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Evaluation of a stand-alone mobile mindfulness app in people experiencing infertility: the protocol for an exploratory randomized controlled trial (MoMiFer-RCT).

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TITLE

Evaluation of a stand-alone mobile mindfulness app in people experiencing infertility: the protocol for an exploratory randomized controlled trial (MoMiFer-RCT).

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ABSTRACT

Introduction: Infertility and its treatment bring a considerable emotional burden. Increasing evidence demonstrates the effectiveness of smartphone-delivered mindfulness apps for reducing symptoms of emotional distress in both clinical and non-clinical populations. Evidence on this topic in women, men and couples experiencing infertility is currently underrepresented. The aim of the MoMiFer-study is therefore, to investigate the efficacy of a stand-alone mobile mindfulness app on symptoms of emotional distress and fertility related quality of life in people experiencing infertility.

Methods and analysis: This study is an exploratory randomized controlled trial (RCT) with open enrollment. The primary outcomes are symptoms of emotional distress and fertility related quality of life. Secondary outcomes are mindfulness skills, repetitive negative thinking, self-compassion, user-rated quality of the stand-alone mobile mindfulness app, and use of the app. Experience sampling method (ESM) and standardized self-report questionnaires are combined within a repeated measures design to measure the effects of the stand-alone mobile mindfulness app on the primary and secondary outcomes, apart from the use of the app. The latter will be evaluated through app tracking. People, including women, men and couples, experiencing infertility (n=60) will be randomized to an intervention group receiving the stand-alone mobile mindfulness app for 3 months or a wait-list control group. The app follows the format and content of Mindfulness-Based Stress Reduction (MBSR). Data will be collected at baseline, at 1.5 months, and 3 months after randomization. Analysis will be according to intention to treat and based on general linear modelling and multilevel mixed-effects modelling.

Ethics and dissemination: This study received approval from the Medical Ethical Committee of the Leuven University Hospital (Belgium). The findings of this exploratory RCT will be disseminated through presentations at public lectures, scientific institutions and meetings, and through peer-reviewed scientific articles.

Trial registration: clinical trials.gov: NCT04143828

KEY WORDS

Infertility; emotional distress; quality of life; mindfulness; mobile mindfulness app

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ARTICLE SUMMARY

Strengths and limitations of this study

- Development of the stand-alone mobile mindfulness app is evidence based, which includes involvement of patients with infertility, and health care professionals.
- In the moment measurements through experience sampling method are combined with self-report questionnaires.
- Participants include couples and individuals within a repeated measures design.
- This is an open-label study where only the statistician is blinded.
- Wait-list control group is used which may inflate the estimated effect.

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INTRODUCTION

Infertility is defined as the inability to achieve a clinical pregnancy after one year of regular unprotected sexual intercourse [1]. An estimated 48.5 million couples suffer from infertility worldwide [2]. Consequently, assisted reproductive technology (ART) utilization for infertility treatment including in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) continues to increase [3,4]. Approximately one third of IVF with or without ICSI cycles result in a clinical pregnancy and subsequent life birth in circa 20% [3].

Infertility and its treatment result in considerable emotional burden for women, men, and couples [5–7]. Proportionately more female than male partners report this burden [8–11], which can be seen across distinct cultures [11]. Moreover, several studies have shown that this emotional burden may be an important reason for couples to terminate ART without achieving a live birth [12,13]. Mindfulness-Based Interventions (MBIs), such as Mindfulness-Based Stress Reduction (MBSR) [14] have been found to reduce psychological symptoms, and improve well-being in both clinical and non-clinical populations [15–18]. Multiple meta-analyses show that the strongest effects of MBIs were seen on symptoms of stress, depression, and anxiety [19–22].

Different supportive psychosocial interventions have been developed for people with infertility across the treatment cycle [23], including MBIs targeting women with infertility [21,24]. A systematic review covering face-to-face MBIs found small to moderate reductions in anxiety and depression for women with infertility [25], which appear to be maintained over a longer period of time [26]. Improvements in mindfulness skills [24,27] , quality of life [20,21,28], and stress symptoms [20,27] have been identified as well. However, most findings solely focus on women with infertility [25].

Research regarding the effectiveness of online and smartphone-delivered self-administered interventions as a tool to support mental health is growing [16,29–31]. What is key here, is that such tools make low-intensive psychological help easily accessible for a large audience at low-cost. A recent meta-analysis found promising results for smartphone-delivered mindfulness meditation apps in clinical and non-clinical populations for multiple psychological outcomes including anxiety, depressive symptoms, quality of life, and perceived stress [30]. Moreover, smartphone-delivered apps including mindfulness and acceptance components seem to improve both components [32]. Given the emotional burden of infertility [5] and its treatment [6,7,33], and the time cost of fertility treatment, people experiencing infertility require easily accessible, low intensive strategies to improve their mental health [34].

In this study, we want to target symptoms of emotional distress and quality of life by offering a stand-alone mobile mindfulness app to support people experiencing infertility.

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METHODS AND ANALYSIS

This protocol was written according to Standard Protocol Items: Recommendations for Interventional Trials [35].

Aim

The overall aim of the MoMiFer-study is to examine the effect of a stand-alone mobile mindfulness app on symptoms of emotional distress (symptoms of stress, anxiety and depression) and quality of life in people, including women, men and couples, experiencing infertility.

The objectives are as follows:

- To evaluate the impact of a stand-alone mobile mindfulness app (MoMiFer-app) on symptoms of emotional distress and quality of life in comparison with a control condition. We hypothesize a reduction in symptoms of emotional distress and an increase in quality of life in the experimental group as compared to the control group.
- To explore whether changes in symptoms of emotional distress are associated with improvements in mindfulness skills and self-compassion on the one hand, and a reduction in repetitive negative thinking on the other hand.

Study design and timing

The MoMiFer-RCT is an exploratory study [36]. This trial uses a parallel group design, with allocation ratio 1:1. The experimental group has immediate access to the MoMiFer-app for three months. The control group is wait-listed for three months after which access to the MoMiFer-app is received. The MoMiFer-study is a repeated measures design and will result in 3 waves of time-series data for each participant. Recruitment through open enrolment started on November 24th, 2019. Figure 1 presents an overview of the study design.

Insert Figure 1 about here

Recruitment and study setting

Participants are recruited through two Belgian non-profit organizations for people experiencing infertility “De Verdwaalde Ooievaar” and “Kinderwens”. Both organizations, together with “PraxisP”, promote this study by posting a flyer on their websites and social media accounts at regular times to achieve the targeted sample size. In addition, the study is promoted via social media. Participants who are interested receive detailed information from our researcher sending the informed consent (online supplemental material 1) through mail.

Eligibility criteria

Inclusion criteria are: women, men, and couples speaking and understanding Dutch, and experiencing infertility, defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1], aged 18-43, and who are in the

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Outcomes	Method(s) of assessment	Timing of assessment

possession of a smartphone. Couples undergoing fertility treatment at time of recruitment will also be eligible. Concomitant care (e.g. acupuncture, fertility counsellor) during the study is allowed.

Randomisation, blinding and treatment allocation

A computer-generated blocked randomization procedure via a password protected website (1:1 allocation ratio) with randomly varying the block size after baseline assessment is applied. This guarantees the allocation concealment to the recruiter. Due to the study design, neither the participants, nor the researchers are blinded for treatment allocation, expect for the statistician (data-analysis is done by third party).

Interventions

Through randomization participants are assigned to either an experimental group which receives immediate access to the MoMiFer-app for three months, or to a wait-list condition. When assigned to the control group, participants gain access to the MoMiFer-app after three months. If a clinical pregnancy occurs during the trial, participation to the study ends. The MoMiFer-app includes mindfulness exercises following the format and content of MBSR [14,37,38]. They were originally developed as part of the theory- and evidence-based "Prelife programme" [39], which is based on prior consultation and feedback from patients with infertility, and expert opinion of health care professionals [40,41]. The MoMiFer-app was established by experienced members of the Leuven Mindfulness Centre at KU Leuven and the psychiatrist and mindfulness teacher Dr. Edel Maex [37]. The exercises are spread over six consecutive modules. Each module consists of a short educational video clip (talking head) explaining the content and two audio files (between three and 45 minutes) to guide experiential mindfulness meditation exercises. Participants can follow the different modules based on their own time-schedule. The goal of the mindfulness exercises is to increase awareness of one's present-moment experience with an accepting, open, and non-judgmental attitude. Additionally, answers to frequently asked questions (FAQs) on mindfulness and fertility from patients are included in the app.

Sample size

Sample size is based on the experience sample method (ESM) applying the 30/30 rule, used to determine sample size in multilevel modelling, which recommends sampling 30 participants with 30 observations per group [42]. This sample size is known to achieve a sufficient statistical power to detect a moderate-to-large effect size for a single fixed effect [43,44]. The effect is the change in symptoms of emotional distress as measured by ESM. The same approach was used in previous related research [45].

Outcomes, data collection and management

Data will be collected using self-report questionnaires and ESM [46]. We further evaluate the use of the app for the experimental group through app tracking. Table 1 represents an overview of outcomes, methods, and timing of assessments.

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Primary outcome measures		Baseline	1.5 months	3 months
Fertility related quality of life	Self-report Q	X	X	X
Symptoms of emotional distress	ESM	X	X	X
	Self-report Q	X	X	X
Secondary outcome measures				
Mindfulness skills	Self-report Q	X	X	X
	ESM	X	X	X
Repetitive negative thoughts	Self-report Q	X	X	X
Self-compassion	Self-report Q	X	X	X
User-rated quality of the app	Self-report Q			X
Use of the app	App tracking		X	X
Background information	Self-report Q	X		

Table 1. Outcomes, method(s) of assessment and timing of assessment. Q, questionnaire; ESM, experience sampling method.

Primary outcomes are symptoms of emotional distress and fertility related quality of life**.** Symptoms of emotional distress are operationalized as symptoms of depression, anxiety, and stress measured with the Depression, Anxiety, and Stress scale (DASS-21) [47], and ESM [46]. The DASS-21 contains a depression, anxiety, and stress subscale. The overall score lies between 0 and 126. Higher scores suggest more symptoms of emotional distress.

