treatment allocation. For a detailed description of the examination schedule, please refer to Table 2.

2.9. Technical solutions and data storage

The ePark-CBT study will utilize two technical solutions, the video call platform "Join.nhn.no" by Norsk Helsenett (NHN), and the data-gathering platform TSD – Services for Sensitive Data by the University of Oslo (UiO). The video call platform "Join.nhn.no" by NHN offers end-to-end encrypted virtual meeting-spaces, well suited for online therapy and clinical follow up. This technology was implemented in most Norwegian health regions during the spring of 2020, and is now commonly used in clinical practice. The video call platform will be used to complete clinical evaluation at baseline (T1) and at follow up assessments (T2 to T4), as well as for the clinical intervention. The TSD - Services for

Table 2
Overview of the examination schedule.

Name of test	Test information			Time of assessment			
	Measure of	# of items	Rating type	Baseline	14 weeks	28 weeks	42 weeks
Background and clinical information							
Semi-structured interview for demographics	Demographics		Clinician	x	x[a]	x[a]	x[a]
MDS-Unified Parkinson's Disease Rating Scale (MDS-UPRDS) Part 1 – interview part [25]	Non-motor aspects of PD	6	Clinician	x			
Structured clinical interview for DSM-5 and diagnostic evaluation of depressive symptoms [11,26]	Diagnostic criteria for depression	12	Clinician	x			
Montreal Cognitive Assessment® Blind version (MoCA-B) [27]	Cognitive functioning	9	Clinician	x			
MDS-UPDRS Part 1 – selfreport [25]	Non-motor aspects of PD	20	Self	x			
Primary outcomes							
Clinical Global Impression Scale Severity (CGI-S) [28]	Symptoms severity of depression	1	Clinician	x	x	x	x
The Hospital Anxiety and Depression Scale (HADS) [29]	Symptoms of depression and anxiety	14	Self	x	x	x	x
The 8-item PD Questionnaire (PDQ-8) [30]	Health related quality of life	8	Self	x	x	x	x
Secondary outcomes							
Automatic Thoughts Questionnaire-30 (ATQ-30) [31, 32]	Depressive thoughts	30	Self	x	x	x	x
The Behavioural Activation for Depression Scale (BADS) [33]	Behavioural activation and avoidance	25	Self	x	x	x	x
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) [34]	Impulse control disorders	4	Self	x	x	x	x
The Parkinson Anxiety Scale (PAS) [35]	Anxiety symptoms	12	Self	x	x	x	x
The 20 item Negative Effects Questionnaire (NEQ) [36]	Adverse and unwanted effects for psychological treatments	20	Self		(x)*	x	x
Patient Reported Experience Measure (PREM)	Participants experiences	6	Self	Weekly, following each treatment session			
Working Alliance Inventory, short form (WAI) [37]	Working alliance between patients and the CBT-therapist	12	Self	Weekly, following each treatment session, completed by patient and CBT therapist			

*Will only be administered to patients in the intervention group at the 14 week assessment.
[a] Only questions on medication use is administered.

Sensitive Data platform will be used to gather the informed consent, for the initial screening and to gather information about the acceptability and therapeutic alliance following each session. The TSD platform provides a secure environment that meets legal requirements regarding privacy and protection of sensitive data and includes a platform for gathering of survey-based data online, termed "Sikkert-Nettskjema TSD 2". The TSD services are managed by the University of Oslo (UiO) in accordance with a data-management agreement between Helse Stavanger HF and UiO. The site and platform comply with the General Data Protection Regulation and Norwegian privacy protection laws.

2.10. Ethical approval, security, monitoring and risk

This study has been approved by the Western Norway Regional Committee for Medical and Health Research Ethics (# 87,070). GDPR approval for the project has been granted by the Norwegian Centre for Research Data (# 792,032), and Stavanger University Hospital # 3414-3414. The trial is preregistered in Clinicaltrials.gov NCT05585827.

