BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029665
Article Type:	Protocol
Date Submitted by the Author:	04-Feb-2019
Keywords:	Lifestyle, Infertility, Diet, Physical Activity, Mindfulness

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TITLE

The effectiveness of a mobile preconception lifestyle programme in couples undergoing in vitro fertilisation (IVF): the protocol for the PreLiFe randomised controlled trial (PreLiFe-RCT)

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WORD COUNT

3230

Protocol version 1

ABSTRACT

Introduction: Infertility and *in vitro* fertilization (IVF; with or without intracytoplasmic sperm injection, ICSI) result in considerable emotional and financial burden. Increasing evidence suggests that lifestyle factors, including diet, physical activity and emotional wellbeing, are associated with IVF-success rates. Currently, IVF is not routinely combined with a lifestyle programme. The PreLiFe randomised controlled trial (RCT) assesses the effects of a new mobile preconception lifestyle programme (PreLiFe-programme) in couples undergoing IVF.

Methods and analysis: A multicentre RCT including heterosexual couples starting IVF in Belgian fertility clinics. IVF-Couples are randomised between an attention control group or the PreLiFe-programme for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound. The attention control programme includes a mobile application with treatment information (i.e. appointments and medication instructions) in addition to standard care. The PreLiFe-programme includes a mobile application with the same treatment information in combination with a lifestyle programme. This new lifestyle programme includes tailored advice and skills training on diet, physical activity and mindfulness in combination with text messages and telephone interaction with a health care professional trained in motivational interviewing. The primary outcome of this RCT is the cumulative ongoing pregnancy rate within 12 months after randomisation. Secondary outcomes include changes in diet, physical activity, emotional distress, body mass index (BMI), waist circumference, quality of life and other reproductive outcomes including IVF-discontinuation, clinical pregnancy rate, and time to pregnancy. Additionally, partner support and the feasibility (use and acceptability) of the PreLiFe-programme will be evaluated in the intervention group. Analysis will be according to intention to treat.

Ethics and dissemination: This study has been approved by the Medical Ethical Committee of the Leuven University Hospital (Belgium) and the other recruiting clinics. The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications.

Trial registration: clinicaltrials.gov: NCT03790449

KEY WORDS

Lifestyle; infertility; fertility treatment; IVF; reproductive outcome; mHealth; diet; physical activity; mindfulness

ARTICLE SUMMARY

Strengths and Limitations of this Study

- An adequately powered multicentre randomised controlled trial (RCT).
- The development of the PreLiFe-programme was theory- and evidence-based.
- Both partners are included as infertility is a condition affecting couples.
- This is an open-label study, which can be considered a limitation.
- Acceptance of the hypothesis of this RCT, would have major impact on clinical practice.

INTRODUCTION

Infertility, defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, affects one in ten heterosexual couples and about half of them seeks fertility treatment.[1] Infertility and its treatment, including *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), result in considerable emotional and financial burden.[2 3] In Belgium, the IVF-success rate, i.e. a live born baby is approximately 50% after one year of treatment.[4 5] However, during this period, one out of three couples discontinue IVF, mainly due to the IVF-related burden.[4 6] Improving IVF-success rates and reducing the burden of IVF are, therefore, important research priorities for reproductive medicine.[7]

One potential option for improving IVF-success rates and reducing the burden of IVF is an interdisciplinary developed lifestyle programme. Observational and interventional studies have recently shown that a healthy lifestyle is not only beneficial for infertile patients' general health but also for their IVF-success rate and for reducing IVF-burden. More specifically, observational studies showed that couples' healthy diet, normal body mass index (BMI) and moderate physical activity are associated with increased IVF-pregnancy rates.[8-15] One non-randomised controlled trial (RCT) reports improved diet, physical activity and increased pregnancy rates in infertile women receiving lifestyle education on diet and physical activity in addition to IVF.[16] Regarding personal wellbeing, two meta-analyses of observational studies came to contradictory conclusions on whether couples' personal wellbeing is associated with their IVF-outcome.[17 18] A meta-analysis of interventional studies, recently concluded that psychosocial interventions for couples undergoing IVF are effective, both in reducing emotional distress and in improving IVF-pregnancy rates.[19] Psychosocial interventions focussing on mindfulness are promising as it has recently been shown to result in significant improvements in the fertility related quality of life of women and in IVF-pregnancy rates.[20] A guideline of the European Society of Human Reproduction and Embryology (ESHRE) highlighted the importance of interdisciplinary support programmes, which can be provided by all staff members during routine fertility care.[21] So far, no lifestyle programme is offered routinely to IVF-couples and this results in one out of three couples deciding for themselves to seek complementary therapy outside of the fertility clinic, including lifestyle and/or psychosocial support.[22 23]

Mobile health (mHealth) as mode of delivery of support programmes has been recognised by (inter-)national policy makers as a promising method for promoting healthy behaviour in both the general population and couples trying to conceive.[24-26] A recent Dutch study showed that a mHealth intervention, targeting amongst others diet and physical activity of the population of reproductive age, improved their lifestyle and pregnancy rate, especially if both partners participated.[14 25] Nevertheless, no mobile preconception lifestyle programme addressing both infertile men and women and integrating advice on diet and physical activity with mindfulness exercises is available in routine fertility care.

METHODS AND ANALYSIS

This protocol was based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-)guidelines.[27]

Aim

The PreLiFe-RCT aims to assess the effects of a new mobile preconception lifestyle programme for couples undergoing IVF, the PreLiFe-programme. This RCT hypothesizes that following the PreLiFe-programme results in a higher cumulative ongoing pregnancy rate within 12 months as compared to an attention control group.

