Research paper

The effect of smartphone-based monitoring and treatment on the rate and duration of psychiatric readmission in patients with unipolar depressive disorder: The RADMIS randomized controlled trial

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ABSTRACT

Background: Patients with unipolar depressive disorder are frequently hospitalized, and the period following discharge is a high-risk-period. Smartphone-based treatments are receiving increasing attention among researchers, clinicians, and patients. We aimed to investigate whether a smartphone-based monitoring and treatment system reduces the rate and duration of readmissions, more than standard treatment, in patients with unipolar depressive disorder following hospitalization.

Methods: We conducted a pragmatic, investigator-blinded, randomized controlled trial. The intervention group received a smartphone-based monitoring and treatment system in addition to standard treatment. The system allowed patients to self-monitor symptoms and access psycho-educative information and cognitive modules. The patients were allocated a study-nurse who, based on the monitoring data, guided and supported them. The control group received standard treatment. The trial lasted six months, with outcome assessments at 0, 3, and 6 months.

Results: We included 120 patients with unipolar depressive disorder (ICD-10). Intention-to-treat analyses showed no statistically significant differences in time to readmission (Log-Rank p=0.9) or duration of readmissions (B=-16.41,95%CI:-47.32;25.5,p=0.3) (Primary outcomes). There were no differences in clinically rated depressive symptoms (p=0.6) or functioning (p=0.1) (secondary outcomes). The intervention group had higher levels of recovery (B=7,29, 95%CI:0.82;13,75,p=0.028) and a tendency towards higher quality of life (p=0.07), well-being (p=0,09) satisfaction with treatment (p=0.05) and behavioral activation (p=0.08) compared with the control group (tertiary outcomes).

Limitations: Patients and study-nurses were unblinded to allocation.

Conclusions: We found no effect of the intervention on primary or secondary outcomes. In tertiary outcomes, patients in the intervention group reported higher levels of recovery compared to the control group.

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1. Introduction

Unipolar depressive disorder is a common mental illness with a lifetime prevalence of 15-20% (Kessler et al., 2003). Unipolar depressive disorder is the leading cause for all Years Lived With Disabilities (YLDs) among mental illnesses (Rehm and Shield, 2019) and burden society with high health care costs (Olesen et al., 2012). Patients with unipolar depressive disorder are often hospitalized, with high costs to patients and society (Ekman et al., 2013; Health, 2018). The period following discharge is a high-risk period with an increased risk of suicide and readmission (Hansen et al., 2012; Kessing et al., 2004; Mortensen et al., 2000). In the case of relapse of symptoms following discharge, real-time reporting of symptoms might not be available to the clinicians in standard clinical settings. Approaches allocating the right treatment to the right patient at the right time are warranted to prevent relapse and readmissions and allocate the limited treatment resources appropriately. New technologies and treatment modalities seek to address this treatment gap (WHO, 2011).

Today, a median of 76% of adults in 18 advanced economies report having a smartphone (Taylor, 2019), and many people use a smartphone on a daily basis (Ericsson, 2018). Smartphones comprise a unique platform for real-time monitoring and treatment. Smartphone-based treatment tools in psychiatry are receiving increasing attention among researchers, clinicians, and patients (Miralles et al., 2020). The ambitions of delivering high-quality, effective, and timely interventions to more patients at a lower cost are driving forces. Nonetheless, despite the hype, current clinical evidence is sparse (Hidalgo-Mazzei et al., 2020; Tønning et al., 2019), and randomized controlled trials (RCTs) on smartphone-based treatments in psychiatry are essential to provide this evidence. However, existing RCTs lack methodological rigor and robust objective outcome measures (Tønning et al., 2019).

Our group has previously conducted the MONARCA I and II trials, showing that smartphone-based monitoring and treatment was useful, feasible, and valid for monitoring symptoms in patients with bipolar disorder. The MONARCA I and II trials found no effect of smartphone-based monitoring and treatment on depressive and manic symptoms, but a higher quality of life and reduced perceived stress in patients receiving smartphone-based monitoring and treatment (Faurholt-Jepsen et al., 2019; Faurholt-Jepsen et al., 2015).

Previous reviews have identified several RCTs on the effects of smartphone-based treatments on depressive symptoms (Firth et al., 2017; Linardon et al., 2019). However, many of the included trials measured depressive symptoms in other diagnoses, conditions, and non-clinical samples (e.g., self-reported depression, anxiety, sleep disorders, and the general population). A recent review by the authors (Tønning et al., 2019) identified only seven RCTs investigating the effect of smartphone-based treatment in patients with a validated diagnosis of a depressive disorder (Hur et al., 2018; Ly et al., 2015; Ly et al., 2014; Mantani et al., 2017; Roepke et al., 2015; Stiles-Shields et al., 2019; Watts et al., 2013). Moreover, only one of these RCTs (Mantani et al., 2017) was conducted in a clinical setting, and the remaining RCTs recruited patients online and validated the diagnosis using questionnaires as well as telephone interviews (Hur et al., 2018; Ly et al., 2015; Ly et al., 2014; Roepke et al., 2015; Stiles-Shields et al., 2019; Watts et al., 2013). Previous non-RCT studies have shown that self-monitoring is feasible in patients with unipolar depressive disorder following discharge from the hospital (Lauritsen et al., 2017).

Thus, limited RCT-research concerning the use of smartphone-based monitoring and treatment in patients diagnosed with unipolar depressive disorder has been published in general, even less in clinical settings and none concerning patients following discharged from psychiatric hospitalization.

Therefore, we conducted the Reducing the rate and duration of readmission among patients with unipolar depressive disorder trial (the RADMIS trial) and hypothesized that add-on of a smartphone-based monitoring and treatment system to standard care would reduce the rate and duration of readmissions compared to the standard treatment in patients diagnosed with unipolar depressive disorder following discharge from psychiatric hospitalization for a depressive episode.

We expected that by using the smartphone-based system, it would be possible to catch relapses in an earlier stage, intervene adequately, and hereby, prevent readmissions. Furthermore, we expected that if readmission were necessary, a more timely readmission would lead to a shorter duration of readmissions.