While in Norway monitoring is not required for behavioural trials, addressing and reviewing safety aspects of this trial is paramount before and during the trial. A reference group, comprised of independent researchers on PD and CBT and a user representative, will oversee the project. The reference group will review the safety aspects of this online trial ahead of its initiation, and monitor participant safety during the trial. In case of serious adverse events (SAE), the reference group may move to suspend the trial. All study personnel providing eCBT will be also trained in a standardized procedure for dealing with acute suicidal ideation, and protocol fidelity will be monitored using the Cognitive Therapy Adherence and Competence Scale. Participants may leave the study at any time for any reason if they wish to do so, without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. Before the study initiation, study nurses will for each participant create a security card detailing contact information for emergency contacts, their general practitioner, nearby ambulatory mental health services and emergency services.

Adverse events are defined as any undesirable experience occurring to a participant during the study, which may or may not be related to the trial and procedure or experimental intervention. All spontaneously reported study-related adverse events by the subject or observed adverse events by the investigator will be recorded. Reported SAE, suspected unexpected serious adverse reactions will be reported to the reference group, Regional ethics committee and other relevant authorities without delay. For this trial, SEAs include suicide attempts, completed suicides, and psychiatric hospitalizations. Lastly, potentially adverse and unwanted events typical for psychological interventions will be measured for all participants using a validated self-report measure (NEQ).

Also, due to the online design of this study several additional security precautions will be in place before initiation of the study. These include procedures of how to address acute medical situations, such as suicidal ideation or acute psychosis. For each participants a security card, with emergency contacts, contact information to nearby emergency services, ambulatory mental health services and general practitioner, will be prepared before the initiation of interventions. These data will be gathered during the second screening/baseline assessment. In case of increased suicidal ideation during the course of treatment, clinicians will follow local clinical guidelines for increased suicidal ideation. Clinicians are free to admit patients to acute outpatient or inpatient care in case of acute suicidal ideation. Participants with acute suicidal ideation will be excluded from the study.

3. Analysis plan

All analyses in this project will be performed using IBM SPSS Statistics version 26.0.0.1 or R 4.2.1, or more recent versions if available. An alpha-level of 0.05 will be used to indicate statistical significance. Descriptive statistics will be summarized using means, median, standard deviations and ranges for numerical variables, and frequencies and percentages for categorical variables. Relevant univariate and multivariate analytic strategies will be used to test hypotheses h^{i}-h^{viii}.

For aim 1 (h^{i}-h^{iii}), linear mixed model analysis (LMM) with maximum likelihood estimation, based on an intent-to-treat protocol, will be used to gauge the between-group differences from baseline to the 14 week follow up. LMM will limit the impact of type 1 errors, and fully use the available data (in case of missing data). A random intercept for each participant and random slope will be included if they enhanced the model fit (evaluated using Akaike's information criteria and Schwarz's Bayesian criterion). In these analyses, a sum score from the primary and secondary outcomes will be used as dependent variables, and with significant covariates including treatment group, age, gender, duration of PD, and medication use. Medication use will be converted to levodopa equivalent dosages, using previously described procedures [18]. This analysis will be repeated using a per-protocol approach, where only completers (completed all core sessions) are included. Effect sizes will be calculated using Cohen's d, with pooled pre- and post-SD adjustment for sample size.

For aim 2 and 3, linear regression analysis will be used to estimate group differences in depression scores at the end of the study (h^{iv}), and the association between working alliance and acceptability (h^{viii}). Independent variables include, gender, treatment group, age, duration of PD and medication use. Predictors for treatment effect will be investigated using (h^{v}, h^{vi} and h^{vii}) LMM, as described above.

4. Discussion

CBT is the first line treatment of choice for depression in the general population [19], and a number of studies have confirmed its effectiveness in patients with PD [9,20,21]. The limited availability of this treatment, especially in specialized treatment centres, such as movement disorder clinics, motivated earlier trials to conduct CBT remotely, e.g. via telephone [6,8,22,23]. However, this is the first trial using video-assisted online CBT in this population. The great advantage of video-assisted CBT over telephone-administered CBT is the fact that patient and therapist are able to see each other, including facial expressions and body language, which may be beneficial for the working alliance. However, no information on how working alliance is affected by online-therapy exists in patients with PD.

This is the first RCT to evaluate the effectiveness of online video-assisted CBT for depressive symptoms in people with PD and to study working alliance in this online setting. By following a fully online design for gathering informed consent, assessment and treatment delivery, we are able to include patients nation-wide. This will increase the clinical applicability of our findings, and allows for future implementation in sparsely populated settings where clinical services may be physically located far away from the patient.