Study Design, Setting and Timing

The PreLiFe-RCT is a non-commercial randomised controlled trial in which the fertility clinics of the following five Belgian hospitals are involved: University Hospitals Leuven, Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint-Jan Bruges. Eligible couples starting IVF are randomised (1:1 allocation ratio) to the PreLife-programme or to an attention control group for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age. Recruitment started in November 2018.

Recruitment

The treating gynaecologist introduces the study to eligible couples during the consultation prior to starting IVF. Couples who are interested, are referred to a researcher, who explains the PreLiFe-RCT in detail and asks the couples for written informed consent. The multicentre set-up of the study ensures that a sufficient number of participants can be included.

Inclusion Criteria

Dutch speaking infertile heterosexual couples starting a first IVF cycle (with or without ICSI; irrespective of the IVF indication), in which the women is maximally 38 years old and in which both partners have a smartphone are eligible.

Exclusion Criteria

Couples, who were previously treated with IVF and/or who need preimplantation genetic testing (PGT) or donor gametes are not eligible. In addition, couples are excluded if one of the partners has special dietary requirements due to amongst others bariatric surgery, coeliac disease or renal disease and/or has movement constraints due to amongst others cerebral palsy or hemiparesis.

Randomisation, Blinding and Treatment Allocation

Block randomisation (stratified by clinic) with a 1:1 allocation ratio of eligible, consenting couples is performed with the aid of an online password-protected programme to prevent disclosing the allocation sequence to recruiters. In view of the nature of the intervention, this is an open-label study where only the statistician is blinded.

Interventions

During the first 12 months after randomisation or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age, participating couples receive standard medical treatment, i.e. IVF with or without ICSI according to the local protocol of the participating hospital and without guidance on lifestyle.

Both partners of couples randomised to the control group additionally receive an attention control programme, which mimics the amount of attention received by the intervention group, but is thought not have a specific effect.[28] More specifically, the attention control group receives a mobile application (app) with treatment information detailing medication instructions and planned appointments.

Both partners of couples randomised to the intervention group additionally receive the new PreLiFe-programme. The PreLiFe-programme has been developed at KU Leuven, after following multiple steps for developing complex health promotion interventions in line with theory and evidence and after consulting patients and health care professionals.[29 30] The main theory followed to improve healthy lifestyle behaviour is the self-determination theory (SDT), which requires meeting participants need for autonomy, competence and relatedness.[31] The PreLiFe-programme includes a mobile application (PreLiFe-app) with treatment information and tailored advice and skills training on diet, physical activity and mindfulness in combination with (i.e. blended care) interaction with a health care professional, trained in motivational interviewing.[32 33] Regarding diet, the PreLiFe-app focusses on improving food literacy, which is described as an interrelated combination of knowledge, skills and self-efficacy on food planning, selecting foods, food preparation, eating and evaluating information about food.[34 35] Food literacy is an evidence-base model to develop a lifelong healthy, sustainable and gastronomic relationship with food. The PreLiFe-app tailors the dietary advise and skills with the aid of a limited set of questions on food literacy, resulting in tailored goals, tips and recipes. Regarding physical activity, the PreLiFe-app focusses on improving daily physical activity (at moderate intensity) and reducing sedentary behaviour as advised by the World Health Organization (WHO).[36] The physical activity advice and skills training is tailored based on a pedometer linked to the PreLiFe-app and a limited set of questions on the PreLiFe-app, resulting in tailored goals and tips. To improve emotional wellbeing, an evidence-based mindfulness program, is included in the PreLiFe-app.[37 38] The mindfulness exercises follow the format and content of mindfulness based stress reduction.[39-41] Participants are instructed to select specific guided exercises based on their own time-schedule. The advice and skills training of the different components has different formats including: movies (animation and talking heads), audio files, text supported by graphic figures and photos. Blended care is implemented by allowing couples to ask lifestyle-related questions via text messages in the PreLiFe-app and couples receive a telephone call every 3 months (1, 4, 7 and 10 months after randomisation).

Outcomes, Data Collection and Data Management

The primary outcome of this RCT is cumulative ongoing pregnancy rate within 12 months after randomisation. The secondary biomedical outcomes are: BMI, waist circumference, IVF-discontinuation, clinical pregnancy rate and time to pregnancy. The secondary outcomes in which changes are assessed with Patient Reported Outcome Measures (PROMs) are: diet, physical activity, emotional distress and quality of life. In the intervention group, partner support and the feasibility of the PreLiFe-programme (i.e. use and acceptability) are additionally evaluated. Table 1 describes outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome. Data are extracted from medical records, self-administered online questionnaires, the PreLiFe-app or additionally assessed by the researchers (i.e. BMI and waist circumference). Local researchers will enter all data in the Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, 'Castor EDC'.[42] The combination of this web-based, instantaneous electronic validation, and regular on-site monitoring safeguards quality and completeness of the data.