ESM items question symptoms of depression, anxiety, and stress with a sliding bar ranging from 0 to 100 resulting in a total score of symptoms of emotional distress. Lower scores reflect less symptoms of emotional distress. ESM is a validated, structured diary technique to assess participants in the context of their daily living environment. It is a momentary assessment method providing repeated, in-the-moment micro-measurements of core psychological and behavioural variables in a prospective and ecologically valid manner [46]. The ESM questions will be administered via the app. In each of the three assessment phases, participants' smartphones, via the app, will beep 10 times/day for 4 consecutive days according to a semi-stratified interval scheme (waking hours will be divided into 10 equal intervals and in each interval one beep will be randomly programmed). At each beep, participants will be asked to indicate their current experience of emotions (e.g., sad mood), repetitive negative thinking, and mindfulness skills.

Fertility related quality of life is surveyed with the Fertility related Quality of Life questionnaire (FertiQoL) [48,49]. The Core FertiQoL total score is calculated across the emotional, relational, mind-body, and social subdomains and lies between 0 and 100. Higher scores indicate better fertility related quality of life.

Secondary outcomes are mindfulness skills, repetitive negative thoughts, self-compassion, user-rated quality of the app, and use of the app. Mindfulness skills are measured with ESM and the Comprehensive Inventory of Mindfulness Experiences-Short Form (CHIME-SF) [50]. ESM measurement encompasses questions on state mindfulness using a sliding bar. Total score varies between 0 and 100, with higher scores indicating better mindfulness skills. CHIME-SF questions aspects of mindfulness in daily life. The subscales are inner awareness, outer awareness, acting with awareness, acceptance, decentring/nonreactivity, openness, relativity, and insight. The total score lies between 24-144, with higher scores representing

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better mindfulness skills. Repetitive negative thinking is assessed with the Perseverative Thinking Questionnaire (PTQ) [51,52]. The PTQ covers questions on repetitive negative thinking (RNT) containing the following subscales: Core features of RNT (repetitiveness, intrusiveness, and difficulties to disengage), perceived unproductiveness of RNT, and RNT capturing mental capacity subscales. Total score ranges from 0-60, with higher scores indicating more RNT. The Self-Compassion Scale-Short Form (SCS-SF) [53–55] measures self-compassion through six subscales: self-kindness, common-humanity, mindfulness, self-judgment, isolation, and over-identification. Total score ranges from 12 to 60 with higher scores indicating more self-compassion.

All prior mentioned assessments will be gathered for both the experimental and the control group at baseline, and 1.5 months and 3 months after randomization (table 1).

For the experimental group, the user-rated quality of the app will be obtained at the end of the study using the short version of the subjective quality subscale of the Mobile App Rating Scale (MARS) [56]. It offers questions on recommendation and scoring of the app. Total score lies between 0 and 8, with higher scores meaning higher quality. Use of the stand-alone mobile mindfulness app will be monitored through app tracking. We will track how often participants in the experimental group open the application, which exercises they perform, and whether or not they finish the exercises.

Socio-demographic characteristics, fertility-related information (i.e. fertility treatment, infertility diagnosis, causes of infertility, complementary therapy, and time spent trying to get pregnant), and prior experience with mindfulness are reported by the participants during baseline measurements.

Questionnaire data will be collected using Qualtrics® and experience sampling method in the MoMiFer-app[46]. Storage and analysis will be done by the study investigator in SPSS according to Good Clinical Practice (GCP). Deviation of maximally 1 week before and after the planned time point is allowed. The data from the mobile mindfulness application can be retrieved from the secured website of MoMiFer of which only the research team and the participants have access.

Participant timeline

Figure 1 provides an overview of the study procedure. The informed consent is sent to potential participants through electronic mail. Consenting people with infertility are invited for study intake through an online video call. During this standard intake additional questions regarding the study are answered and the assessment methods are explained. Once consent is given, participants complete the baseline measurements (T0). These consist of web-based questionnaires. Only after this baseline assessment, participants will be randomized to prevent bias. Next, the MoMiFer-app is installed, providing the complete stand-alone mobile mindfulness application (experimental group) or the version with solely information regarding the study and the ESM (wait-list control group). Participants receive an overview of individualized assessment moments, and reminders via the app and electronic mail to

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promote participant retention and complete follow-up measurements. Subsequently, participants will be asked to fill out ESM on their smartphone via the app for 4 consecutive days (T0). During these 4 days, participants' smartphones will beep 10 times a day to remind them (through beeps and pop-up messages) to answer a set of short questions about their mood and thoughts, which takes about 90 seconds. Follow-up measurements, including ESM and similar questionnaires to the baseline assessment, take place at 1.5 (T1) and 3 months (T2) after randomisation. At T2 (i.e., the end of the study) the experimental group will be asked to fill out a questionnaire about the user-rated quality of the app.

Data analysis

Intention to treat analysis (ITT) was performed in the statistical software program SPSS. Descriptive statistics on baseline characteristics will be presented for the two arms. We will use hierarchical linear modelling to examine differential trajectories [57]. Estimator for missing data is full information maximum likelihood. To test the experimental effect, we will use a multilevel model with two levels: time-points (Level-1) will be nested within persons (Level-2). In this model, (a) the dummy-coded assessment time (as a level-1 variable), (b) the treatment condition (as a level-2 variable), and (c) their cross-level interactions are included in predicting the outcome. We will also use Cohen's d statistic to calculate within- and between-group effect sizes. A $p < .05$ will be used to determine statistical significance for the experimental group. The attrition rate regarding enrolment and drop-out will be reported and compared between the two arms.

Harms

Expectation concerning harms for participants is minimal. Each participant signs an informed consent which includes a list of (mental) health care organizations. This information is furthermore provided at each of the three assessments. All solicited and spontaneously reported adverse events and other unintended effects of the MoMiFer study will be collected, assessed, reported and managed according to good clinical practice (GCP) guidelines.

Patient and public involvement

A human-centred design was applied for creating the MoMiFer-app by involving both patients and healthcare professionals in the development process [34]. Moreover, an advisory committee was inherently part of the project, consisting of representatives of the Belgian non-profit patient organisation "De Verdwaalde Ooievaar" and of the "Belgian Society for Reproductive Medicine". In addition, participants are recruited through two non-profit patient organizations: "De Verdwaalde Ooievaar" and "Kinderwens". If the study indicates the MoMiFer-app adds value to reducing symptoms of emotional distress and improving fertility related quality of life in people experiencing infertility, the app might become available to both organisations afterwards.

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ETHICS AND DISSIMINATION

This study was approved by the Ethics Committee Research UZ/KU Leuven (Belgium) (S62323). Any subsequent protocol amendments will be submitted to the appropriate Ethics Committees and national Regulatory Authorities for approval. Participants IDs are used to guarantee confidentiality of participant's data (i.e., coding of dataset). The document linking the IDs to the identifiable information is stored separately. Access to coded data is only allowed for the MoMiFer research team. The investigators will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publications in scientific journals. International Committee of Medical Journal Editors recommendations will be followed regarding authorship to publications. We do not intend to use professional writers.

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DISCUSSION

With this exploratory RCT, we examine the impact of a stand-alone mobile mindfulness app on symptoms of emotional distress and fertility related quality of life of people experiencing infertility, including women, men, and couples. The MoMiFer-app provides several mindfulness exercises varying in length accompanied with talking heads, and information regarding mindfulness and infertility. The app was developed at the KU Leuven following an evidence-based approach, based on qualitative data from patients with infertility and an expert panel opinion of healthcare professionals [40,41]. An important strength of this exploratory study is the combination of self-report questionnaires with in the moment measurements through ESM [46] within a repeated measures design. Secondly, given the smartphone-delivered, stand-alone character of the app, the MoMiFer-app can reach a broad audience in an accessible and cost-efficient way. Thereby, offering a first introduction to app-delivered mindfulness exercises. Moreover this research will focus on women, men, and couples experiencing infertility, as the majority of studies have been focusing exclusively on women with infertility [25,58]. Finally, objectively evaluating the use of the app through app tracking and querying the user-rated quality of the app will give insight in how people use and experience the stand-alone mobile mindfulness app. In this study participants are self-decisive to practice mindfulness through the app to evaluate the use of the app. However, research points out that regular practice is recommended to enhance mindfulness skills and the associated outcomes [29,32,59,60]. Another limitation related to the study design, is that this is an open-label trial where solely the statistician is masked. Furthermore, infertility treatment and concomitant care (e.g. acupuncture, fertility coach) are allowed during the trial which may bias the outcome measures. This is taken into account in analysis as both topics are questioned during baseline measurements. Future more in-depth research could integrate a third active control group as a wait-list control condition may inflate estimates of the experimental effect [61]. If the MoMiFer-app would prove to be effective, it could be integrated in standard care, offering an easily accessible, low-intensive, and a more cost-efficient strategy for people experiencing infertility to improve their mental health.

Author contributions

TB, NW, CM, ED, CP, KVdG, PC, and FR designed the trial, developed the protocol, and applied for funding. TB, NW, FR, and KVdG applied for ethical approval. TB, NW, and KVdG implemented the logistics of the trial. All authors read, revised, and approved the final manuscript.

Funding statement

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Competing interests

Katleen Van der Gucht and Filip Raes are founders and members of the managing committee of the Leuven Mindfulness Centre Fund. Filip Raes and Katleen Van der Gucht receive

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payments for workshops and presentations related to mindfulness. The remaining authors made no disclosures.

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Patient consult for publication

Not applicable.

Availability of data and material

Questionnaire data is collected through the online survey platform Qualtrics according to GCP. The data from the stand-alone mobile mindfulness application can be retrieved from the secured website of MoMiFer. Once all data of this RCT are gathered, the MoMiFer research team will focus on data-analysis. Regarding data sharing, the International Committee of Medical Journal Editors recommendations will be followed. Individual deidentified participant data will be shared. In particular, individual participant data that underlie the results reported in our article, after deidentification (text, tables, figures, and appendices) will be shared. Data will become available from 9-36 months after the publication of the RCT-results. Data sharing with research groups interested in performing further data-analysis is stimulated.

Provenance and peer review

Not commissioned; externally peer reviewed.