2. Methods

The present trial is reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher et al., 2012), with additions from the consort E-health guidelines (Eysenbach, 2011). Further details concerning design and methods have previously been published (Faurholt-Jepsen et al., 2017).

2.1. Design, settings, and patients

The RADMIS trial was a pragmatic, parallel-group, rater-blinded randomized controlled trial with a balanced randomization ratio (1:1) of adult patients with unipolar depressive disorder with a 6-months follow-up period. Patients with a diagnosis of unipolar depressive disorder were recruited from psychiatric hospitals in The Capital Region in Denmark, corresponding to 1.6 million people during the period from May 2017 to August 2019.

Inclusion criteria: Age over 18 years; unipolar depressive disorder diagnosis according to the International Classification of Diseases, version 10 (ICD-10) using Schedules for Clinical Assessments in Neuropsychiatry (SCAN) (Wing et al., 1990); discharge from a psychiatric hospital following hospitalization for a depressive episode.

Exclusion criteria: Pregnancy; insufficient Danish language skills; any kind of compulsory hospitalization or treatment at the time of inclusion.

We had no upper age limit or exclusion of patients with comorbidities, including alcohol/drug abuse, as long as they had a primary diagnosis of unipolar depressive disorder. Patients were included in the trial as close to the day of discharge as possible, with a 14 days margin in both ends.

2.2. Randomization and allocation

The included patients were randomized with a balanced ratio of 1:1 to either 1) the intervention group with active use of the smartphone-based monitoring and treatment system + standard treatment or 2) the control group (standard treatment alone). Numbered, sealed, and opaque envelopes were provided by the Pharma Consulting Group (http://www.pharmaconsultinggroup.com), who generated random allocation numbers with random block sizes (6-10). Randomization was stratified according to the psychiatric center from which the patients were discharged (five centers) and the number of previous psychiatric admissions (0-3 or >3). The envelopes were stored in a locked cabinet of an unknown location to the blinded researchers.

2.3. Blinding

The RADMIS trial was a single-blinded trial. Due to the nature of the intervention, it was not possible to blind patients nor the study nurses. Researchers responsible for outcome assessments, data entry, data analyses, interpretation of analyses, and writing of papers (MLT and MFJ) were kept blinded to allocation. In the case of unblinding, the patients were seen by another researcher.

2.4. Intervention

2.4.1. Intervention group

Following discharge, patients allocated to the intervention group received multimodal monitoring and treatment based on a smartphone-based system (the Monsenso system). The smartphone-based system builds upon the MONARCA system previously developed and used by our research group (Bardram et al., 2013; Bardram et al., 2012; Faurholt-Jepsen et al., 2019; Faurholt-Jepsen et al., 2015). Based on a user-centered design process, the system was improved and adapted to fit patients with unipolar depressive disorder. The Monsenso system consists of several modules with various functions:

2.4.2. Symptom monitoring and clinical feedback loop

The smartphone-based system collected data through daily patient-reported entries (subjective data: e.g., mood, sleep, and activity) and automatically collected smartphone sensor data (objective data: e.g., phone usage, mobility measures, and voice features). Information was presented to the patient for self-monitoring on their smartphone screen and the study nurse on a desktop-computer (Faurholt-Jepsen et al., 2014).

The study nurses checked the data three times a week and reacted according to the data presented, providing a double feedback loop between the study nurse and the patient (Fig. 1). Daily notifications reminded patients to fill out self-rating questions. In the case of several missing days, patients were contacted by the study nurse.

2.4.3. Smartphone-based cognitive behavioral therapy

The smartphone-based cognitive-behavioral therapy (CBT) modules included psychoeducation, cognitive restructuring, and rumination-focused CBT. The psychoeducation was delivered as both text and small cartoons and include strategies for detecting and intervening with early signs of relapse.

Patients were encouraged, as a minimum, to fill in the daily self-rating, which would take 2-5 minutes. Based on the patients' needs, skills, and clinical status, the remaining functions in the app would be used based on an individual assessment by the patient and the study nurse on how to best help the patient. Further details concerning the smartphone-based monitoring and treatment system and technical aspects are described in the study protocol (Faurholt-Jepsen et al., 2017).

2.4.4. Changes in the intervention during the trial

During the trial period, there were no long-lasting breakdowns. However, several times one or more functions were unavailable for a period of maximum 1-2 days. The psychoeducation module and the cognitive restructuring and rumination-focused CBT were shortly delayed and added to the app at the beginning of the trial period.

2.4.5. Control group and standard treatment

The patients who were randomized to the control group received standard treatment. The control group had the smartphone app installed on their smartphone to collect objective data, but with no access to the content of the smartphone-based system.

All patients received standard treatment, decided by their treating physician with no restrictions, regardless of their allocation. Outpatient treatment in Denmark is given either by the patients' family doctor (general practitioner), by a private psychiatrist, in an outpatient clinic with monthly consultations, or in an intensive, multidisciplinary outpatient clinic with psychiatrists, psychologists, and nurses. The treatment options consist of psychopharmacology, psychotherapy, various nurse-guided support, psychoeducation, and physical activity. Treatment is public and in large free of charge. Patients can be readmitted through psychiatric emergency rooms, or by referral/recommendation of treatment-system and various 24/7 phone helplines.

2.5. Outcomes and assessments

Outcome measures were defined a priori (Faurholt-Jepsen et al., 2017). Outcome assessments and baseline interviews were conducted by research-trained, non-specialist, medical doctors (MLT, MFJ, SAM, DTP) who were blinded to allocation status. Outcome assessments were done at 0, 3, and 6 months. Assessors and researchers had access to patients' electronic medical records. If a patient was admitted at the time for a follow-up assessment, the researchers visited the ward. If follow-up was not possible face to face in any way, it was done via telephone. Secondary and tertiary outcome measures were regarded as valid within +/- 14 days for the scheduled date for outcome assessment.