Participant Timeline

Figure 1 provides an overview of all PreLiFe-RCT procedures from recruitment, until the end of the study. Couples, who consented during their consultation prior to IVF, receive a PreLiFe-RCT intake on the same day of their IVF-intake. The PreLiFe-intake consists of the following elements: addressing questions of couples about the study; collecting baseline measurements, extracting patients' medical and fertility related history from medical records; randomisation and configuring the PreLiFe-programme. At baseline, 3, 6, 9 and 12 months after randomisation, the researcher sends a link with self-administered online questionnaires on lifestyle behaviour and partner support to participating couples through email and through the mobile app. The follow-up measurements of physical health including height, weight and waist circumference are planned about every 3 months, simultaneously with standard appointments during fertility treatment. Reminders are sent to participants to ensure attendance at follow-up and prevent dropout of the study. A deviation of two weeks before and after the planned time of measurement is allowed. IVF-trajectories include two different phases. Phase one, where all couples undergo a fresh IVF cycle and phase two with possible pregnancies, follow-up frozen-thawed embryo transfer cycles (if available) and subsequent fresh cycles for which planning differs in time for all couples (see figure 1). The course and outcome of the treatment of the couples is extracted from medical records by the researcher for a period up to 12 months after randomisation. The study ends 12 months after randomisation or if an ongoing pregnancy confirmed by ultrasound (at 12 weeks of gestational age) occurs within 12 months after randomisation. At the end of the study period the feasibility (use and acceptability) of the PreLiFe-programme will be assessed in the intervention group through self-administered online questionnaires. App-based tracking is used throughout the study to evaluate the use of the PreLiFe-programme. Participants can withdraw from the study at any time for any reason if they wish to do so without any consequences on their IVF trajectory.

Table 1: Outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome.

Outcomes	Definitions/Methods of assessment	Timing of assessments					
		Baseline	3 months	6 months	9 months	12 months	Continuously
Patient Reported Outcome Measures	**Questionnaire name (abbreviation)** - **Content of questions** - **Details on evaluation, subscales and scoring**						
General Lifestyle Behaviour	Self-developed General Lifestyle Questionnaire. - Questions on smoking, alcohol use, supplement intake and complementary therapy. - Descriptive evaluation.	x	x	x	X	X	
Diet	Food Frequency Questionnaire (FFQ).[43] - Questions on frequency and portion size of consumption of foods and beverages. - Evaluation of dietary pattern and diet quality (index to reflect compliance with food based dietary guidelines[44]). Diet quality score: 0-100 (the higher, the better diet quality).	x	x	x	X	X	
Physical Activity	International Physical Activity Questionnaire Short Form (IPAQ-SF).[45] - Questions on duration and frequency of different intensities of physical activity. - Evaluation based on WHO recommendations[36].	x	x	x	X	X	
Personal Wellbeing	Depression, Anxiety and Stress Scale (DASS-21).[46 47] - Questions on symptoms of stress, anxiety and depression (emotional distress). - Stress, anxiety and depression subscales, overall score: 0-126 (the higher, the more emotional distress).	x	x	x	X	X	
Quality of Life (QOL)	Fertility Quality of Life Tool (FertiQOL).[48 49] - Questions on fertility related quality of life. - Emotional, mind-body, relational and social subscales, overall score: 0-100 (the higher, the better quality of life).	x	x	x	X	X	
Partner support *	Questionnaire based on the social support for diet and exercise scales.[50] - Questions on partner support for diet, physical activity and mindfulness. - Support for diet (0-15), physical activity (0-15), and mindfulness (0-10) subscales (the higher, the better partner support).		x	x	X	X	
Acceptability of PreLiFe-programme *	A short version of the subjective quality subscale of the Mobile App Rating Scale (MARS).[51] - Questions on the acceptability and subjective quality of the PreLiFe-programme. - Descriptive evaluation + subjective quality: 0-10 (the higher the better subjective quality of the PreLiFe-programme).					X	
Outcomes collected from PreLiFe-app	**Definition/Specification**						
Use of PreLiFe-programme *	App-based-tracking to evaluate the percentage of participants (couples) using the PreLiFe-programme in combination with a question on their motivation of (not) using the PreLiFe-programme.		x	x	X	X	
Outcomes extracted from medical records	**Definition/Specification**						
Socio-demographic background	Age; Ethnicity; Level of education; Profession.	x					
Medical history	Current and resolved medical conditions; Current medication use.	x					
Fertility history	Duration of self-reported infertility; Indication of infertility: male, female or mixed factor infertility; Primary or secondary infertility.	x					
Course of IVF treatment	Details on fresh and frozen-thawed IVF/ICSI cycles such as date and type of stimulation, date of aspiration, number of oocytes, total motile sperm count, date of fresh embryo transfer, date of frozen-thawed embryo transfer, in case of a cancelled cycle, date and reason of cancellation; outcome of the cycle (detection of hCG) and any adverse events.						x
Clinical pregnancy	A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy.[52]						x
Time to (clinical) pregnancy	The time taken to establish a pregnancy, measured in months.[52]						x
Ongoing pregnancy	A viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan.[53]						x
IVF-discontinuation	Couples who had quit IVF before the achievement of a pregnancy.[54]						x
Outcomes measured by the researcher	**Definition/Specification**						
Body Mass Index	To estimate nutritional status. BMI is defined as a person's weight in kilograms divided by the square of the person's height in metres (kg/m^2). Weight is measured when wearing light clothes and no shoes on a calibrated scale Height is measured without shoes on a stadiometer.	x	x	x	X	x	
Waist circumference	To estimate abdominal fat. Waist circumference is measured with a waist circumference measuring tape according to international Standards for Anthropometric Assessment.	x	x	x	X	x	
*Only Measured in the intervention group							