Figures

Figure 1: Overview of the MoMiFer-RCT

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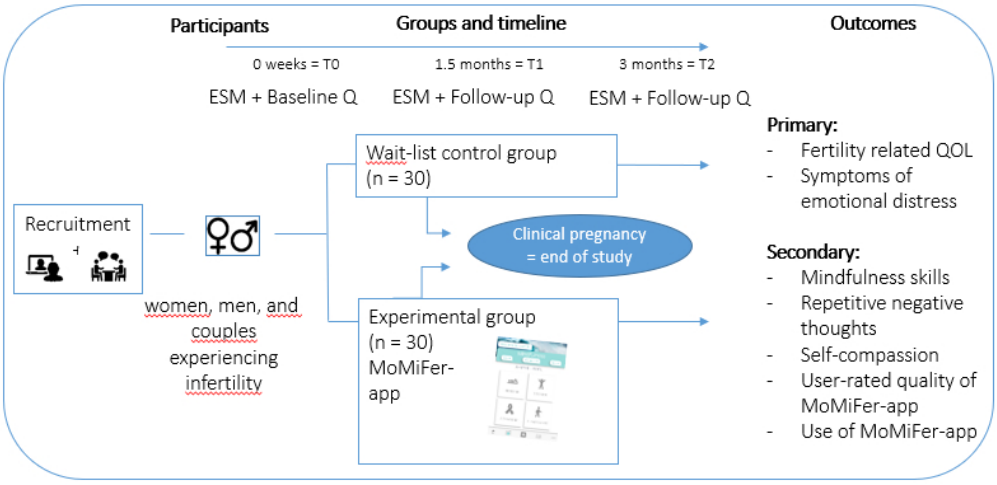

Figure 1: Overview of the MoMiFer-RCT. RCT, randomized controlled trial; ESM, experience sampling method; QOL, quality of life; Q, questionnaire; T, timing of assessment.

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Evaluatie van een Mobiel Mindfulness Programma (mMP) bij individuen/koppels met Fertiliteitsproblemen: MoMiFer studie

Opdrachtgever: KU Leuven

Onderzoeksinstelling*:* Leuven Mindfulness Centre (LMC), KU Leuven, Faculteit Psychologische en Pedagogische Wetenschappen, Tiensestraat 102, 3000 Leuven

Comité voor Medische Ethiek:

Centraal Ethisch Comité: Ethische Commissie Onderzoek UZ/KU Leuven

Plaatselijke onderzoekers: Prof. Dr. Filip Raes (LMC), Dr. Katleen Van der Gucht (LMC), Tessy Boedt (KU Leuven), Dr. Sharon Lie Fong (LUFC), Prof. Dr. Peter Kuppens (LMC), Prof. Dr. Ir. Christophe Matthys (KU Leuven), Nele Willaert (studente KU Leuven)

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Geachte mevrouw, mijnheer,

U wordt uitgenodigd om deel te nemen aan een studie ter evaluatie van een mobiel mindfulness programma voor individuen/koppels met fertiliteitsproblemen.

Voordat u akkoord gaat om deel te nemen aan deze studie willen we u wat meer informatie geven over wat dit betekent op organisatorisch vlak en wat de eventuele voordelen en risico's voor u zijn. Zo kan u een beslissing nemen op basis van de juiste informatie. Dit wordt 'geïnformeerde toestemming' genoemd.

Wij vragen u de volgende pagina's met informatie aandachtig te lezen. Heeft u vragen, dan kan u terecht bij de onderzoeker of haar/zijn vertegenwoordiger.

I Noodzakelijke informatie voor uw beslissing om deel te nemen

Als u aan deze klinische studie deelneemt, moet u weten dat:

- deze studie is opgesteld na evaluatie door een ethisch comité.
- uw deelname vrijwillig is; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is uw ondertekende toestemming nodig. Ook nadat u hebt getekend, kan u de onderzoeker laten weten dat u uw deelname wilt stopzetten.
- de gegevens die in het kader van uw deelname worden verzameld, vertrouwelijk zijn. Bij de publicatie van de resultaten is uw anonimiteit verzekerd.
- er u geen kosten worden aangerekend in het kader van deze studie.
- er een verzekering is afgesloten voor het geval dat u schade zou oplopen in het kader van uw deelname aan deze studie.
- U geen vergoeding/compensatie zal ontvangen voor deze studie
- indien u extra informatie wenst, u altijd contact kan opnemen met de onderzoeker of de medewerker van haar team.

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Doelstelling en beschrijving van deze studie

Deze studie onderzoekt of het volgen van een mindfulness programma aangeboden via een mobiele applicatie (mMP) een meerwaarde kan bieden voor individuen/koppels met fertiliteitsproblemen. Er zijn aanwijzingen dat mindfulness zou kunnen bijdragen aan beter mentaal welzijn bij individuen/koppels met fertiliteitsproblemen. Een mobiel mindfulnessprogramma is laagdrempelig en minder tijdsintensief dan een klassiek mindfulnessprogramma. Omdat het effect van een mobiel mindfulnessprogramma voor individuen/koppels met fertiliteitsproblemen nog niet grondig onderzocht is, weten we nog niet zeker of dergelijke ondersteuning werkt. Daarom werd deze studie opgezet.

Wat is mindfulness?:

De basis van mindfulness is het trainen van aandacht: we leren onze aandacht heel bewust op het hier en nu te richten in plaats van ons continu te verliezen in negatieve gedachten. De voorbije tien jaar heeft wetenschappelijk onderzoek overtuigend aangetoond dat mindfulness kan helpen bij de aanpak en het voorkomen van stress, langdurige pijn, angst en depressie.

Voorwaarde voor deelname

U komt in aanmerking om deel te nemen aan onze studie indien u aan volgende voorwaarden voldoet:

- U en/of uw partner ervaren fertiliteitsproblemen
- U en/of uw partner zijn beide in het bezit van een smartphone
- U en/of uw partner begrijpen voldoende de Nederlandse taal

Verloop van de studie

Indien u beslist om deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet, zal u via loting aan een bepaalde groep toegewezen worden:

Groep 1: krijgt onmiddellijk toegang tot een mindfulnessprogramma aangeboden via een mobiele applicatie;

Groep 2: is een wachtlijst-controle groep. Dit betekent dat u eerst op een wachtlijst komt. U krijgt toegang tot een mindfulnessprogramma via een mobiele applicatie na 3 maanden.

We vragen u deze mobiele applicatie te gebruiken. U kan zelf kiezen welke oefeningen u precies uitvoert of volgt.

Om een goede vergelijking van de resultaten in beide onderzoeksgroepen mogelijk te maken, vragen wij aan iedereen om 1 week voor de studie en na 1.5 en 3 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers ongeacht de groep. Deze vragenlijsten peilen naar uw levenskwaliteit, hoe u zich voelt (stemming, stress, angst, depressieve gevoelens), hoe u denkt (bijvoorbeeld over uzelf) en hoe het met uw aandacht gesteld is. Het invullen van de vragenlijsten duurt ongeveer 45 minuten. Naast het invullen van de vragenlijsten zal u ook gevraagd worden om gedurende 4 dagen een soort van dagboek bij te houden op uw smartphone. Tijdens deze 4 dagen wordt u gedurende de dag 10 maal opgepiept, waarbij zal gevraagd worden een aantal korte vragen te beantwoorden over uw stemming en gedachten. Het beantwoorden van deze vragen duurt ongeveer 90 seconden.

Voor de analyse van onze onderzoeksbevindingen zullen we ook registreren hoe vaak en hoe lang u de mindfulness app gebruikt.

Risico's, nadelen en voordelen

Er zijn geen extra risico's door het deelnemen aan deze studie in vergelijking met individuen/koppels die niet deelnemen aan deze studie.

Een nadeel aan deelnemen aan deze studie zou kunnen zijn dat wij u vragen om, onafhankelijk van de groep waarvoor u loot, verscheidene online vragenlijsten in te vullen op verschillende momenten in de tijd, wat tijd vergt.

Een voordeel van deelname aan deze studie, is dat de informatie die dankzij deze studie verkregen wordt, kan bijdragen tot een betere kennis van de impact van een mobiel mindfulness programma bij fertiliteitsproblemen.

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Stopzetting van de deelname/intrekking van toestemming

Uw deelname is geheel vrijwillig. U hebt het recht om uw deelname aan de studie om eender welke reden en zonder opgave van redenen stop te zetten. U kan om eender welke reden en zonder opgave van redenen uw toestemming tot deelname aan de studie intrekken. Hiermee trekt u de toestemming inzake de verwerking van uw gegevens in. Wel kan het voor de onderzoeker nuttig zijn om te weten of u zich terugtrekt omdat de aan de studie verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel follow-up vragenlijsten).

Indien u aan deze studie deelneemt, vragen wij u het volgende:

- Ten volle mee te werken voor een correct verloop van de studie.
- Geen informatie over uw emotionele of gezondheidstoestand of de symptomen die u ervaart, te verzwijgen.

Contact

Als u bijkomende informatie wenst, maar ook ingeval van problemen of als u zich zorgen maakt, kan u contact opnemen met de onderzoekers (Nele Willaert, Tessy Boedt en Katleen Van der Gucht) op de telefoonnummers respectievelijk (+32479566999 +3216329946 of +3216373183) of via nele.willaert@student.kuleuven.be tessy.boedt@kuleuven.be of katleen.vandergucht@kuleuven.be

Als u vragen hebt met betrekking tot uw rechten als deelnemer aan de studie, kan u contact opnemen met de ombudsdienst op het telefoonnummer: +3216344818 of via ombudsdienst@uzleuven.be. Indien nodig kan de ombudsdienst u in contact brengen met het Ethisch Comité.

Extra nuttige contactgegevens

Als u wel eens vaker last hebt van sombere of angstige gevoelens of wanneer u merkt dat u vaker piekert dan u eigenlijk zou willen, dan wilt u daar misschien over praten met iemand. Weet dat u daarvoor steeds terecht kan bij onder andere deze diensten en centra:

- Indien u behoefte heeft aan een gesprek, zonder dat u wil zeggen wie u bent (dus 'anoniem'), kan u daarvoor steeds terecht bij de telefonische dienst Tele-Onthaal bel 106 (voor iedereen 24/24u en 7/7 dagen toegankelijk).
- U kan ook terecht op www.tele-onthaal.be voor chatsessies en meer info.
- U kan een Centrum voor Geestelijke Gezondheidszorg contacteren bij u in de buurt (http://www.geestelijkgezondvlaanderen.be/centrum-geestelijke-gezondheidszorg-cgg).
- Uiteraard kan u zich ook altijd wenden tot uw eigen huisarts of de huisarts van wacht in uw buurt (zie: www.mediwacht.be).

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Titel van de studie: **Evaluatie van een Mobiel Mindfulness Programma (mMP) bij individuen/koppels met Fertiliteitsproblemen: MoMiFer studie.**

II Geïnformeerde toestemming

Deelnemer

Vooraleer u start met deze studie, dient u uw geïnformeerde toestemming te geven voor de deelname aan deze studie. Daarvoor is het noodzakelijk dat u onderstaande informatie grondig doorneemt.
Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Dit houdt het volgende in:

- Het volgen een mindfulness programma (onmiddellijk of na een wachtlijst) via een mobiele applicatie gedurende 3 maanden. Het gebruik van deze applicatie wordt geregistreerd door de onderzoekers.
- Op 3 momenten (bij start van de studie, na 1,5 maanden en na 3 maanden) online vragenlijsten invullen betreffende mijn mentaal welzijn.
- Op diezelfde meetmomenten gedurende 4 dagen, 10 keer per dag enkele vragen beantwoorden via mijn smartphone betreffende mijn mentaal welzijn.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat aan mijn deelname geen enkel risico verbonden is.