Primary outcomes: The rate and accumulated duration of psychiatric readmissions. Readmissions were assessed at follow-up visits and by checking the electronic medical records. Secondary outcomes: Severity of depressive symptoms measured using the Hamilton Depression Rating Scale 17-items (HDRS-17) (Hamilton, 1960); Psychosocial functioning according to the Functional Assessment Short Test (FAST) (Rosa et al., 2007); Number of depressive episodes defined as HDRS-17> 13. Tertiary outcomes: Paper-based questionnaires on Perceived stress according to Cohen's Perceived Stress Scale (PSS) (Cohen et al., 1983); Quality of life according to the WHO Quality of Life-BREF (WHO-QOL-BREF) (1998); Self-rated depressive symptoms according to Beck's Depressive Inventory (BDI) (Beck et al., 1961); Self-rated depressive symptoms according to the Hamilton Depression Self-rating Scale 6-item (HAM-D6) (Bech et al., 1981; Bech et al., 1975); Recovery according to the Recovery Assessment Scale (RAS) (Corrigan et al., 2004) Empowerment according to Roger's Empowerment Scale (Rogers et al., 1997); Adherence to medication according to the Medicine Adherence Rating Scale (MARS) (Fialko et al., 2008; Thompson et al., 2000); Wellbeing according to the WHO (five) (WHO5) Wellbeing Index (Bech et al., 2003); Rumination according to the Ruminative Response Scale (RRS)
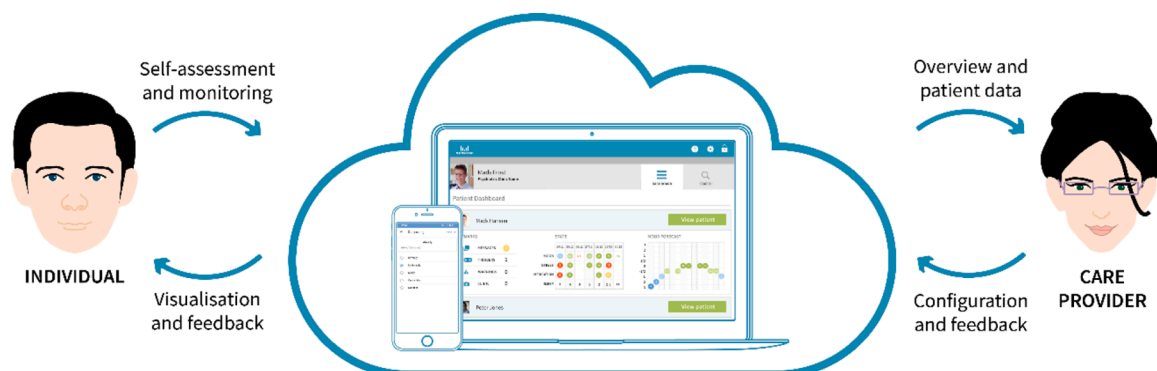

Fig. 1. The double feedback loop between patient and study-nurse, with Monsenso system displayed in the middle.

(Treynor et al., 2003); Worrying according to the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990); Satisfaction with care according to the Verona Satisfaction Scale-Affective Disorder (VSS-A) (Kessing et al., 2006); Behavioral Activation for Depression Scale (BADS) (Kanter et al., 2006).

2.6. Statistical analyses

The statistical analyses were defined á priori (Faurholt-Jepsen et al., 2017) and conducted using an intention-to-treat (ITT) approach. The sample size calculations on primary and secondary outcomes are described in detail elsewhere (Faurholt-Jepsen et al., 2017). The ITT analysis includes all randomized participants regardless of the adherence to treatment. Differences in the primary outcome (readmission) were investigated using survival analysis with reasons for censoring being death, leaving the country, or end-of-study, and event being the first day of the first readmission. Time was calculated from the day of the discharge. Proportional hazards were assessed by goodness of fit models and graphical presentation.

Differences in the duration of readmissions were investigated, for patients who were readmitted, in a general linear model regression analysis using parametric statistics. First, in an unadjusted model with allocation status (intervention or control) as the independent variable and the total number of days admitted during the trial as the dependent variable. Further, in a model adjusted for the stratification variables, age, and sex.

Differences in secondary and tertiary outcomes were calculated using two-level linear mixed effect models, including a fixed effect of visit number and a patient-specific random effect (Table 2). Level 1 represented intra-individual variation in repeated outcome measures of symptoms (e.g., HDRS-17), and level 2 represented repeated inter-individual variation. Differences in outcomes between the intervention group and the control group were analyzed in: Model 1, adjusting for differences in baseline values of the outcome variable and the two stratification variables (1) psychiatric center and (2) the number of prior hospitalizations (0-3 or >3); in Model 2, adjusting further for age and sex, and in Model 3 further adjusting for scores on the HDRS-17 (except for measures of depression). Potential interactions between randomization group and visit number on any specific outcome variable were investigated and reported if significant. Linear mixed model analysis implicitly imputes missing data from dropouts under the assumption that these are missing at random. As such, handling missing data is embedded in the procedure.

For subanalyses, we calculated the six core depression items (HDRS-6) of the HDRS-17. Further, we used cox regression analysis to calculate the hazard ratio of developing a depressive episode (HDRS-17 > 13) during the trial for patients in remission (HDRS-17 <13) at baseline, using follow-up visits as time.

Model assumptions with analyses of residuals and covariance were calculated and assessed for all outcomes. Missing items in the questionnaires were not included in the summed scores, and no imputations or assumptions on missing items were made. Single questionnaires with more than 20 % missing items were discarded.

The statistical threshold for significance was p≤ 0.05 (two-tailed). Analyses were done using IBM SPSS statistics version 25.

3. Ethical considerations

Ethical permission was obtained from the ethics committee in The Capital Region of Denmark (H-16046093) and The Data Agency (RHP-2017-005, I-Suite: 05365). The law on handling personal data, as well as the European General Data Protection Regulation (GDPR) was respected. The trial was registered at ClinicalTrials.gov as NCT03033420. All researcher collected data was stored in Research Electronic Data Capture (REDCap) electronic data capture tools (Harris et al., 2019; Harris et al., 2009). Electronic data from the Monsenso app was stored by

Monsenso with a data-storage-agreement between Monsenso and The Capital Region of Copenhagen. All patients were given written and oral information and gave informed consent, according to the Helsinki declaration. Any desire to leave the trial was accepted. Patients were encouraged to continue their participation, however, not compromising their safety or wellbeing. In case of significant concerns regarding the patients' condition (i.e., high suicidality), relevant precautions were taken to secure the safety of the patients. Study-nurse and researchers consulted professor LVK for supervision when needed.