Sample Size

A sample size for an intention-to-treat analysis of the primary outcome (cumulative ongoing pregnancy rate) was calculated, in collaboration with a statistician from KU Leuven. The calculations were based on literature from the field of reproductive medicine regarding: (i) the optimistic, realistic and pessimistic cumulative IVF-success rates in Belgium[4 5], (ii) the IVF-discontinuation rates in Belgium[4], (iii) data on the impact of a preconception lifestyle intervention on IVF-success rates[16] (iv) data on the impact of a psychosocial intervention on IVF-discontinuation rates[55] and (v) data on withdrawal of fertility patients from lifestyle interventions.[55 56] Assuming a cumulative ongoing pregnancy rate of 50% in the control group[4 5] and 63% in the intervention group dictates a sample size of 230 couples per group or 460 couples in total (two-sided test; power of 80% and alpha of 5%). The 13% increase in cumulative ongoing pregnancy rate within the first 12 months after starting IVF is partly expected by assuming improved IVF-success rates and partly by assuming decreased IVF-discontinuation rates. More specifically, a preconception lifestyle programme targeting physical activity, diet and stress-management increased the clinical pregnancy rates of one IVF-cycle from 19.2% to 46.1%.[16] Regarding decreasing IVF-discontinuation-rates, a cognitive coping and relaxation programme had a tendency to decrease the IVF-discontinuation rate within 12 months from 15.2% to 5.5%.[55] Calculations were performed using PASS14 software.[57]

Data Analysis

Analysis will be according to the intention-to-treat. Descriptive statistics for baseline characteristics in the two arms will be presented and the withdrawal rate from the study will be assessed and compared between the two arms. The primary outcome is cumulative ongoing pregnancy rate (COPR) within 12 months after randomization. To calculate this, an ongoing pregnancy conceived within 12 months after randomization will be counted as a positive event, whereas IVF-discontinuation and absence of pregnancy will be counted as a negative event. The COPR in both groups will be compared using multivariate logistic regression models with controlling for potential confounders such as age and BMI. Odds ratios with 95% confidence intervals will be reported. A p-value <0.05 will be used to determine statistical significance for the intervention. Furthermore, cumulative incidences of ongoing pregnancy and IVF-discontinuation in the intervention and control group will be described. Similar analysis will be performed for binary secondary outcomes such as clinical pregnancy. Additionally we will evaluate changes in lifestyle parameters including changes in the diet, physical activity, emotional distress, BMI, waist circumference and fertility related quality of life over time and we will evaluate the differences between the intervention and control group in these parameters. Mixed models for repeated measurements (MMRM) will be used to evaluate treatment, time and interactive effects on these secondary outcomes. The determination of statistical significance will not be central to the analysis of secondary endpoints, yet nominal p-values may be reported. Descriptive analysis will be conducted on additional parameters measured only in the intervention group, more specifically: partner

support and feasibility of the PreLiFe-programme. Regarding missing data, MMRM is used which is consistent under the 'missing at random' assumption and in line with the intention-to-treat principle.[58] For the primary outcome we do not expect missing data.

Harms

Throughout the PreLiFe-RCT, all solicited and spontaneously reported adverse events and other unintended effects of the PreLiFe-programme or RCT will be collected, assessed, reported and managed according to good clinical practice (GCP).

Patient and Public Involvement

For the development of the PreLiFe-programme and the PreLife-RCT, we applied a human-centred design, consulting both patients and health care professionals. Additionally, an advisory committee has been installed from the start of the development of the project and includes representatives of the Belgian patient association 'De Verdwaalde Ooievaar' and of the 'Belgian Society for Reproductive Medicine' (BSRM).

ETHICS AND DISSEMINATION

This study has been approved by the Medical Ethical Committee of the University Hospitals Leuven (Belgium) and the local ethics committees of the participating clinics (i.e. Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint Jan Bruges)(s61596). If any protocol amendments would have to be made, they will be reported and submitted to all medical ethical committees.

Confidentiality of the participant's data is ensured by using participant IDs rather than identifiable information in the data set (i.e. coding) and by storing the document linking the IDs to the identifiable information separately. Only researchers from the study have access to the coded data.

The findings of this RCT will be disseminated through presentations at international scientific meetings and in peer-reviewed publications in accordance with academic standards. The participating sites are not allowed to publish any data or results from the study prior the multicentre publication. Authorship to publications will be in accordance with the requirements published by the International Committee of medical Journal Editors, in accordance with the requirements of the respective medical journal and according to the KU Leuven Publication Policy. We do not intend to collaborate with a medical writer.

DISCUSSION

The PreLiFe-RCT examines a novel preconception lifestyle programme for couples undergoing IVF, including tailored advice and skills training on diet, physical activity and mindfulness, in a mHealth format combined with motivational interviewing via text messages and telephone interaction. This PreLife-programme is theory- and evidence-based and has been developed systematically.[30 59] Besides examining a novel lifestyle intervention for couples undergoing IVF, with the potential of low-cost widespread implementation, this RCT has several strengths. First, this RCT has adequate power, which is enabled by the multicentre setting. Second, This RCT includes couples rather than individuals in the light of the evidence that addressing couples in lifestyle interventions provides extra support and maximises compliance.[25 60] Third, this RCT has an attention control condition rather than standard care.[28] A limitation, which is inevitable due to the nature of the intervention, is that this is an open-label study where only the statistician could be blinded. Finally, publishing this protocol outlines our effort to limit the risk of bias in our RCT.

With this RCT, we expect to demonstrate the added value of a mobile preconception lifestyle programme for reproductive and lifestyle outcomes in couples undergoing IVF. If this RCT proves that our lifestyle programme is effective, lifestyle support programmes should be implemented in standard care in each fertility clinic.