Ik begrijp dat mijn deelname aan deze studie geheel vrijwillig is en dat er dus geen enkele sprake van dwang is. Ik heb het recht op elk moment mijn deelname stop te zetten. Bij het stopzetten van mijn deelname hoef ik geen reden te geven en brengt dit in geen enkel geval nadelen of enig ander gevolg met zich mee.

Ik begrijp dat alle informatie vertrouwelijk is en mijn anonimiteit wordt gegarandeerd. Dit wil zeggen dat mijn naam niet terug gelinkt kan worden met mijn ingevulde online vragenlijst en dat er nergens gevraagd wordt mijn naam of andere namen te vermelden. De resultaten van dit onderzoek kunnen gebruikt worden voor wetenschappelijke doeleinden en mogen gepubliceerd worden. Mijn naam wordt daarbij niet gepubliceerd, anonimiteit en de vertrouwelijkheid van de gegevens is in elk stadium van het onderzoek gewaarborgd.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.
Indien ik nog vragen heb omtrent de studie of extra informatie wil, kan ik terecht bij: Nele Willaert: nele.willaert@student.kuleuven.be (gsmnummer: 0479566999) of Tessy Boedt: tessy.boedt@kuleuven.be (telefoonnummer: +3216329946)

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn gegevens die voor de hier vermelde studie worden verzameld, later zullen worden verwerkt, op voorwaarde dat deze verwerking beperkt blijft tot de context van de hier vermelde studie voor een betere kennis van de impact van mindfulness bij fertiliteitsproblemen.

Naam, voornaam, datum en handtekening van de deelnemers:

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Onderzoeker

Ik ondergetekende, ... verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemers is uitgeoefend om hem/haar te doen toestemmen tot deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de laatste versie van de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naam, Voornaam, Datum en handtekening van de onderzoeker:

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III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Om een goede vergelijking van de resultaten in beide onderzoeksgroepen mogelijk te maken vragen wij aan iedereen om bij het begin van de studie en na 1,5 en 3 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers, ongeacht de groep die geloot wordt. Het invullen van deze vragenlijsten neemt ongeveer 45 minuten per meetmoment van uw tijd in beslag. Deze vragenlijsten hebben betrekking op uw algemeen welbevinden. Deze studie eindigt na 3 maanden. Naast het invullen van de vragenlijsten zal aan de deelnemers ook gevraagd worden om gedurende 4 dagen een soort van dagboek bij te houden via de smartphone. Tijdens deze 4 dagen worden deelnemers gedurende de dag 10 maal opgepiept, daarbij wordt gevraagd een aantal korte vragen te beantwoorden over stemming en gedachten. Het beantwoorden van deze vragen duurt ongeveer 90 seconden.

2. Aanvullende informatie over de risico's die verbonden zijn aan deelname aan de studie

Niet van toepassing.

3 : Aanvullende informatie over de bescherming en de rechten van deelnemers aan een klinische studie

Ethische comités

Deze studie werd geëvalueerd door een onafhankelijk ethisch comité (Ethische Commissie Onderzoek UZ/KU Leuven) dat een gunstig advies heeft uitgebracht. De ethische comités hebben als taak de personen die aan studies deelnemen te beschermen. Ze controleren of uw rechten als deelnemer aan een studie gerespecteerd worden, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

Vrijwillige deelname

Aarzel niet om alle vragen te stellen die bij u opkomen voordat u tekent.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen, zonder dat u hiervoor een reden hoeft te geven, zelfs al hebt u eerder toegestemd om aan deze studie deel te nemen.

Als u aanvaardt om aan deze studie deel te nemen, ondertekent u het toestemmingsformulier. De onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij u de noodzakelijke informatie over deze studie heeft gegeven. U zal het voor u bestemde exemplaar ontvangen.

Het is wel aanbevolen om de onderzoeker op de hoogte te stellen, indien u besluit uw deelname aan de studie stop te zetten.

Kosten in verband met uw deelname

Indien u besluit aan deze studie deel te nemen, worden alle onderzoeken en procedures in het kader van de studie door de opdrachtgever betaald.

Vertrouwelijkheidsgarantie

Als opdrachtgever van het onderzoek, is KU Leuven de verwerkingsverantwoordelijke van uw persoonlijke gegevens die verwerkt worden in het kader van het onderzoek. Uw deelname aan de studie betekent dat u ermee akkoord gaat dat de onderzoeker gegevens over u verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties. Uw gegevens zullen worden verwerkt overeenkomstig met de Europese Algemene verordening inzake gegevensbescherming (AVG/GDPR).

U hebt het recht om aan de onderzoeker te vragen welke gegevens zij over u heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op uw huidige situatie, maar ook op

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uw voorgeschiedenis. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn[1].

De onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat zij zich ertoe verbindt om uw naam nooit bekend te maken, bv. in het kader van een publicatie of een conferentie en dat zij uw gegevens zal coderen (uw identiteit zal worden vervangen door een identificatiecode in de studie) voordat zij ze doorgeeft aan de beheerder van de databank (KU Leuven).

De onderzoeker en haar team zullen gedurende de volledige studie de enige personen zijn, die een verband kunnen leggen tussen de overgedragen gegevens en uw dossier[2].

De overgedragen persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is u te identificeren[3].

De door de opdrachtgever aangestelde beheerder van de onderzoeksgegevens kan u niet identificeren op basis van de overgedragen gegevens. Deze persoon is verantwoordelijk voor het verzamelen van de gegevens, die door alle onderzoekers die deelnemen aan de studie zijn verzameld en voor de verwerking en de bescherming van die gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kunnen uw gegevens worden ingekeken door personen die gebonden zijn aan het beroepsgeheim, zoals vertegenwoordigers van de ethische comités, van de opdrachtgever van de studie, of een door hen aangesteld extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de onderzoeker en onder zijn/haar toezicht (of van één van zijn/haar onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de betrokken ethische comités, aan andere onderzoekers en/of instellingen die samenwerken met de opdrachtgever.

Ze kunnen ook doorgegeven worden aan andere sites van de opdrachtgever in België. Dit gebeurt dan steeds in gecodeerde vorm zoals hierboven uitgelegd.

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat u akkoord gaat dat uw gecodeerde gegevens gebruikt worden voor doeleinden die in dit informatieformulier beschreven staan en dat ze overgedragen worden aan bovenvermelde personen en/of instellingen.

De opdrachtgever zal de verzamelde gegevens gebruiken in het kader van de studie waaraan u deelneemt, maar wil ze ook kunnen aanwenden in het kader van andere studies over dezelfde problemen als de uwe. Buiten de context die beschreven wordt in dit document, kunnen uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd. Er zal geen enkel nieuw gegeven aan de opdrachtgever worden doorgegeven.
Indien u vragen hebt over hoe wij uw gegevens gebruiken, dan kan u hiervoor steeds terecht bij uw onderzoeker.
Ook de functionarissen voor gegevensbescherming van het onderzoekcentrum staan ter uwer beschikking.
De contactgegevens van deze laatste zijn als volgt:
DPO - UZ Leuven, Herestraat 49, 3000 Leuven, “het privacy-team” van KU Leuven.
Tot slot heeft u ook het recht om een klacht in te dienen over hoe uw gegevens worden behandeld, bij de Belgische toezichthoudende instantie die verantwoordelijk is voor het handhaven van de wetgeving inzake gegevensbescherming:
Gegevensbeschermingsautoriteit (GBA), Drukpersstraat 35, 1000 Brussel, Tel. +32 2 274 48 00

[1] Deze rechten zijn bepaald door de Algemene Verordening Gegevensbescherming , EU verordening 2016/679 en door de wet van 22 augustus 2002 betreffende de rechten van de patiënt.

[2] Voor klinische studies verplicht de wet om het verband met uw dossier gedurende 20 jaar te behouden. In geval van een studiegeneesmiddel voor een innoverende therapie waarbij gebruik wordt gemaakt van menselijk lichaamsmateriaal, bedraagt deze periode minimaal 30 jaar en maximaal 50 jaar in overeenstemming met de Belgische wet van 19 december 2008 inzake het gebruik van menselijk lichaamsmateriaal en de geldende Koninklijke Besluiten..

[3] De gegevensbank met onderzoeksresultaten bevat dus geen verband met elementen zoals uw initialen, uw geslacht en uw volledige geboortedatum (dd/mm/jjjj).

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E-mail: contact@apd-gba.be, Website: www.gegevensbeschermingsautoriteit.be

Verzekering

Conform de Belgische wet van 7 mei 2004 betreffende experimenten op de menselijke persoon is de opdrachtgever, KU Leuven - ook indien er geen sprake is van fout - aansprakelijk voor de schade die u als deelnemer en/of uw rechthebbenden, oplopen en die rechtstreeks of onrechtstreeks verband houdt met deelname aan de studie. U moet hiervoor dus geen fout aantonen. KU Leuven heeft voor deze aansprakelijkheid een verzekering afgesloten[4]. Indien u dit wenselijk acht kan u zelf de verzekeraar dagvaarden.
De contactgegevens van de verzekeraar zijn de volgende:
Amlin Insurance SE, Vanbreda Risk & Benefits NV, Plantin en Moretuslei, 297, 2140 Antwerpen.

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[4] In overeenstemming met artikel 29 van de Belgische Wet inzake experimenten op de menselijke persoon (7 mei 2004)
Informatie- en toestemmingsdocument3, gedateerd op 19/02/2019- pagina 8 van 8

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2____
	2b	All items from the World Health Organization Trial Registration Data Set	___1,2,4-8,11___
Protocol version	3	Date and version identifier	_____1_____
Funding	4	Sources and types of financial, material, and other support	_____11_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1,11,12___
	5b	Name and contact information for the trial sponsor	_____11_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6-9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10,12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11,12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Evaluation of a stand-alone mobile mindfulness app in people experiencing infertility: the protocol for an exploratory randomized controlled trial (MoMiFer-RCT).