Patients could use their own smartphones. Alternatively, they were offered to loan an Android-based smartphone free of charge during the trial period and instructed to use it as their primary phone. Any travel expenses concerning the trial were refunded. The patients received no additional payment or gifts.

4. Results

4.1. Background characteristics

Fig. 2 presents the flow of patients in the RADMIS trial. During the trial period, a total of 609 patients with unipolar depressive disorder from psychiatric hospitalization were assessed for eligibility. Of these, a total of 158 were excluded for various reasons (e.g., change in diagnosis (n=48), not deemed capable of participating in research by ward staff or study nurse (n=55)). A total of 81 patients were discharged before it was possible to invite for participation, and 188 patients did not wish to participate (not wanting to or able to use a smartphone, did not want to monitor, or did not want further contacts). Finally, a total of 62 patients were interested in participation and followed until discharge; however, upon inclusion, they could not oversee participation/did not show up or did not return calls and were not included, randomized, or assed further. Thus, a total of 120 patients were included and randomized to either the intervention group or the control group. The last patient's last visit for outcome assessment was in March 2020. Sociodemographic and clinical characteristics at baseline are presented in Table 1. All patients had been diagnosed with moderate-severe depression during the hospitalization leading to the inclusion, with a high amount of comorbidity (22% of patients in the active arm and 29% in control arm) and thus composed a group of severely ill patients.

4.2. Assessments adherence and intervention

The number of patients completing intervention and assessments can be seen in Fig. 2. Two patients were included without sufficient consent to assess medical records. They did not show up for follow-up visits and provided no further data than baseline. In three cases, patients were rated by an unblinded assessor. Seven patients in the intervention group withdraw from the trial, with the intervention as the explicit reason: (found monitoring stressful (n=3) could not oversee it (n=3) or did not find it helpful (n=1)). They all dropped out between 27-89 days after inclusion and had an average of 25 days of self-monitoring (range: 7-50; SD=4.6). Additional five patients discontinued the intervention before the end of the trial (lost contact or change of diagnosis). They had an average of 41.6 days of self-monitoring (range: 20-90; SD=30,1). The remaining patients (n=47) had regular contact with study nurses and registrations throughout the trial period but with variation in use depending on the patients' needs and abilities. The average number of days with self-monitoring for these patients was 151 (range 49-198; SD=34).

During the trial period, the study nurse registered 143 text correspondences, 303 telephone conversations, and 73 face to face conversations with patients from the intervention group.

Both groups received equally high levels of standard treatment: A total of 82.5 % of all patients were treated in hospital-based outpatient clinics, with 87% of these receiving frequent multidisciplinary treatment often on a weekly basis. The 17.5% not treated in a hospital setting were
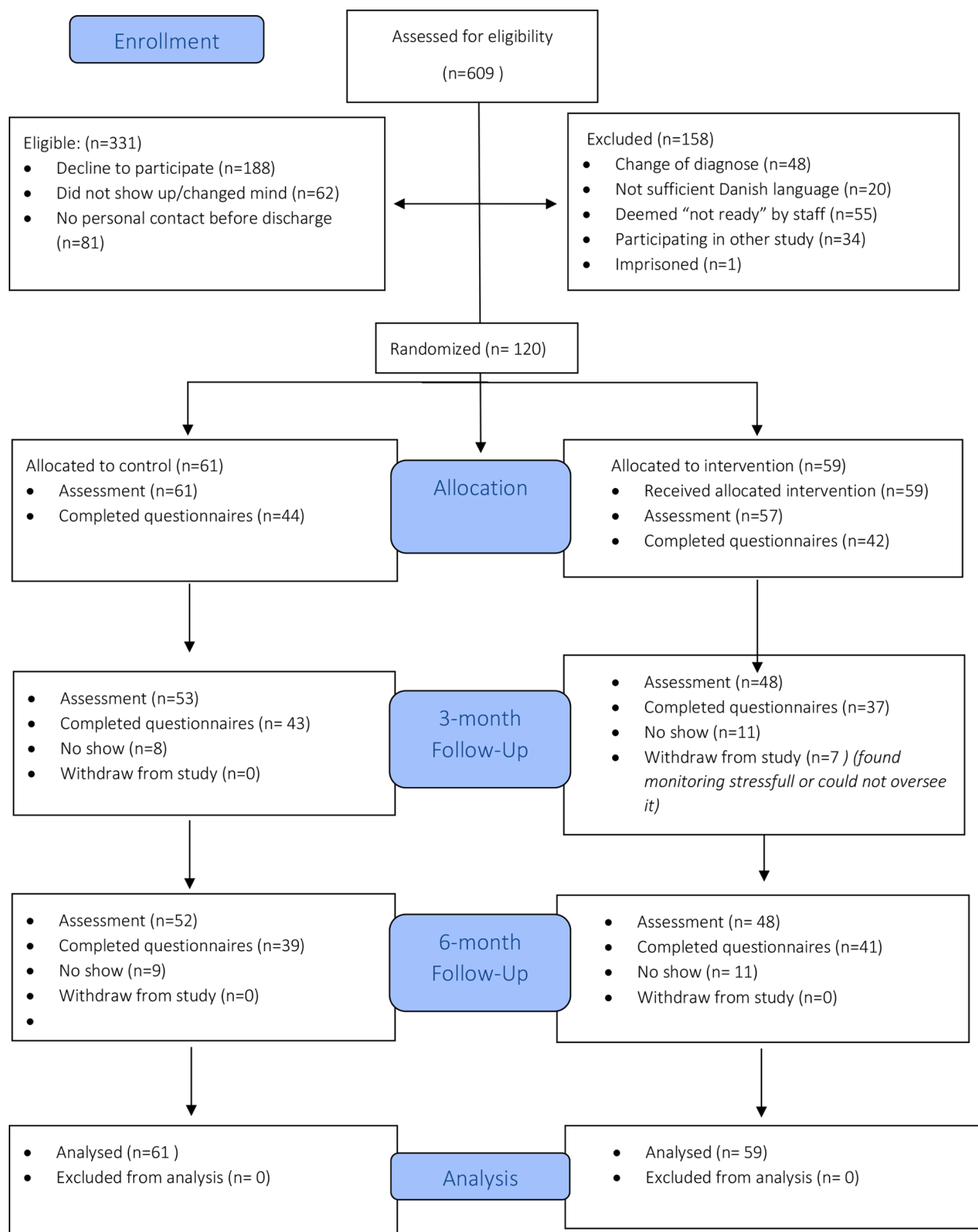
Enrollment