Author Contributions

TB, ED, KVDG, JS, BVC, CS and CM designed the trial, developed the protocol and applied for funding. TB, KP, DDN, SP, AVDV and SLF applied for ethical approval and implemented the logistics of the trial. All authors read, revised and approved the final manuscript.

Funding Statement

This work was supported by the Research foundation Flanders (Belgium).
(FWO-TBM; reference: T005417N).

Competing Interests

The authors declare to have no financial or non-financial conflicts of interest.

Acknowledgements

We acknowledge Barbara Weyn and Steve De Backer for the technical development of the PreLiFe-programme; Roos Voorend and Jan Derboven for contributing to the human centred design of the PreLiFe-programme, as well as all the patients, midwives and gynaecologists participating in the human centred design research; Edel Maex, Filip Raes, and Peter Kuppens for contributing to the development of the mindfulness part of our PreLiFe-programme; An Bogaerts for contributing to the development of the physical activity part of our PreLiFe-programme and the Nutrition Unit of University Hospitals Leuven for contributing to the development of the diet part of our PreLiFe-programme. Additionally we want to acknowledge our advisory committee of our FWO-TBM project and all clinics who are contributing to patient recruitment or are preparing to do so.

Other declarations

The following other declarations are not applicable to this manuscript: consent for publication, availability of data and material and endnotes.

List of abbreviations

BSRM: Belgian Society for Reproductive Medicine; BMI: body mass index; COPR: cumulative ongoing pregnancy rate; DASS21: depression, anxiety and stress scale; EDC: electronic data capture; ESHRE: European Society of Human Reproduction and Embryology; ET: embryo transfer; FertiQOL: fertility related quality of life questionnaire; FFQ: food frequency questionnaire; GCP: good clinical practice; hCG: human chorionic gonadotropin ICSI: intracytoplasmic sperm injection; IPAQ: international physical activity questionnaire; IVF: in vitro fertilization; MARS: mobile app rating scale; MMRM: mixed models for repeated measurements; PGT: preimplantation genetic testing; PROMs: patient reported outcome measures; QOL: quality of life; RCT: randomised controlled trial; SPIRIT: standard protocol items recommendations for interventional trials; WHO: World Health Organization.

Availability of data and material

All data is stored in a Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, i.e. Castor EDC. A link to the study protocol, secured EDC platform and other study documents can be found on the study website. Upon completion of the data collection, this RCT will be analyzed by the PreLiFe research team. This PreLiFe research team will facilitate data-sharing with other interested research groups wishing to perform additional analysis.

Figures

Figure 1: Overview of PreLiFe-RCT

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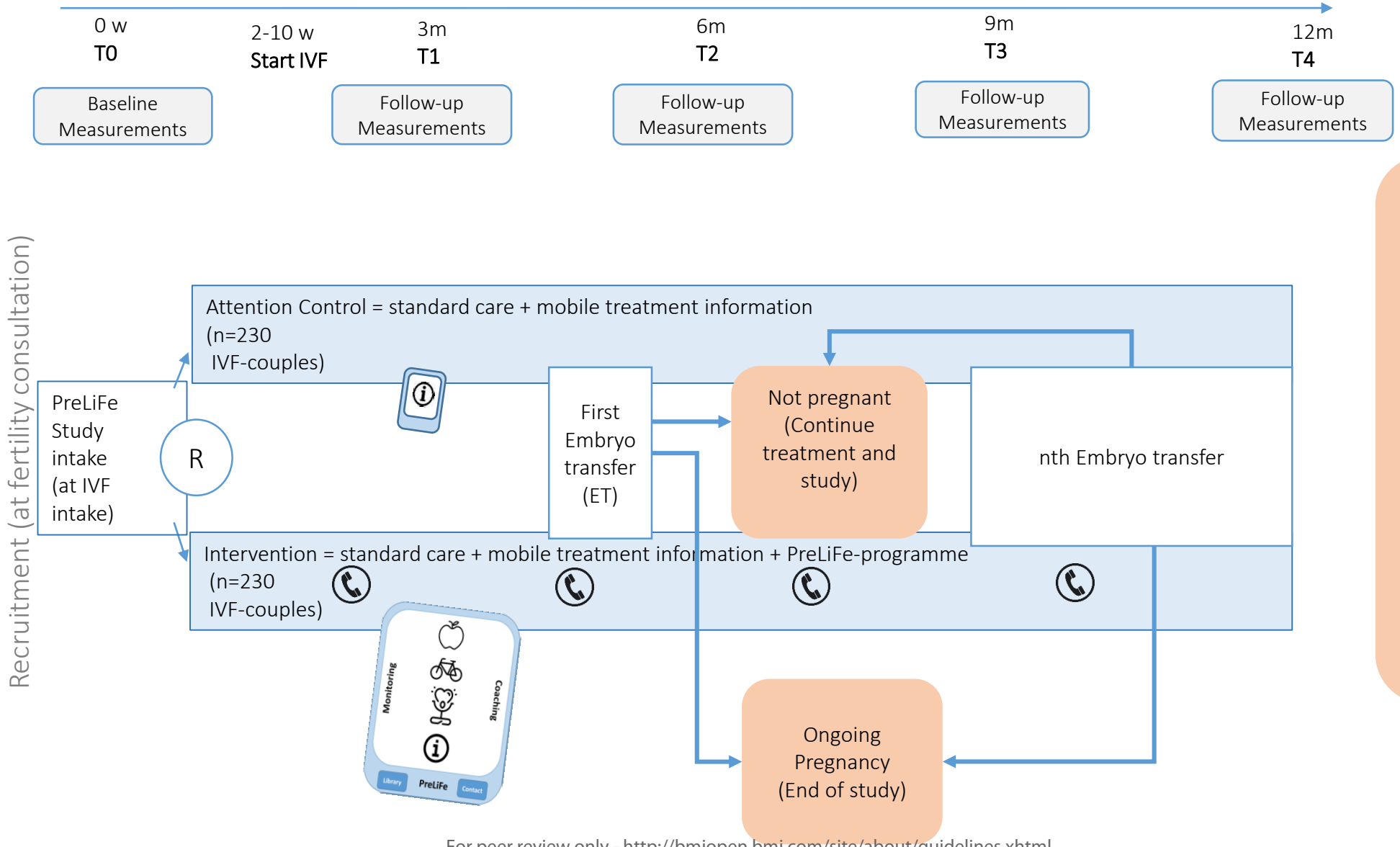
Participants