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Primary Subject Heading:	Reproductive medicine
Secondary Subject Heading:	Mental health
Keywords:	Subfertility < GYNAECOLOGY, MENTAL HEALTH, PUBLIC HEALTH

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TITLE

Evaluation of a stand-alone mobile mindfulness app in people experiencing infertility: the protocol for an exploratory randomized controlled trial (MoMiFer-RCT).

AUTHORS

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WORD COUNT

3355

Protocol version 1, 25th October 2019

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ABSTRACT

Introduction: Infertility and its treatment bring a considerable emotional burden. Increasing evidence demonstrates the effectiveness of smartphone-delivered mindfulness apps for reducing symptoms of emotional distress in both clinical and non-clinical populations. Evidence on this topic in women, men and couples experiencing infertility is currently underrepresented. The aim of the MoMiFer-study is therefore, to investigate the efficacy of a stand-alone mobile mindfulness app on symptoms of emotional distress and fertility related quality of life in people experiencing infertility.

Methods and analysis: This study is an exploratory randomized controlled trial (RCT) with open enrollment. The primary outcomes are symptoms of emotional distress and fertility related quality of life. Secondary outcomes are mindfulness skills, repetitive negative thinking, self-compassion, user-rated quality of the stand-alone mobile mindfulness app, and use of the app. Experience sampling method (ESM) and standardized self-report questionnaires are combined within a repeated measures design to measure the effects of the stand-alone mobile mindfulness app on the primary and secondary outcomes, apart from the use of the app. The latter will be evaluated through app tracking. People, including women, men and couples, experiencing infertility (n=60) will be randomized to an intervention group receiving the stand-alone mobile mindfulness app for 3 months or a wait-list control group. The app follows the format and content of Mindfulness-Based Stress Reduction (MBSR). Data will be collected at baseline, at 1.5 months, and 3 months after randomization. Analysis will be according to intention to treat and based on general linear modelling and multilevel mixed-effects modelling.

Ethics and dissemination: This study received approval from the Medical Ethical Committee of the Leuven University Hospital (Belgium). The findings of this exploratory RCT will be disseminated through presentations at public lectures, scientific institutions and meetings, and through peer-reviewed scientific articles.

Trial registration: clinical trials.gov: NCT04143828

KEY WORDS

Infertility; emotional distress; quality of life; mindfulness; mobile mindfulness app

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ARTICLE SUMMARY

Strengths and limitations of this study

- Development of the stand-alone mobile mindfulness app is evidence based, which includes involvement of patients with infertility, and health care professionals.
- In the moment measurements through experience sampling method are combined with self-report questionnaires.
- Participants include couples and individuals within a repeated measures design.
- This is an open-label study where only the statistician is blinded.
- Wait-list control group is used which may inflate the estimated effect.

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INTRODUCTION

Infertility is defined as the inability to achieve a clinical pregnancy after one year of regular unprotected sexual intercourse [1]. An estimated 48.5 million couples suffer from infertility worldwide [2]. Consequently, assisted reproductive technology (ART) utilization for infertility treatment including in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) continues to increase [3,4]. Approximately one third of IVF with or without ICSI cycles result in a clinical pregnancy and subsequent life birth in circa 20% [3].

Infertility and its treatment result in considerable emotional burden for women, men, and couples [5–7]. Proportionately more female than male partners report this burden [8–11], which can be seen across distinct cultures [11]. Moreover, several studies have shown that this emotional burden may be an important reason for couples to terminate ART without achieving a live birth [12,13]. Mindfulness-Based Interventions (MBIs), such as Mindfulness-Based Stress Reduction (MBSR) [14] have been found to reduce psychological symptoms, and improve well-being in both clinical and non-clinical populations [15–18]. Multiple meta-analyses show that the strongest effects of MBIs were seen on symptoms of stress, depression, and anxiety [19–22].

Different supportive psychosocial interventions have been developed for people with infertility across the treatment cycle [23], including MBIs targeting women with infertility [21,24]. A systematic review covering face-to-face MBIs found small to moderate reductions in anxiety and depression for women with infertility [25], which appear to be maintained over a longer period of time [26]. Improvements in mindfulness skills [24,27] , quality of life [20,21,28], and stress symptoms [20,27] have been identified as well. However, most findings solely focus on women with infertility and exclude the male partner [25].

Research regarding the effectiveness of online and smartphone-delivered self-administered interventions as a tool to support mental health is growing [16,29–31]. What is key here, is that such tools make low-intensive psychological help easily accessible for a large audience at low-cost. A recent meta-analysis found promising results for smartphone-delivered mindfulness meditation apps in clinical and non-clinical populations for multiple psychological outcomes including anxiety, depressive symptoms, quality of life, and perceived stress [30]. Moreover, smartphone-delivered apps including mindfulness and acceptance components seem to improve both components [32]. Given the emotional burden of infertility [5] and its treatment [6,7,33], and the time cost of fertility treatment, people experiencing infertility require easily accessible, low intensive strategies to improve their mental health [34].

In this study, we want to target symptoms of emotional distress and quality of life by offering a stand-alone mobile mindfulness app to support people experiencing infertility.

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METHODS AND ANALYSIS

This protocol was written according to Standard Protocol Items: Recommendations for Interventional Trials [35].

Aim

The overall aim of the MoMiFer-study is to examine the effect of a stand-alone mobile mindfulness app on symptoms of emotional distress (symptoms of stress, anxiety and depression) and quality of life in people, including women, men and couples, experiencing infertility.

The objectives are as follows:

- To evaluate the impact of a stand-alone mobile mindfulness app (MoMiFer-app) on symptoms of emotional distress and quality of life in comparison with a control condition. We hypothesize a reduction in symptoms of emotional distress and an increase in quality of life in the experimental group as compared to the control group.
- To explore whether changes in symptoms of emotional distress are associated with improvements in mindfulness skills and self-compassion on the one hand, and a reduction in repetitive negative thinking on the other hand.

Study design and timing

The MoMiFer-RCT is an exploratory study [36]. This trial uses a parallel group design, with allocation ratio 1:1. The experimental group has immediate access to the MoMiFer-app for three months. The control group is wait-listed for three months after which access to the MoMiFer-app is received. The MoMiFer-study is a repeated measures design and will result in 3 waves of time-series data for each participant. Recruitment through open enrolment started on November 24th, 2019. Figure 1 presents an overview of the study design.

Insert Figure 1 about here

Recruitment and study setting

Participants are recruited through two Belgian non-profit organizations for people experiencing infertility “De Verdwaalde Ooievaar” and “Kinderwens”. Both organizations, together with “PraxisP”, promote this study by posting a flyer on their websites and social media accounts at regular times to achieve the targeted sample size. In addition, the study is promoted via social media. Participants who are interested receive detailed information from our researcher sending the informed consent (online supplemental material 1) through mail.

Eligibility criteria

Inclusion criteria are: women, men, and couples speaking and understanding Dutch, and experiencing infertility, defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1], aged 18-43, and who are in the

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Outcomes	Method(s) of assessment	Timing of assessment

possession of a smartphone. Couples undergoing fertility treatment at time of recruitment will also be eligible. Concomitant care (e.g. acupuncture, fertility counsellor) during the study is allowed.

Randomisation, blinding and treatment allocation

A computer-generated blocked randomization procedure via a password protected website (1:1 allocation ratio) with randomly varying the block size after baseline assessment is applied. This guarantees the allocation concealment to the recruiter. Due to the study design, neither the participants, nor the researchers are blinded for treatment allocation, expect for the statistician (data-analysis is done by third party).

Interventions

Through randomization participants are assigned to either an experimental group which receives immediate access to the MoMiFer-app for three months, or to a wait-list condition. When assigned to the control group, participants gain access to the MoMiFer-app after three months. If a clinical pregnancy occurs during the trial, participation to the study ends. The MoMiFer-app includes mindfulness exercises following the format and content of MBSR [14,37,38]. They were originally developed as part of the theory- and evidence-based "Prelife programme" [39], which is based on prior consultation and feedback from patients with infertility, and expert opinion of health care professionals [40,41]. The MoMiFer-app was established by experienced members of the Leuven Mindfulness Centre at KU Leuven and the psychiatrist and mindfulness teacher Dr. Edel Maex [37]. The exercises are spread over six consecutive modules. Each module consists of a short educational video clip (talking head) explaining the content and two audio files (between three and 45 minutes) to guide experiential mindfulness meditation exercises. Participants can follow the different modules based on their own time-schedule. The goal of the mindfulness exercises is to increase awareness of one's present-moment experience with an accepting, open, and non-judgmental attitude. Additionally, answers to frequently asked questions (FAQs) on mindfulness and fertility from patients are included in the app.

Sample size

Sample size is based on the experience sample method (ESM) applying the 30/30 rule, used to determine sample size in multilevel modelling, which recommends sampling 30 participants with 30 observations per group [42]. This sample size is known to achieve a sufficient statistical power to detect a moderate-to-large effect size for a single fixed effect [43,44]. The effect is the change in symptoms of emotional distress as measured by ESM. The same approach was used in previous related research [45].

Outcomes, data collection and management

Data will be collected using self-report questionnaires and ESM [46]. We further evaluate the use of the app for the experimental group through app tracking. Table 1 represents an overview of outcomes, methods, and timing of assessments.

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Primary outcome measures		Baseline	1.5 months	3 months
Fertility related quality of life	Self-report Q	X	X	X
Symptoms of emotional distress	ESM	X	X	X
	Self-report Q	X	X	X
Secondary outcome measures				
Mindfulness skills	Self-report Q	X	X	X
	ESM	X	X	X
Repetitive negative thoughts	Self-report Q	X	X	X
Self-compassion	Self-report Q	X	X	X
User-rated quality of the app	Self-report Q			X
Use of the app	App tracking		X	X
Background information	Self-report Q	X		

Table 1. Outcomes, method(s) of assessment and timing of assessment. Q, questionnaire; ESM, experience sampling method.

Primary outcomes are symptoms of emotional distress and fertility related quality of life**.** Symptoms of emotional distress are operationalized as symptoms of depression, anxiety, and stress measured with the Depression, Anxiety, and Stress scale (DASS-21) [47], and ESM [46]. The DASS-21 contains a depression, anxiety, and stress subscale. The overall score lies between 0 and 126. Higher scores suggest more symptoms of emotional distress.