Assessed for eligibility
(n=609)

Eligible: (n=331)
- Decline to participate (n=188)
- Did not show up/changed mind (n=62)
- No personal contact before discharge (n=81)

Excluded (n=158)
- Change of diagnose (n=48)
- Not sufficient Danish language (n=20)
- Deemed "not ready" by staff (n=55)
- Participating in other study (n=34)
- Imprisoned (n=1)

Randomized (n= 120)

Allocated to control (n=61)
- Assessment (n=61)
- Completed questionnaires (n=44)

Allocation

Allocated to intervention (n=59)
- Received allocated intervention (n=59)
- Assessment (n=57)
- Completed questionnaires (n=42)

Assessment (n=53)
- Completed questionnaires (n= 43)
- No show (n=8)
- Withdraw from study (n=0)

3-month
Follow-Up

- Assessment (n=48)
- Completed questionnaires (n=37)
- No show (n=11)
- Withdraw from study (n=7) *(found monitoring stressfull or could not oversee it)*

- Assessment (n=52)
- Completed questionnaires (n=39)
- No show (n=9)
- Withdraw from study (n=0)
-

6-month
Follow-Up

- Assessment (n= 48)
- Completed questionnaires (n=41)
- No show (n= 11)
- Withdraw from study (n=0)

- Analysed (n=61)
- Excluded from analysis (n= 0)

Analysis

- Analysed (n= 59)
- Excluded from analysis (n= 0)

Fig. 2. The RADMIS flow diagram of inclusion and completion of patients, including number of patients completing outcomes assessments.

either treated by a general practitioner (5 %), private psychiatrist (9.2%), unknown (1.7 %), or received no treatment (1.7%).

4.3. Primary outcomes

4.3.1. Differences between the intervention group and the control group in rates of readmissions

Differences between the intervention group and the control group in rates of readmission are presented as a Kaplan-Meier survival curve in **Fig. 3**. No statistically significant differences between the two groups

Table 1

Sociodemographic and clinical characteristics of included patients at baseline, N=120

Randomization group (N)	Intervention (59)	Control (61)
Sociodemographic data		
Age, years	44.5 (14.0)	43.4 (14.3)
Female sex, % (n)	47.5 (28)	57.4 (35)
Years of education after primary school	4.5 (2.6)	5.5 (3.11)
Highschool, % (n)	55.9 (33)	63.9 (39)
University degree, % (n)	16.9 (10)	32.8 (20)
In relationship, % (n)	44. 1 (26)	54.1 (33)
Smartphone usage		
iPhone, % (n)	49.2 (29)	55.7 (34)
Years with smartphone	5.45 (2.1)	6.88 (23)
Borrowing smartphone during the trial, % (n)	6.8 (4)	4.9 (3)
Clinical history		
Hamilton Depression Rating Scale score at baseline	14.5 (5.77)	13.9 (6.26)
Received ECT during hospitalization % (n)	27.1 (16)	23 (14)
Psychiatric comorbidity, % (n)	37.3 (22)	47.5 (29)
Substance abuse, % (n)	10.2(6)	16.4 (10)
Previous suicide attempts, % (n)	27.1(16)	37.7 (23)
Previews received CBT % (n)	37.3 (22)	62.3 (38)
Age at first episode, years	33.3 (14.5)	31.8 (13.9)
Duration of psychiatric hospitalization leading to inclusion, days	35 [25-57]	38 [28-71]
Depressive episodes, number	3 [2-6]	3 [2-5]
Previous psychiatric hospitalizations, number	1 [1-3]	2 [1-3]
Data are mean (S.D.), median [IQR] or % (n) unless otherwise stated		

were found on this primary outcome (log Rank test p=0.9). The survival probability of not being readmitted within the six months following discharge was 0.77 (95%CI:0.67;0.89) in the intervention group and 0.77 (95%CI: 0.67; 0.88) in the control group. Hazard Ratio for readmission in the intervention group compared to the control group was 0.95 (95%CI:0.45;2.02, p=0.9). One patient left the country after 130 days and was censored at the corresponding date.

4.3.2. Differences between the intervention group and the control group in the accumulated duration of readmissions

In the intervention group, 13 patients were readmitted for a total of

458 days. Eight patients were readmitted once, four patients were readmitted twice, and a single patient was readmitted three times. In the control group, 14 patients were readmitted for a total of 723 days. Nine patients were readmitted once, and five patients were readmitted twice. The average length of readmittances among those who were readmitted was 35.2 days (SD=32.6) in the intervention group and 51.6 days (SD=44.0) in the control group. However, a few patients in each group constituted the majority of the total days in the hospital during the trial. The two groups were compared in an unadjusted linear regression model (B= -16.41, 95%CI: -47.32; 25.5, p=0.3), and a model adjusting for the two stratification variables (psychiatric center and the number of previous hospitalizations), age and sex (B= –12.76, 95% CI: -44.42; 18.9, p=0.4). There were no statistically significant differences between the two groups in this primary outcome of the accumulated duration of readmissions.