Groups (Control & Intervention) and measurements moments

Outcomes



Primary:

- Cumulative ongoing pregnancy within 12 months

Secondary:

- Lifestyle parameters (Diet, Physical Activity, Emotional Distress, BMI, Waist Circumference & QOL)
- Partners' Support
- Feasibility of PreLiFe-programme
- IVF and Reproductive outcomes

De PreLiFe-RCT

Evaluatie van een mobiel levensstijl programma voor koppels die IVF ondergaan

Opdrachtgever: KU Leuven en UZ Leuven met sponsering van FWO-TBM
Onderzoeksinstelling*:* Leuvens Universitair Fertiliteitcentrum (LUFC), UZ Leuven, Herestraat 49, 3000 Leuven
Comité voor Medische Ethiek:
Centraal Ethisch Comité: Ethische Commissie Onderzoek UZ/KU Leuven
Lokale Ethisch Comités: Ethisch Comité UZ Antwerpen, Commissie voor Ethiek AZ Sint Jan Brugge-Oostende, Commissie voor Medische Ethiek Imeldaziekenhuis Bonheiden, Commissie voor Medisch Ethiek AZ Diest.

Plaatselijke artsen en onderzoekers: Dr. Sharon Lie Fong (LUFC), Tessy Boedt (KU Leuven), Hilde Morobé (UZ Leuven), Prof. Dr. Diane De Neubourg (UZ Antwerpen), Prof. Dr. Karen Peeraer (LUFC/AZ Diest), Dr. Arne Van De Vijver (AZ Sint Jan Brugge) en Dr. Sofie Pelckmans (Imeldaziekenhuis Bonheiden)

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Geachte mevrouw, mijnheer,

U wordt uitgenodigd om deel te nemen aan een klinische studie ter evaluatie van een mobiel levensstijl programma voor koppels die IVF ondergaan.

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. Hebt u vragen, dan kan u terecht bij de arts-onderzoeker of haar of zijn vertegenwoordiger.

Dit document bestaat uit 3 delen: essentiële informatie die u nodig heeft voor het nemen van uw beslissing, uw schriftelijke toestemming en bijlagen waarin u meer details terugvindt over bepaalde onderdelen van de basisinformatie.

I Noodzakelijke informatie voor uw beslissing om deel te nemen

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

- deze klinische studie is opgesteld na evaluatie door één of meerdere ethische comité(s).
- 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 beslissing om al dan niet (verder) deel te nemen zal geen enkele negatieve invloed hebben op uw behandeling noch op de relatie met uw behandelende arts(en).
- 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 voor specifieke behandelingen, bezoeken/consultaties, onderzoeken 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 klinische studie.
- indien u extra informatie wenst, u altijd contact kan opnemen met de arts-onderzoeker of een medewerker van haar team.

Aanvullende informatie over uw "Rechten van de deelnemer aan een klinische studie" vindt u in deel III aanvullende informatie.

Doelstelling en beschrijving van deze studie

Het doel van deze studie is het vergelijken van de zwangerschapsresultaten, levensstijl en levenskwaliteit bij koppels die een in vitro fertilisatie (IVF) behandeling ondergaan aan de hand van een mobiel levensstijl programma (de PreLiFe app) gedurende een periode van 1 jaar.

Deze studie werd opgezet omdat wetenschappelijk onderzoek aantoonde dat een gezonde levensstijl een positieve invloed kan hebben op de reproductieve gezondheid. In deze studie omvat een gezonde levensstijl, gezonde en gevarieerde voeding, voldoende beweging en een goede mentale gezondheid.

Er zijn nu aanwijzingen dat het aanbieden van een levensstijl programma de zwangerschapskans, levensstijl en de tevredenheid omtrent de behandeling van patiënten kan verhogen. Omdat het effect van een mobiel levensstijl programma voor koppels in een IVF behandeling nog niet grondig onderzocht is, weten we nog niet zeker of dergelijke ondersteuning werkt. Daarom werkt ons ziekenhuis in samenwerking met vele andere ziekenhuizen in België mee aan deze PreLiFe studie.