ESM items question symptoms of depression, anxiety, and stress with a sliding bar ranging from 0 to 100 resulting in a total score of symptoms of emotional distress. Lower scores reflect less symptoms of emotional distress. ESM is a validated, structured diary technique to assess participants in the context of their daily living environment. It is a momentary assessment method providing repeated, in-the-moment micro-measurements of core psychological and behavioural variables in a prospective and ecologically valid manner [46]. The ESM questions will be administered via the app. In each of the three assessment phases, participants' smartphones, via the app, will beep 10 times/day for 4 consecutive days according to a semi-stratified interval scheme (waking hours will be divided into 10 equal intervals and in each interval one beep will be randomly programmed). At each beep, participants will be asked to indicate their current experience of emotions (e.g., sad mood), repetitive negative thinking, and mindfulness skills.

Fertility related quality of life is surveyed with the Fertility related Quality of Life questionnaire (FertiQoL) [48,49]. The Core FertiQoL total score is calculated across the emotional, relational, mind-body, and social subdomains and lies between 0 and 100. Higher scores indicate better fertility related quality of life.

Secondary outcomes are mindfulness skills, repetitive negative thoughts, self-compassion, user-rated quality of the app, and use of the app. Mindfulness skills are measured with ESM and the Comprehensive Inventory of Mindfulness Experiences-Short Form (CHIME-SF) [50]. ESM measurement encompasses questions on state mindfulness using a sliding bar. Total score varies between 0 and 100, with higher scores indicating better mindfulness skills. CHIME-SF questions aspects of mindfulness in daily life. The subscales are inner awareness, outer awareness, acting with awareness, acceptance, decentring/nonreactivity, openness, relativity, and insight. The total score lies between 24-144, with higher scores representing

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better mindfulness skills. Repetitive negative thinking is assessed with the Perseverative Thinking Questionnaire (PTQ) [51,52]. The PTQ covers questions on repetitive negative thinking (RNT) containing the following subscales: Core features of RNT (repetitiveness, intrusiveness, and difficulties to disengage), perceived unproductiveness of RNT, and RNT capturing mental capacity subscales. Total score ranges from 0-60, with higher scores indicating more RNT. The Self-Compassion Scale-Short Form (SCS-SF) [53–55] measures self-compassion through six subscales: self-kindness, common-humanity, mindfulness, self-judgment, isolation, and over-identification. Total score ranges from 12 to 60 with higher scores indicating more self-compassion.

All prior mentioned assessments will be gathered for both the experimental and the control group at baseline, and 1.5 months and 3 months after randomization (table 1).

For the experimental group, the user-rated quality of the app will be obtained at the end of the study using the short version of the subjective quality subscale of the Mobile App Rating Scale (MARS) [56]. It offers questions on recommendation and scoring of the app. Total score lies between 0 and 8, with higher scores meaning higher quality. Use of the stand-alone mobile mindfulness app will be monitored through app tracking. We will track how often participants in the experimental group open the application, which exercises they perform, and whether or not they finish the exercises.

Socio-demographic characteristics, fertility-related information (i.e. fertility treatment, infertility diagnosis, causes of infertility, complementary therapy, and time spent trying to get pregnant), and prior experience with mindfulness are reported by the participants during baseline measurements.

Questionnaire data will be collected using Qualtrics® and experience sampling method in the MoMiFer-app[46]. Storage and analysis will be done by the study investigator in SPSS according to Good Clinical Practice (GCP). Deviation of maximally 1 week before and after the planned time point is allowed. The data from the mobile mindfulness application can be retrieved from the secured website of MoMiFer of which only the research team and the participants have access.

Participant timeline

Figure 1 provides an overview of the study procedure. The informed consent is sent to potential participants through electronic mail. Consenting people with infertility are invited for study intake through an online video call. During this standard intake additional questions regarding the study are answered and the assessment methods are explained. Once consent is given, participants complete the baseline measurements (T0). These consist of web-based questionnaires. Only after this baseline assessment, participants will be randomized to prevent bias. Next, the MoMiFer-app is installed, providing the complete stand-alone mobile mindfulness application (experimental group) or the version with solely information regarding the study and the ESM (wait-list control group). Participants receive an overview of individualized assessment moments, and reminders via the app and electronic mail to

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promote participant retention and complete follow-up measurements. Subsequently, participants will be asked to fill out ESM on their smartphone via the app for 4 consecutive days (T0). During these 4 days, participants' smartphones will beep 10 times a day to remind them (through beeps and pop-up messages) to answer a set of short questions about their mood and thoughts, which takes about 90 seconds. Follow-up measurements, including ESM and similar questionnaires to the baseline assessment, take place at 1.5 (T1) and 3 months (T2) after randomisation. At T2 (i.e., the end of the study) the experimental group will be asked to fill out a questionnaire about the user-rated quality of the app.

Data analysis

Intention to treat analysis (ITT) was performed in the statistical software program SPSS. Descriptive statistics on baseline characteristics will be presented for the two arms. We will use hierarchical linear modelling to examine differential trajectories [57]. Estimator for missing data is full information maximum likelihood. To test the experimental effect, we will use a multilevel model with two levels: time-points (Level-1) will be nested within persons (Level-2). In this model, (a) the dummy-coded assessment time (as a level-1 variable), (b) the treatment condition (as a level-2 variable), and (c) their cross-level interactions are included in predicting the outcome. We will also use Cohen's d statistic to calculate within- and between-group effect sizes. A $p < .05$ will be used to determine statistical significance for the experimental group. The attrition rate regarding enrolment and drop-out will be reported and compared between the two arms.

Harms

Expectation concerning harms for participants is minimal. No exclusion criteria are applied in the area of people at high risk (for example mental illness) [32]. Each participant signs an informed consent which includes a list of (mental) health care organizations. This information is furthermore provided at each of the three assessments. All solicited and spontaneously reported adverse events and other unintended effects of the MoMiFer study will be collected, assessed, reported and managed according to good clinical practice (GCP) guidelines.

Patient and public involvement

A human-centred design was applied for creating the MoMiFer-app by involving both patients and healthcare professionals in the development process [34]. Moreover, an advisory committee was inherently part of the project, consisting of representatives of the Belgian non-profit patient organisation "De Verdwaalde Ooievaar" and of the "Belgian Society for Reproductive Medicine". In addition, participants are recruited through two non-profit patient organizations: "De Verdwaalde Ooievaar" and "Kinderwens". If the study indicates the MoMiFer-app adds value to reducing symptoms of emotional distress and improving fertility related quality of life in people experiencing infertility, the app might become available to both organisations afterwards.

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ETHICS AND DISSIMINATION

This study was approved by the Ethics Committee Research UZ/KU Leuven (Belgium) (S62323). Any subsequent protocol amendments will be submitted to the appropriate Ethics Committees and national Regulatory Authorities for approval. Participants IDs are used to guarantee confidentiality of participant's data (i.e., coding of dataset). The document linking the IDs to the identifiable information is stored separately. Access to coded data is only allowed for the MoMiFer research team. The investigators will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publications in scientific journals. International Committee of Medical Journal Editors recommendations will be followed regarding authorship to publications. We do not intend to use professional writers.

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DISCUSSION

With this exploratory RCT, we examine the impact of a stand-alone mobile mindfulness app on symptoms of emotional distress and fertility related quality of life of people experiencing infertility, including women, men, and couples. The MoMiFer-app provides several mindfulness exercises varying in length accompanied with talking heads, and information regarding mindfulness and infertility. The app was developed at the KU Leuven following an evidence-based approach, based on qualitative data from patients with infertility and an expert panel opinion of healthcare professionals [40,41]. An important strength of this exploratory study is the combination of self-report questionnaires with in the moment measurements through ESM [46] within a repeated measures design. Secondly, given the smartphone-delivered, stand-alone character of the app, the MoMiFer-app can reach a broad audience in an accessible and cost-efficient way. Thereby, offering a first introduction to app-delivered mindfulness exercises. Moreover this research will focus on women, men, and couples experiencing infertility, as the majority of studies have been focusing exclusively on women with infertility [25,58]. Finally, objectively evaluating the use of the app through app tracking and querying the user-rated quality of the app will give insight in how people use and experience the stand-alone mobile mindfulness app. In this study participants are self-decisive to practice mindfulness through the app to evaluate the use of the app. However, research points out that regular practice is recommended to enhance mindfulness skills and the associated outcomes [29,32,59,60]. Another limitation related to the study design, is that this is an open-label trial where solely the statistician is masked. Furthermore, infertility treatment and concomitant care (e.g. acupuncture, fertility coach) are allowed during the trial which may bias the outcome measures. This is taken into account in analysis as both topics are questioned during baseline measurements and at the end of the study. Future more in-depth research could integrate a third active control group as a wait-list control condition may inflate estimates of the experimental effect [61]. If the MoMiFer-app would prove to be effective, it could be integrated in standard care, offering an easily accessible, low-intensive, and a more cost-efficient strategy for people experiencing infertility to improve their mental health.

Author contributions

TB, NW, CM, ED, CS, KVdG, SLF, and FR designed the trial, developed the protocol, and applied for funding. TB, NW, FR, and KVdG applied for ethical approval. TB, NW, and KVdG implemented the logistics of the trial. All authors read, revised, and approved the final manuscript.

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Competing interests

Katleen Van der Gucht and Filip Raes are founders and members of the managing committee of the Leuven Mindfulness Centre Fund. Filip Raes and Katleen Van der Gucht receive

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Patient consult for publication

Not applicable.

Availability of data and material

Questionnaire data is collected through the online survey platform Qualtrics according to GCP. The data from the stand-alone mobile mindfulness application can be retrieved from the secured website of MoMiFer. Once all data of this RCT are gathered, the MoMiFer research team will focus on data-analysis. Regarding data sharing, the International Committee of Medical Journal Editors recommendations will be followed. Individual deidentified participant data will be shared. In particular, individual participant data that underlie the results reported in our article, after deidentification (text, tables, figures, and appendices) will be shared. Data will become available from 9-36 months after the publication of the RCT-results. Data sharing with research groups interested in performing further data-analysis is stimulated.

Provenance and peer review

Not commissioned; externally peer reviewed.