4.3.3. Exploratory analyses on the primary outcome

We conducted several exploratory subanalyses in relation to the primary outcome, stratifying on stratification variables, age, sex, and comorbidity as well as analysis on admittances longer than three days and possible early or late effect. There were no significant results on any of the models, and estimates are therefore not reported. Further, we incorporated data on adherence to the survival analysis: We used the percentage of days with completed self-monitoring as an operational proxy for adherence to the intervention as a whole. The median value of 80% completed days of self-monitoring was used to divide the intervention group into two groups. We compared the groups using Kaplan Meier curves, with corresponding log Rank test. We found no statistically significant differences between the two groups (log Rank test p=0.93). We applied similar analyses for various levels of adherence with no relevant nor statistically significant findings.

Additionally, to reduce confounding, we calculated adherence in the first 28 days. The intervention group was divided as above based on initial adherence levels. We conducted survival analysis for the subsequent trial period to calculate differences in risk of readmission following the first 28 days based on initial adherence. There were no relevant or statistically significant differences between various levels of initial adherence.
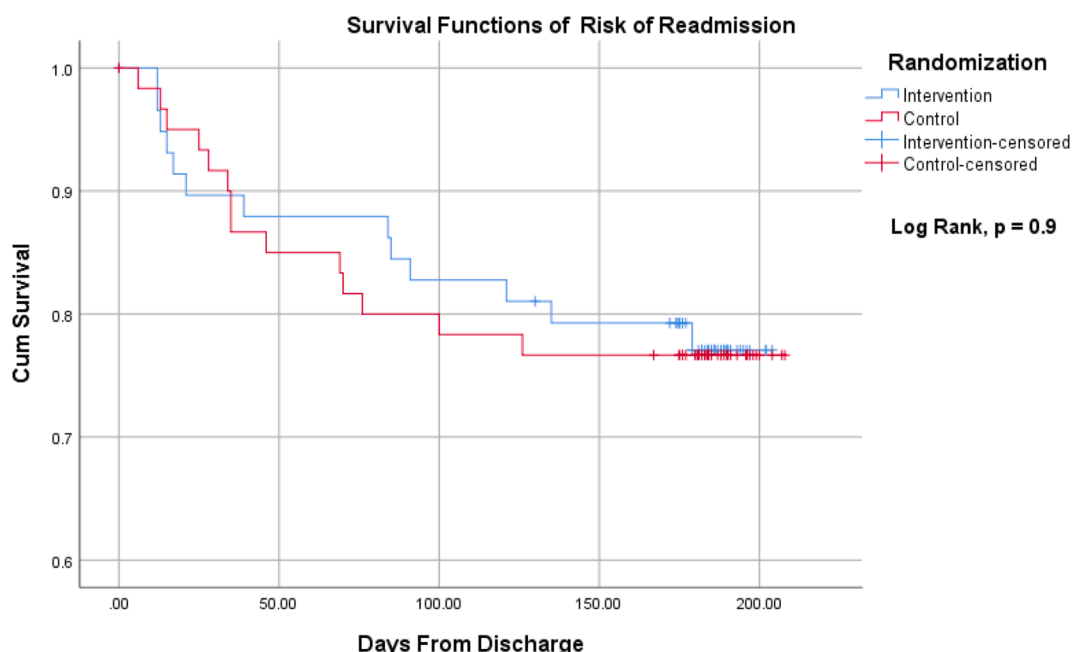
Fig. 3. Kaplan-Meier survival curve of the ITT analysis on time to readmission with the corresponding Log Rank test.

4.4. Secondary outcomes

Differences between the intervention group and the control group on secondary outcomes (HDRS-17 and FAST) and tertiary outcomes (questionnaires) are presented in Table 2. As can be seen, in models adjusting for baseline values of the outcome variable and the two stratification variables (Model 1), further adjusting for age and sex (Model 2), and further adjusting for HDRS-17 scores (except for outcome measures of depression) (Model 3), there were no statistically significant differences between the intervention group and the control group in the secondary outcomes (HDRS-17: Model 2; B= 0.62, 95% CI: -1.81; 3.05, p= 0.6. FAST: Model 3; B= -2.78, 95% CI: -6.19; 0.63, p=0.1) (Table 2).

Explorative analyses on the HDRS-17 were conducted on subgroups of patients based on their baseline scores on the HDRS-17. We used cut-offs at 7 "symptom-free"and 14 "depressive."All analyses were statistically non-significant.

Survival analyses using Cox regression on the risk of developing a depressive episode (HDRS >13) during the trial period for patients presenting with HDRS score< 14 at baseline are also presented in Table 2. There was no statistically significant difference in the hazard rate between the two groups (Model 2: HR= 0.88, 95%CI: 0.31; 2.48, p=0.8).

4.5. Tertiary outcomes

Tertiary outcomes were calculated like secondary outcomes and are presented in Table 2. All tertiary outcomes were insignificant in model 1 and model 2. In model 3, further adjusting for HDRS-17 scores, there were statistically significantly higher levels of recovery measured using the RAS in the intervention group compared with the control group (Model 3; B= 7.29, 95% CI: 0.82; 13.75, p=0.028). Further, in model 3 there was borderline statistically significantly higher levels of quality of life measured by WHOQOL, higher levels of wellbeing measured by WHO5, higher satisfaction with care measured using the VSSA and higher levels of behavioral activation measured using the BADS in the intervention group compared with the control group: (WHOQOL: Model 3; B= 4.09, 95% CI: -0.30; 8.47, p= 0.067) (WHO5: Model 3; B= 1.59, 95% CI: -0.027; 3.44, p=0.092) (VSSA: Model 3; B= 7.80, 95% CI: -0.025; 15.63, p=0.051) (BADS: Model 3; B= 8.00, 95% CI: -0.88; 16.88, p=0.076). The remaining tertiary outcomes were insignificant.

4.6. Post hoc statistical power analysis based on the obtained sample size

The trial included 120 patients, which was less than the calculated sample size of 200 patients (Faurholt-Jepsen et al., 2017). Despite

Table 2
Estimated differences between the intervention group and the control group (control group serve as reference) on secondary and tertiary outcomes, N=120.