Voorwaarde voor deelname

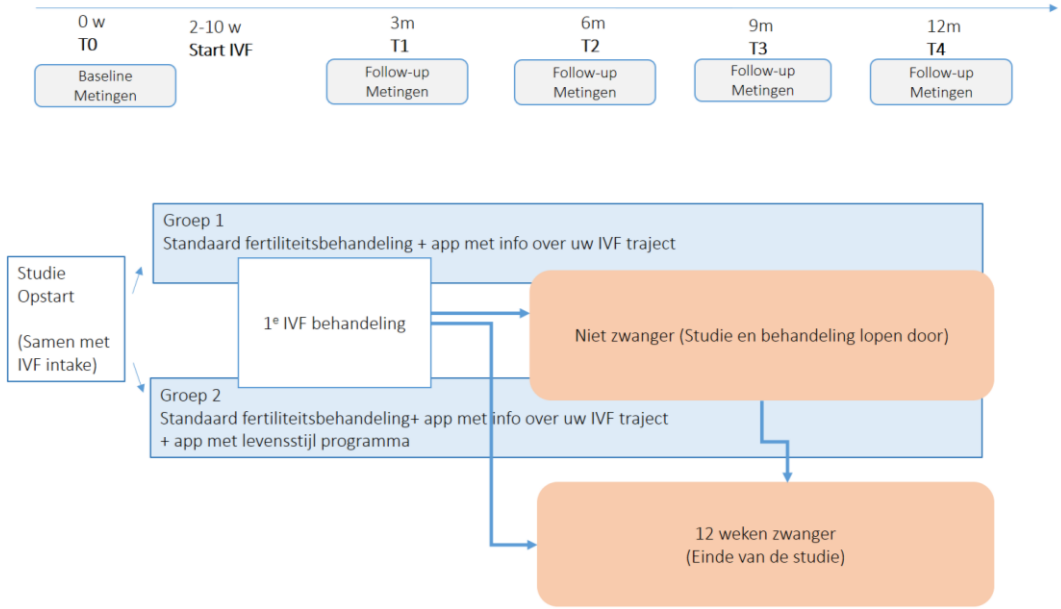
U komt in aanmerking om deel te nemen aan onze studie indien u aan volgende voorwaarden voldoet:

- U en uw partner starten een eerste IVF behandeling
- De vrouwelijke partner mag maximaal 38 jaar oud zijn
- U en uw partner zijn beide in het bezit van een smartphone
- U en uw partner begrijpen voldoende de Nederlandse taal

U komt niet in aanmerking voor onze studie indien u een fertiliteitsbehandeling ondergaat met donor gameten, donor embryo's of pre-implantatie diagnose. Koppels waar een van de partners een aandoening heeft die specifieke voedings- of bewegingsgewoonten met zich meebrengen zoals diabetes of coeliakie komen ook niet in aanmerking om deel te nemen aan de studie.

Verloop van de studie

Uw deelname aan de studie neemt maximaal 12 maanden in beslag en omvat geen extra bezoeken aan het fertiliteitcentrum in vergelijking met een behandeling zonder deelname aan de studie. Figuur 1 geeft een overzicht van de studie weer.



Figuur 1 : Overzicht PreLiFe studie

Indien u beslist om deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet zullen u en uw partner via loting toegewezen worden aan een bepaalde groep:
Groep 1: Standaard fertiliteitsbehandeling + een app waarin u uw IVF traject kan opvolgen en behandeling specifieke informatie kan terugvinden.

Groep 2: Standaard fertiliteitsbehandeling + een app waarin u uw IVF traject kan opvolgen en behandeling specifieke informatie kan terugvinden. Daarnaast krijgt u via deze versie van de PreLiFe app ook een levensstijl programma aangeboden. Dit programma bestaat uit 3 modules met name voeding, beweging en persoonlijk welbevinden. Voor de module **voeding** en **beweging** krijgt u na het invullen van een vragenlijst via de PreLiFe app gepersonaliseerde informatie, doelen en tips betreffende een gezond en gevarieerd voedings- en beweegpatroon. Er is ook de mogelijkheid om via de PreLiFe app je eigen dagelijkse stappen te registreren en je bewegingsmomenten in een online agenda in te plannen en op te volgen. Voor de module **persoonlijk welbevinden** is er de mogelijkheid om via de PreLiFe app mindfulness te beoefenen. Wij vragen aan alle deelnemers van deze groep om alle modules te overwegen, maar u kan zelf kiezen wat u net uitvoert of volgt. Verder is er de mogelijkheid om via e-mail vragen te stellen rond levensstijl, aan de PreLiFe coach. Deze coach wordt bijgestaan door een team van gynaecologen, vroedvrouwen, voedingsdeskundigen, bewegingsexperten en psychologen. Deze PreLiFe coach zal u ook om de 3 maanden opbellen om te luisteren hoe het loopt met het levensstijl programma. Voor de analyse van onze onderzoeksbevindingen zullen we ook registreren hoe vaak en hoe lang u de PreLiFe app gebruikt.

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 3, 6, 9 en 12 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers ongeacht de groep. Deze vragenlijsten hebben betrekking op uw levensstijl en uw algemeen welbevinden. Verder zal rond deze momenten ook uw gewicht, lengte en middelomtrek gemeten worden. Hiervoor hoeft u niet extra naar het fertiliteitscentrum te komen. Deze metingen worden samen met uw afspraken in kader van uw fertiliteitsbehandeling gepland.

Deze studie eindigt na 12 maanden of wanneer u of uw partner zwanger is. Indien er na deze 12 maanden geen zwangerschap is vastgesteld zal de normale patiëntenzorg worden vervolgd. Indien u of uw partner zwanger bent geworden tijdens de duur van de studie dan willen we graag weten hoe deze zwangerschap is verlopen en of deze zwangerschap heeft geleid tot de geboorte van een gezond kind. Daarom vragen wij vooraf ook uw toestemming om uzelf of uw arts die de zwangerschap opgevolgd heeft, te benaderen voor aanvullende gegevens over uw zwangerschap en bevalling. Dit gebeurt rond 12 weken en na de geboorte.