Figures

Figure 1: Overview of the MoMiFer-RCT

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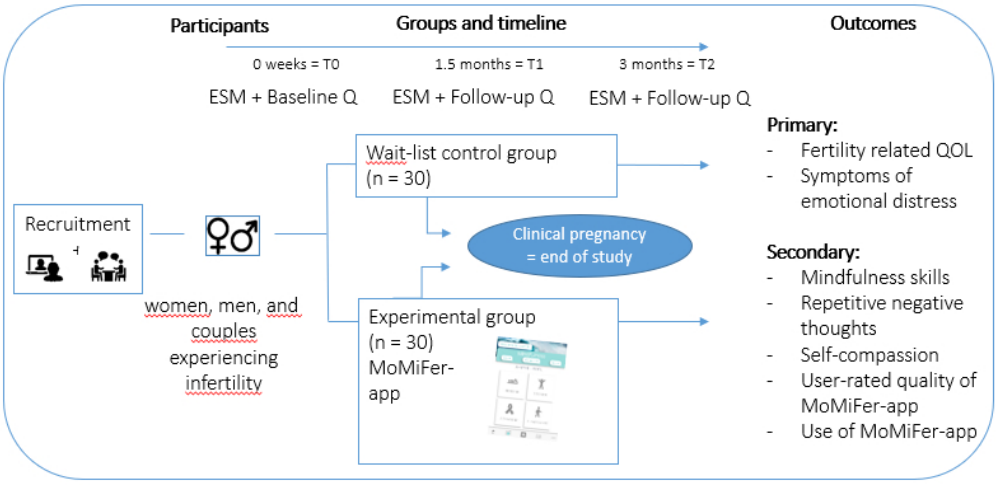

Figure 1: Overview of the MoMiFer-RCT. RCT, randomized controlled trial; ESM, experience sampling method; QOL, quality of life; Q, questionnaire; T, timing of assessment.

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Evaluatie van een Mobiel Mindfulness Programma (mMP) bij individuen/koppels met Fertiliteitsproblemen: MoMiFer studie

Opdrachtgever: KU Leuven

Onderzoeksinstelling*:* Leuven Mindfulness Centre (LMC), KU Leuven, Faculteit Psychologische en Pedagogische Wetenschappen, Tiensestraat 102, 3000 Leuven

Comité voor Medische Ethiek:

Centraal Ethisch Comité: Ethische Commissie Onderzoek UZ/KU Leuven

Plaatselijke onderzoekers: Prof. Dr. Filip Raes (LMC), Dr. Katleen Van der Gucht (LMC), Tessy Boedt (KU Leuven), Dr. Sharon Lie Fong (LUFC), Prof. Dr. Peter Kuppens (LMC), Prof. Dr. Ir. Christophe Matthys (KU Leuven), Nele Willaert (studente KU Leuven)

Contactpersoon: Nele Willaert**,** Tessy Boedt of Katleen Van der Gucht

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katleen.vandergucht@kuleuven.be +3216373183

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Geachte mevrouw, mijnheer,

U wordt uitgenodigd om deel te nemen aan een studie ter evaluatie van een mobiel mindfulness programma voor individuen/koppels met fertiliteitsproblemen.

Voordat u akkoord gaat om deel te nemen aan deze studie willen we u wat meer informatie geven over wat dit betekent op organisatorisch vlak en wat de eventuele voordelen en risico's voor u zijn. Zo kan u een beslissing nemen op basis van de juiste informatie. Dit wordt 'geïnformeerde toestemming' genoemd.

Wij vragen u de volgende pagina's met informatie aandachtig te lezen. Heeft u vragen, dan kan u terecht bij de onderzoeker of haar/zijn vertegenwoordiger.

I Noodzakelijke informatie voor uw beslissing om deel te nemen

Als u aan deze klinische studie deelneemt, moet u weten dat:

- deze studie is opgesteld na evaluatie door een ethisch comité.
- uw deelname vrijwillig is; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is uw ondertekende toestemming nodig. Ook nadat u hebt getekend, kan u de onderzoeker laten weten dat u uw deelname wilt stopzetten.
- de gegevens die in het kader van uw deelname worden verzameld, vertrouwelijk zijn. Bij de publicatie van de resultaten is uw anonimiteit verzekerd.
- er u geen kosten worden aangerekend in het kader van deze studie.
- er een verzekering is afgesloten voor het geval dat u schade zou oplopen in het kader van uw deelname aan deze studie.
- U geen vergoeding/compensatie zal ontvangen voor deze studie
- indien u extra informatie wenst, u altijd contact kan opnemen met de onderzoeker of de medewerker van haar team.

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Doelstelling en beschrijving van deze studie

Deze studie onderzoekt of het volgen van een mindfulness programma aangeboden via een mobiele applicatie (mMP) een meerwaarde kan bieden voor individuen/koppels met fertiliteitsproblemen. Er zijn aanwijzingen dat mindfulness zou kunnen bijdragen aan beter mentaal welzijn bij individuen/koppels met fertiliteitsproblemen. Een mobiel mindfulnessprogramma is laagdrempelig en minder tijdsintensief dan een klassiek mindfulnessprogramma. Omdat het effect van een mobiel mindfulnessprogramma voor individuen/koppels met fertiliteitsproblemen nog niet grondig onderzocht is, weten we nog niet zeker of dergelijke ondersteuning werkt. Daarom werd deze studie opgezet.

Wat is mindfulness?:

De basis van mindfulness is het trainen van aandacht: we leren onze aandacht heel bewust op het hier en nu te richten in plaats van ons continu te verliezen in negatieve gedachten. De voorbije tien jaar heeft wetenschappelijk onderzoek overtuigend aangetoond dat mindfulness kan helpen bij de aanpak en het voorkomen van stress, langdurige pijn, angst en depressie.

Voorwaarde voor deelname

U komt in aanmerking om deel te nemen aan onze studie indien u aan volgende voorwaarden voldoet:

- U en/of uw partner ervaren fertiliteitsproblemen
- U en/of uw partner zijn beide in het bezit van een smartphone
- U en/of uw partner begrijpen voldoende de Nederlandse taal

Verloop van de studie

Indien u beslist om deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet, zal u via loting aan een bepaalde groep toegewezen worden:

Groep 1: krijgt onmiddellijk toegang tot een mindfulnessprogramma aangeboden via een mobiele applicatie;

Groep 2: is een wachtlijst-controle groep. Dit betekent dat u eerst op een wachtlijst komt. U krijgt toegang tot een mindfulnessprogramma via een mobiele applicatie na 3 maanden.

We vragen u deze mobiele applicatie te gebruiken. U kan zelf kiezen welke oefeningen u precies uitvoert of volgt.

Om een goede vergelijking van de resultaten in beide onderzoeksgroepen mogelijk te maken, vragen wij aan iedereen om 1 week voor de studie en na 1.5 en 3 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers ongeacht de groep. Deze vragenlijsten peilen naar uw levenskwaliteit, hoe u zich voelt (stemming, stress, angst, depressieve gevoelens), hoe u denkt (bijvoorbeeld over uzelf) en hoe het met uw aandacht gesteld is. Het invullen van de vragenlijsten duurt ongeveer 45 minuten. Naast het invullen van de vragenlijsten zal u ook gevraagd worden om gedurende 4 dagen een soort van dagboek bij te houden op uw smartphone. Tijdens deze 4 dagen wordt u gedurende de dag 10 maal opgepiept, waarbij zal gevraagd worden een aantal korte vragen te beantwoorden over uw stemming en gedachten. Het beantwoorden van deze vragen duurt ongeveer 90 seconden.

Voor de analyse van onze onderzoeksbevindingen zullen we ook registreren hoe vaak en hoe lang u de mindfulness app gebruikt.

Risico's, nadelen en voordelen

Er zijn geen extra risico's door het deelnemen aan deze studie in vergelijking met individuen/koppels die niet deelnemen aan deze studie.

Een nadeel aan deelnemen aan deze studie zou kunnen zijn dat wij u vragen om, onafhankelijk van de groep waarvoor u loot, verscheidene online vragenlijsten in te vullen op verschillende momenten in de tijd, wat tijd vergt.

Een voordeel van deelname aan deze studie, is dat de informatie die dankzij deze studie verkregen wordt, kan bijdragen tot een betere kennis van de impact van een mobiel mindfulness programma bij fertiliteitsproblemen.

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Stopzetting van de deelname/intrekking van toestemming

Uw deelname is geheel vrijwillig. U hebt het recht om uw deelname aan de studie om eender welke reden en zonder opgave van redenen stop te zetten. U kan om eender welke reden en zonder opgave van redenen uw toestemming tot deelname aan de studie intrekken. Hiermee trekt u de toestemming inzake de verwerking van uw gegevens in. Wel kan het voor de onderzoeker nuttig zijn om te weten of u zich terugtrekt omdat de aan de studie verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel follow-up vragenlijsten).

Indien u aan deze studie deelneemt, vragen wij u het volgende:

- Ten volle mee te werken voor een correct verloop van de studie.
- Geen informatie over uw emotionele of gezondheidstoestand of de symptomen die u ervaart, te verzwijgen.

Contact

Als u bijkomende informatie wenst, maar ook ingeval van problemen of als u zich zorgen maakt, kan u contact opnemen met de onderzoekers (Nele Willaert, Tessy Boedt en Katleen Van der Gucht) op de telefoonnummers respectievelijk (+32479566999 +3216329946 of +3216373183) of via nele.willaert@student.kuleuven.be tessy.boedt@kuleuven.be of katleen.vandergucht@kuleuven.be

Als u vragen hebt met betrekking tot uw rechten als deelnemer aan de studie, kan u contact opnemen met de ombudsdienst op het telefoonnummer: +3216344818 of via ombudsdienst@uzleuven.be. Indien nodig kan de ombudsdienst u in contact brengen met het Ethisch Comité.

Extra nuttige contactgegevens

Als u wel eens vaker last hebt van sombere of angstige gevoelens of wanneer u merkt dat u vaker piekert dan u eigenlijk zou willen, dan wilt u daar misschien over praten met iemand. Weet dat u daarvoor steeds terecht kan bij onder andere deze diensten en centra:

- Indien u behoefte heeft aan een gesprek, zonder dat u wil zeggen wie u bent (dus 'anoniem'), kan u daarvoor steeds terecht bij de telefonische dienst Tele-Onthaal bel 106 (voor iedereen 24/24u en 7/7 dagen toegankelijk).
- U kan ook terecht op www.tele-onthaal.be voor chatsessies en meer info.
- U kan een Centrum voor Geestelijke Gezondheidszorg contacteren bij u in de buurt (http://www.geestelijkgezondvlaanderen.be/centrum-geestelijke-gezondheidszorg-cgg).
- Uiteraard kan u zich ook altijd wenden tot uw eigen huisarts of de huisarts van wacht in uw buurt (zie: www.mediwacht.be).