* Indicates that a large score is favorable to the patient	Model 1[a]			Model 2[b]			Model 3[c]		
Secondary outcome	Difference between groups	95 % CI	p	Difference between groups	95% CI	p	Difference between groups	95% CI	p
HDRS-17	0.36	-2.07; 2.78	0.77	0.62	-1.81; 3.05	0.61	-	-	-
FAST	-3.13	-8.13; 1.86	0.22	-2.76	-7.82; 2.30	0.28	-2.78	-6.19; 0.63	0.11
Subanalyses on secondary outcomes									
HDRS-6	0.25	-1.12; 1.62	0.72	0.41	-0.95; 1.77	0.55	-	-	-
	Hazard Ratio	**95 % CI**	**p**	**Hazard Ratio**	**95 % CI**	**p**			
Depressive episode (COX) (n=54)	1.11	0.41; 2.97	0.84	0.88	0.31; 2.48	0.81	-	-	-
Tertiary outcome	Difference between groups	95 % CI	p	Difference between groups	95% CI	p	Difference between groups	95% CI	p
PSS	-0.90	-4.65; 2.85	0.63	-0.84	-4.71; 3.02	0.66	-1.26	-3.75; 1.24	0.32
WHOQOL Bref*	1.30	-5.04; 7.64	0.68	1.78	-4.49; 8.04	0.57	4.09	-0.30; 8.47	**0.067**
BDI 21	-0.46	-4.43; 3.52	0.82	-0.50	-4.62; 3.62	0.81	-	-	-
HAM-D6 self-rating	-0.39	-2.46; 1.68	0.71	-0.27	-2.42; 1.88	0.80	-	-	-
RAS*	5.73	-2.31; 13.77	0.16	7.60	-0.32; 15.52	**0.06**	7.29	0.82; 13.75	**0.028**
Rogers Empowerment*	-0.99	-4.76; 2.78	0.60	-0.71	-4.67; 3.25	0.72	-0.76	-4.52; 3.00	0.68
MARS*	0.46	-0.28; 1.20	0.22	0.43	-0.35; 1.21	0.27	0.43	-0.35; 1.22	0.27
WHO-5*	1.03	-1.56; 3.63	0.43	0.99	-1.62; 3.59	0.45	1.59	-0.27; 3.44	**0.092**
RRS	2.67	-3.06; 8.40	0.35	2.68	-3.31; 8.66	0.37	2.58	-2.56; 7.72	0.32
PSWQ	1.08	-5.07; 7.22	0.73	1.38	-4.90; 7.65	0.66	1.02	-4.31; 6.36	0.70
VSS-A*	6.03	-2.06; 14.12	0.14	-	-	-	7.80	-0.025; 15.63	**0.051**
BADS*	6.66	-6.07; 19.39	0.30	7.60	-5.23; 20.44	0.24	8.00	-0.88; 16.88	**0.076**

BADS= Behavioral Activation for Depression Scale, BDI 21= Beck's Depressive Inventory 21 item, FAST= Functional Assessment Short Test, HAM-D6= Hamilton Depression Self-rating Scale 6-item, HDRS-17= Hamilton Depression Rating Scale 17-items, HDRS-6= Hamilton Depression Rating Scale 6-items subscale, MARS= Medicine Adherence Rating Scale PSWQ= Penn State Worry Questionnaire, PSS= Cohen's Perceived Stress Scale, RAS= Recovery Assessment Scale RRS= Ruminative Response Scale VSS-A= Verona Satisfaction Scale-Affective Disorder, WHO-5 = WHO (five) Wellbeing Index, WHOQOL=WHO Quality of Life-BREF

[a] Adjusted for baseline values, psychiatric center, and number of admittances
[b] Adjusted for baseline values, psychiatric center, number of admittances, age, and sex
[c] Adjusted for baseline values, psychiatric center, number of admittances, age, sex and HDRS-17.

intense recruiting, expansion of the recruitment area, and a double in recruitment time, it was not possible to obtain the desired number. Nevertheless, it is clear from the Kaplan-Meir curves in Fig. 3 and the p-value of 0.9 from the log-rank test that the sample size of 120 patients was sufficient to exclude a type II error in relation to time to readmission as one of the primary outcome measures. Similarly, the trial resulted in a statistical power of 97% to detect a statistically significant difference at a p-level of 5% between the obtained difference in cumulated days of readmission (35 days (SD=33) versus 52 days (SD=44.0).

5. Discussion

We investigated the effect of a smartphone-based monitoring and treatment system in patients with unipolar depressive disorder following discharge from hospitalization for a depressive episode. In the present single-blinded trial, patients with unipolar depressive disorder were randomized to either a smartphone-based monitoring and treatment system, including a clinical feedback loop as an add-on to standard treatment or to standard treatment alone. The intervention lasted six months following discharge from hospitalization for a depressive episode. Overall, we found no effect on time to readmission or the duration of readmissions. Furthermore, there was no effect on clinically rated depressive symptoms and clinically rated functioning. However, patients in the intervention group reported statistically significantly higher recovery compared with the control group. Furthermore, there was a tendency towards patients reported a higher quality of life, higher wellbeing, more satisfaction with treatment, and higher behavioral activation in the intervention group compared with the control group. Although not statistically significant at a 0.05 level, analyses pointed in the same direction of a possible improvement on these outcome measures in patients in the intervention group compared with the control group.

The lack of effect on primary and secondary outcomes is in contrast to our hypothesis. We do not think this is a false negative finding due to low power (type II error) as there are only minor differences between the two groups. Possible explanations on the lack of effect could be 1) a large number of all patients (71.7%) received intensive, coordinated hospital-based outpatient treatment with frequent multidisciplinary contacts. This is a part of an intense focus in recent years in the region on reducing readmissions by providing quick and intense outpatient treatment; 2) the intervention was not integrated into the standard treatment but as an external research project and 3) we expected 30% readmissions in the control group; however, only 22% were readmitted in both groups. Thus, baseline risk was lower than expected, possibly due to the general focus on reducing readmissions.