Choice of research design: Blinded, randomized controlled trials (RCTs) are considered the gold standard for ascertaining the efficacy and safety of a clinical intervention. The prospective RCT-design is well-suited method to evaluate the immediate and long-term effect of psychological interventions, including CBT [24,25]. For this trial, a delayed start design, where all participants over time receive the clinical intervention, was chosen for a number of reasons. Due to the duration of the trial (42 weeks) and relative high target N (N = 120), a parallel arm design is difficult to implement. Based on feedback from user representatives in the "reference group", recruitment of participants would be difficult if participants are not guaranteed treatment during the course of the trial. Also, given the relatively long duration of this RCT, keeping participants away from treatment for an extensive period of time is ethically problematic. Furthermore, a delayed start design will enable us to control for natural remission of depressive symptoms by monitoring the development of depressive symptoms in a TAU-group over the first 14 weeks. Finally, we will be able to address the treatment response not only immediately after intervention but also in a longer time

perspective, particularly in the early intervention group.

4.1. Reliance on self-report data

A possible key challenge in online trials is the reliance on self-report data. While our recruitment strategy specifically targets people with PD, the initial screening of inclusion criteria relies on self-report. This might pose an issue, with patients misremembering if they have PD or a different parkinsonian syndrome, or exaggerating complaints in order to take part in the trial. In order to prevent this potential issue, the inclusion phase is divided into two parts, where the second part also includes online clinical assessments done by a trained research nurse. This includes semi-structured interviews to assess depression, including the depression part from the Structured Clinical Interview for the DSM-5, and assessing PD severity using the UPDRS part 1. Also, the participants' treating GPs and neurologists will be informed, and asked to contact the study personnel if the patients have not in fact been diagnosed with idiopathic PD.

Online clinical trials: While hybrid approaches combining digital technologies and traditional approaches are common, this study is designed to be completely online. Online clinical trials are a promising new avenue of clinical research. Major advantages of online designs include reduced costs, increased trial efficiency, and reaching a geographically broader population in recruitment of participants, and when proven effective, will give more patients access to specialized expertise [26]. Indeed, significant barriers may hinder older adults living in rural areas from participating in in-person clinical trials [27]. However, implementation of an online RCT relies on sufficient digital infrastructure and competence in the target population. Stable, affordable, and available access to a fast internet connection is a necessity to ensure the representativeness in recruitment. The general digital competence of the target population is also essential to ensure successful participation. In this study the target population is comprised of people with PD, whom are predominantly elderly. In Norway, the digital literacy of seniors is generally high, especially among male seniors [28]. Also, regulatory limitations, in particular for how to gather informed consent from participants, may hinder implementation of a fully online trial.

4.2. Role of working alliance on CBT effectiveness

Previous trials on CBT for PD have failed to take into account important variables pertaining to the efficacy of psychotherapeutic interventions. The working alliance, a pan-theoretical concept in psychotherapy which comprises the agreement between patient and therapist on therapeutic goals, their consensus on how to achieve those goals, as well as their interpersonal bond, has been robustly associated with treatment outcomes in CBT [29]. In PD, CBT-trials have shown heterogeneity in effect sizes [3], which can be a direct result of unmeasured differences in working alliance in their designs. CBT-protocols for groups, telephone-administered brief CBT, and videoconference have all showed merit in previous studies, but the nature of developing therapeutic alliances has not been explored in previous studies [3,6,8,23]. Thus, development of flexible, generic CBT manuals which take into account the variability in working alliance, is called for. This is especially prudent for CBT-protocols using innovative modes of delivery.

5. Conclusion

This is the first RCT of online video-assisted CBT for depression in patients with PD. It is novel not only in this way, but also in explicitly assessing the working alliance between patient and therapist, and the fact that the intervention will be done entirely online. If proven effective, it will bring highly specialized expertise to a greater number of patients.

Authors roles

Aleksander H. Erga: Conceptualization, funding acquisition, methodology, project administration, writing – original draft.

Guido Alves: Conceptualization, supervision, writing – review & editing.

Albert F.G. Leentjens: Methodology, writing – review & editing.

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Data availability

No data was used for the research described in this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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