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Titel van de studie: **Evaluatie van een Mobiel Mindfulness Programma (mMP) bij individuen/koppels met Fertiliteitsproblemen: MoMiFer studie.**

II Geïnformeerde toestemming

Deelnemer

Vooraleer u start met deze studie, dient u uw geïnformeerde toestemming te geven voor de deelname aan deze studie. Daarvoor is het noodzakelijk dat u onderstaande informatie grondig doorneemt.
Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Dit houdt het volgende in:

- Het volgen een mindfulness programma (onmiddellijk of na een wachtlijst) via een mobiele applicatie gedurende 3 maanden. Het gebruik van deze applicatie wordt geregistreerd door de onderzoekers.
- Op 3 momenten (bij start van de studie, na 1,5 maanden en na 3 maanden) online vragenlijsten invullen betreffende mijn mentaal welzijn.
- Op diezelfde meetmomenten gedurende 4 dagen, 10 keer per dag enkele vragen beantwoorden via mijn smartphone betreffende mijn mentaal welzijn.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat aan mijn deelname geen enkel risico verbonden is.

Ik begrijp dat mijn deelname aan deze studie geheel vrijwillig is en dat er dus geen enkele sprake van dwang is. Ik heb het recht op elk moment mijn deelname stop te zetten. Bij het stopzetten van mijn deelname hoef ik geen reden te geven en brengt dit in geen enkel geval nadelen of enig ander gevolg met zich mee.

Ik begrijp dat alle informatie vertrouwelijk is en mijn anonimiteit wordt gegarandeerd. Dit wil zeggen dat mijn naam niet terug gelinkt kan worden met mijn ingevulde online vragenlijst en dat er nergens gevraagd wordt mijn naam of andere namen te vermelden. De resultaten van dit onderzoek kunnen gebruikt worden voor wetenschappelijke doeleinden en mogen gepubliceerd worden. Mijn naam wordt daarbij niet gepubliceerd, anonimiteit en de vertrouwelijkheid van de gegevens is in elk stadium van het onderzoek gewaarborgd.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.
Indien ik nog vragen heb omtrent de studie of extra informatie wil, kan ik terecht bij: Nele Willaert: nele.willaert@student.kuleuven.be (gsmnummer: 0479566999) of Tessy Boedt: tessy.boedt@kuleuven.be (telefoonnummer: +3216329946)

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn gegevens die voor de hier vermelde studie worden verzameld, later zullen worden verwerkt, op voorwaarde dat deze verwerking beperkt blijft tot de context van de hier vermelde studie voor een betere kennis van de impact van mindfulness bij fertiliteitsproblemen.

Naam, voornaam, datum en handtekening van de deelnemers:

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Onderzoeker

Ik ondergetekende, ... verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemers is uitgeoefend om hem/haar te doen toestemmen tot deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de laatste versie van de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naam, Voornaam, Datum en handtekening van de onderzoeker:

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III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Om een goede vergelijking van de resultaten in beide onderzoeksgroepen mogelijk te maken vragen wij aan iedereen om bij het begin van de studie en na 1,5 en 3 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers, ongeacht de groep die geloot wordt. Het invullen van deze vragenlijsten neemt ongeveer 45 minuten per meetmoment van uw tijd in beslag. Deze vragenlijsten hebben betrekking op uw algemeen welbevinden. Deze studie eindigt na 3 maanden. Naast het invullen van de vragenlijsten zal aan de deelnemers ook gevraagd worden om gedurende 4 dagen een soort van dagboek bij te houden via de smartphone. Tijdens deze 4 dagen worden deelnemers gedurende de dag 10 maal opgepiept, daarbij wordt gevraagd een aantal korte vragen te beantwoorden over stemming en gedachten. Het beantwoorden van deze vragen duurt ongeveer 90 seconden.

2. Aanvullende informatie over de risico's die verbonden zijn aan deelname aan de studie

Niet van toepassing.

3 : Aanvullende informatie over de bescherming en de rechten van deelnemers aan een klinische studie

Ethische comités

Deze studie werd geëvalueerd door een onafhankelijk ethisch comité (Ethische Commissie Onderzoek UZ/KU Leuven) dat een gunstig advies heeft uitgebracht. De ethische comités hebben als taak de personen die aan studies deelnemen te beschermen. Ze controleren of uw rechten als deelnemer aan een studie gerespecteerd worden, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

Vrijwillige deelname

Aarzel niet om alle vragen te stellen die bij u opkomen voordat u tekent.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen, zonder dat u hiervoor een reden hoeft te geven, zelfs al hebt u eerder toegestemd om aan deze studie deel te nemen.

Als u aanvaardt om aan deze studie deel te nemen, ondertekent u het toestemmingsformulier. De onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij u de noodzakelijke informatie over deze studie heeft gegeven. U zal het voor u bestemde exemplaar ontvangen.

Het is wel aanbevolen om de onderzoeker op de hoogte te stellen, indien u besluit uw deelname aan de studie stop te zetten.

Kosten in verband met uw deelname

Indien u besluit aan deze studie deel te nemen, worden alle onderzoeken en procedures in het kader van de studie door de opdrachtgever betaald.

Vertrouwelijkheidsgarantie

Als opdrachtgever van het onderzoek, is KU Leuven de verwerkingsverantwoordelijke van uw persoonlijke gegevens die verwerkt worden in het kader van het onderzoek. Uw deelname aan de studie betekent dat u ermee akkoord gaat dat de onderzoeker gegevens over u verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties. Uw gegevens zullen worden verwerkt overeenkomstig met de Europese Algemene verordening inzake gegevensbescherming (AVG/GDPR).

U hebt het recht om aan de onderzoeker te vragen welke gegevens zij over u heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op uw huidige situatie, maar ook op

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uw voorgeschiedenis. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn[1].

De onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat zij zich ertoe verbindt om uw naam nooit bekend te maken, bv. in het kader van een publicatie of een conferentie en dat zij uw gegevens zal coderen (uw identiteit zal worden vervangen door een identificatiecode in de studie) voordat zij ze doorgeeft aan de beheerder van de databank (KU Leuven).

De onderzoeker en haar team zullen gedurende de volledige studie de enige personen zijn, die een verband kunnen leggen tussen de overgedragen gegevens en uw dossier[2].

De overgedragen persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is u te identificeren[3].

De door de opdrachtgever aangestelde beheerder van de onderzoeksgegevens kan u niet identificeren op basis van de overgedragen gegevens. Deze persoon is verantwoordelijk voor het verzamelen van de gegevens, die door alle onderzoekers die deelnemen aan de studie zijn verzameld en voor de verwerking en de bescherming van die gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kunnen uw gegevens worden ingekeken door personen die gebonden zijn aan het beroepsgeheim, zoals vertegenwoordigers van de ethische comités, van de opdrachtgever van de studie, of een door hen aangesteld extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de onderzoeker en onder zijn/haar toezicht (of van één van zijn/haar onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de betrokken ethische comités, aan andere onderzoekers en/of instellingen die samenwerken met de opdrachtgever.

Ze kunnen ook doorgegeven worden aan andere sites van de opdrachtgever in België. Dit gebeurt dan steeds in gecodeerde vorm zoals hierboven uitgelegd.

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat u akkoord gaat dat uw gecodeerde gegevens gebruikt worden voor doeleinden die in dit informatieformulier beschreven staan en dat ze overgedragen worden aan bovenvermelde personen en/of instellingen.

De opdrachtgever zal de verzamelde gegevens gebruiken in het kader van de studie waaraan u deelneemt, maar wil ze ook kunnen aanwenden in het kader van andere studies over dezelfde problemen als de uwe. Buiten de context die beschreven wordt in dit document, kunnen uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd. Er zal geen enkel nieuw gegeven aan de opdrachtgever worden doorgegeven.
Indien u vragen hebt over hoe wij uw gegevens gebruiken, dan kan u hiervoor steeds terecht bij uw onderzoeker.
Ook de functionarissen voor gegevensbescherming van het onderzoekcentrum staan ter uwer beschikking.
De contactgegevens van deze laatste zijn als volgt:
DPO - UZ Leuven, Herestraat 49, 3000 Leuven, "het privacy-team" van KU Leuven.
Tot slot heeft u ook het recht om een klacht in te dienen over hoe uw gegevens worden behandeld, bij de Belgische toezichthoudende instantie die verantwoordelijk is voor het handhaven van de wetgeving inzake gegevensbescherming:
Gegevensbeschermingsautoriteit (GBA), Drukpersstraat 35, 1000 Brussel, Tel. +32 2 274 48 00

[1] Deze rechten zijn bepaald door de Algemene Verordening Gegevensbescherming , EU verordening 2016/679 en door de wet van 22 augustus 2002 betreffende de rechten van de patiënt.

[2] Voor klinische studies verplicht de wet om het verband met uw dossier gedurende 20 jaar te behouden. In geval van een studiegeneesmiddel voor een innoverende therapie waarbij gebruik wordt gemaakt van menselijk lichaamsmateriaal, bedraagt deze periode minimaal 30 jaar en maximaal 50 jaar in overeenstemming met de Belgische wet van 19 december 2008 inzake het gebruik van menselijk lichaamsmateriaal en de geldende Koninklijke Besluiten..

[3] De gegevensbank met onderzoeksresultaten bevat dus geen verband met elementen zoals uw initialen, uw geslacht en uw volledige geboortedatum (dd/mm/jjjj).

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E-mail: contact@apd-gba.be, Website: www.gegevensbeschermingsautoriteit.be

Verzekering

Conform de Belgische wet van 7 mei 2004 betreffende experimenten op de menselijke persoon is de opdrachtgever, KU Leuven - ook indien er geen sprake is van fout - aansprakelijk voor de schade die u als deelnemer en/of uw rechthebbenden, oplopen en die rechtstreeks of onrechtstreeks verband houdt met deelname aan de studie. U moet hiervoor dus geen fout aantonen. KU Leuven heeft voor deze aansprakelijkheid een verzekering afgesloten[4]. Indien u dit wenselijk acht kan u zelf de verzekeraar dagvaarden.
De contactgegevens van de verzekeraar zijn de volgende:
Amlin Insurance SE, Vanbreda Risk & Benefits NV, Plantin en Moretuslei, 297, 2140 Antwerpen.

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[4] In overeenstemming met artikel 29 van de Belgische Wet inzake experimenten op de menselijke persoon (7 mei 2004)
Informatie- en toestemmingsdocument3, gedateerd op 19/02/2019- pagina 8 van 8

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2____
	2b	All items from the World Health Organization Trial Registration Data Set	___1,2,4-8,11___
Protocol version	3	Date and version identifier	_____1_____
Funding	4	Sources and types of financial, material, and other support	_____11_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1,11,12___
	5b	Name and contact information for the trial sponsor	_____11_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6-9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10,12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11,12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10,12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental material 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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