The pragmatic design and the setting where the trial was conducted may have ended up opaquing the effects of the intervention to some extent. The multidisciplinary mental health care of patients after an affective episode in Denmark is well-known to be one of the most comprehensive and effective in the world, according to many studies (Hansen et al., 2012). Hence, it might be difficult to enhance a system that is already enhanced and providing close, continuous, and high-quality care to discharged patients. The same intervention in many other contexts or in a non-pragmatic RCT might have yielded different results

Patient-Reported Outcome Measures (PROMs) (McKenna, 2011) are central patient-experienced outcomes, and the results from the present trial are in line with previous findings from our group (the MONARCA II trial) (Faurholt-Jepsen et al., 2019), where we found improved quality of life in patients with bipolar disorder using a smartphone-based monitoring system like the one used in the present trial. Interestingly, during recent years there has been increasing international attention regarding the use of PROMs as a quality indicator of patient care and safety (Roe et al., 2019). This reflects the ongoing health service commitment of involving patients and the public within the broader context of the development and evaluation of health care service

delivery and quality improvement. The higher improvement in recovery and possible higher improvement on other PROMs in the intervention group compared to the control group could indicate relevant improvements in the patient's life, which is not measured by readmission or clinical rated scores. However, they also represent unblinded, self-reported, tertiary outcomes and must be interpreted with caution.

Seven patients explicitly discontinued the intervention. The intensive monitoring and extra contact were deemed stressful by some patients and indicated that such treatment systems might not be to everyone, and such dropouts should be expected and accepted. To minimize side effects and dropouts in this vulnerable patient group, we recommend: 1) Thorough face to face information on implications of participating in the study with the study nurse as well as a researcher before inclusion 2) Scalable intervention to suit the patients' clinical status 3) Experienced psychiatric nurses to guide and support the patient.

The rapid evolution of smartphone technology has resulted in the increasing development of tools for remote self-monitoring (Lal and Adair, 2014; Roberts et al., 2018; WHO, 2011) with the opportunity to collect fine-grained data unobtrusively and outside the clinical setting (Ebner-Priemer and Trull, 2009) This comprise a unique platform for real-time monitoring and treatment. However, existing RCTs lack methodological rigor and robust objective outcome measures (Tønning et al., 2019). Thus, the present trial adds to the evidence within this area.

Given the limited access to appropriate treatment facilities across the globe, smartphone-based monitoring and treatment may represent a flexible real-time system which could be of great support for both patients and health care providers. In this way, outpatient treatment could potentially be optimized and more flexible according to the patients' needs. The treatment-system tested in our current trial could possibly work in other settings or patients-subgroups, and it cannot be excluded that there would have been effects on other outcome measures, which we did not include or prioritize in the present trial. We chose to include readmission and duration of readmission as our robust primary outcomes, since patients with unipolar depressive disorder are often hospitalized, and costs due to psychiatric hospitalizations are a major burden for patients and society (Ekman et al., 2013; Health, 2018). Although we only found an effect of recovery, there was a tendency towards a possible effect of the intervention in several PROMs. Trials, including PROMs as primary outcome measures, are common within smartphone-based treatments in psychiatry (Tønning et al., 2019). The effect on these outcome measures must be investigated further, and future trials could include a sham app in standard treatment, potentially longer follow-up times, or integration of smartphone-based interventions in the existing standardized treatment program.

6. Limitations

We did not obtain the intended number of patients, despite prolonging the recruitment period. Patients could not oversee participating in further research or further treatments and contacts besides, often intense, standard treatment. Nevertheless, according to the post hoc statistical power analyses, the trial obtained sufficient power to exclude a type II error at a p-value of 0.05 with a sample size of 120 patients.

There may be different effects of the different components of the intervention. The present RADMIS trial investigated the effect of a combined system, and thus it was not possible to address the potential effect of individual components. Due to the type of intervention is was not possible to blind the patients and the study nurse to allocation status. Although the researchers collecting outcome data were kept blinded to allocation status during the entire trial, the tertiary outcomes were self-reported by non-blinded patients. The possible improvements in the tertiary outcomes could be the digital placebo effect (Torous and Firth, 2016) due to the awareness of being in the intervention group, wanting to please the researcher, or overestimate the positive effect of receiving a new intervention.

The intervention comprised of multiple elements and was not completely static due to minor changes in the smartphone-based system during the trial period, change of study nurse, and learning effect from the study nurses being more familiar with the system during the trial period. However, these minor adjustments resemble real-life settings. Technical issues (either in the system or at a patient-level) possibly affected the intervention, as is common in mHealth trials and real-life settings.

6.1. Generalizability

An RCT represents a trial design with high interval validity, with a possible cost of lower external validity and lower generalizability of the results. The present trial used a single-blinded design, with data on outcome measures collected by a researcher not aware of the randomization group, and therefore data was not affected by bias. Further, the trial had a pragmatic design with few exclusion criteria resembling clinical practice. All patients were thoroughly assessed with clinical evaluation and access to health records. We succeeded in including 120 patients from a very severe population in a critical period of their life and had high follow-up rates.

The results from the present trial reflect the use of smartphone-based monitoring during clinical settings with severely ill patients. Overall, the findings of the present trial are found to be generalizable to patients with a more severe unipolar depressive disorder.

7. Conclusion

Smartphone-based monitoring and treatment in real-time in patients with unipolar depressive disorder did not reduce readmissions and accumulated duration of readmissions or reduce clinical reported outcome measures in the present trial. In tertiary outcomes concerning patient-reported outcomes, patients in the intervention group had a higher level of recovery. However, findings on tertiary outcomes were not based on power calculation made for the present trial, and thus findings should be interpreted with caution. Despite the widespread excitement of smartphone-based monitoring, few clinical studies have investigated possible effects, and further studies are needed with PROMs or smartphone gathered data as possible outcome measures.

Author contribution

LVK and JEB designed the study and obtained funding.

LVK, MFJ, KM, and JEB conceived the trial with revisions from OW, NR, NT, JB, MF, and MLT.

MLT, MFJ, and LVK conducted the trial with help from DTP, SAM, KAA, and LT

MLT and MFJ did all statistical analyses together with LVK.

MLT, MFJ, and LVK wrote the first draft of the manuscript. All authors contributed to the manuscript and approved the final version.

Declaration of Competing Interest

JEB and MF are co-founders, shareholders, and employees in Monsenso. LVK has, within three years, been a consultant for Lundbeck. The Remaining authors declare no conflicts of interest.

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