Risico's, nadelen en voordelen

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

Een nadeel aan deelnemen aan deze studie zou kunnen zijn dat wij u vragen om, onafhankelijk de groep waarvoor u loot, verscheidene online vragenlijsten in te vullen op verschillende momenten in de tijd, wat tijd vergt. Per meetmoment neemt dit ongeveer een half uur van uw tijd in beslag.

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 levensstijl programma bij toekomstige fertiliteitspatiënten.

Indien u loot voor groep 1, de groep zonder mobiel levensstijl programma wordt u behandeld volgens het standaardbeleid.
Indien u loot voor groep 2, de groep met het mobiel levensstijl programma, kan dit volgende voordelen voor u opleveren: gepersonaliseerde informatie betreffende gezonde levensstijl dat mogelijk de kans op zwangerschap bevordert en contact met een zorgverlener met expertise betreffende gezonde levensstijl. U zal wel gevraagd worden om de PreLiFe app door te nemen en te gebruiken, wat tijd zal vergen.

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 gezondheid gegevens in. Wel kan het voor de arts-onderzoeker nuttig zijn om te weten of u zich terugtrekt omdat de aan de studiebehandeling verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel follow-up bezoeken). Wanneer u besluit om niet langer deel te nemen, zal dit geen invloed hebben op uw verdere behandeling en zal u verder behandeld worden volgens de gebruikelijke richtlijnen.

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 gezondheidstoestand, de geneesmiddelen die u gebruikt of de symptomen die u ervaart te verzwijgen.

U moet eveneens weten dat:

- Het voor uw veiligheid aanbevolen is om uw huisarts of andere behandelende artsen die bij uw behandeling betrokken zijn te informeren over uw deelname aan deze studie. Wij raden u dit ten stelligste aan.
- Dit een koppelstudie is. De gegevens rond de behandeling zullen in kader van deze studie naar beide partners gecommuniceerd worden. Wij vragen u om hiervoor uw toestemming te geven. Indien u niet wenst dat uw partner hierover wordt geïnformeerd, zullen wij uw keuze respecteren.

Contact

Als u bijkomende informatie wenst, maar ook ingeval van problemen of als u zich zorgen maakt, kan u contact opnemen met de onderzoekers (Tessy Boedt en Hilde Morobé) op de telefoonnummers (+3216329946 of +3216340748) of via prelife@kuleuven.be.

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

Titel van de studie: **De PreLiFe-RCT: Evaluatie van een mobiel levensstijl programma voor koppels die IVF ondergaan.**

II Geïnformeerde toestemming

Deelnemer

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. Ik heb kennis genomen van het informatiedocument en de bijlagen ervan.

Ik heb voldoende tijd gehad om na te denken en met een door mij gekozen persoon, zoals mijn huisarts of een familielid, te praten.

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

Ik begrijp dat mijn deelname aan deze studie vrijwillig is en dat ik vrij ben mijn deelname aan deze studie stop te zetten zonder dat dit mijn relatie schaadt met het therapeutisch team dat instaat voor mijn gezondheid.

Ik begrijp dat er tijdens mijn deelname aan deze studie gegevens over mij zullen worden verzameld en dat de arts-onderzoeker en de opdrachtgever de vertrouwelijkheid van deze gegevens verzekeren overeenkomstig de Belgische wetgeving ter zake.

Ik stem in met de verwerking van mijn persoonlijke gegevens volgens de modaliteiten die zijn beschreven in de rubriek over het verzekeren van de vertrouwelijkheid (aanvullende informatie III).

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat de studiegegevens 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 ziekte en de behandeling ervan.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn gegevens rond mijn behandeling ook naar mijn partner gecommuniceerd zullen worden.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam, datum en handtekening van de deelnemers (man en vrouw):

Arts-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

Titel van de studie: **De PreLiFe-RCT: Evaluatie van een mobiel levensstijl programma voor koppels die IVF ondergaan.**

III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Deelname aan deze studie omvat geen extra bezoeken aan het fertiliteitcentrum in vergelijking met een behandeling zonder deelname aan 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 3, 6, 9 en 12 maanden online vragenlijsten in te vullen. Dit geldt voor alle deelnemers ongeacht de groep die geloot wordt. Het invullen van deze vragenlijsten neemt ongeveer een half uur per meetmoment van uw tijd in beslag. Deze vragenlijsten hebben betrekking op uw levensstijl en uw algemeen welbevinden. Verder zal rond deze momenten ook uw gewicht, lengte en middelomtrek gemeten worden. Hiervoor hoeft u niet extra naar het fertiliteitscentrum te komen. Deze meting wordt samen met u afspraken in kader van uw fertiliteitsbehandeling gepland.

Deze studie eindigt na 12 maanden of wanneer u of uw partner zwanger is. Indien er na deze 12 maanden geen zwangerschap is vastgesteld zal de normale patiëntenzorg worden vervolgd. Indien u of uw partner zwanger bent geworden tijdens de duur van de studie dan willen we graag weten hoe deze zwangerschap is verlopen en of deze zwangerschap heeft geleid tot de geboorte van een gezond kind. Daarom vragen wij vooraf ook uw toestemming om uzelf of uw arts die de zwangerschap opgevolgd heeft te benaderen voor aanvullende gegevens over uw zwangerschap en bevalling.

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 (Commissie voor Medische Ethiek van UZ Leuven) dat een gunstig advies heeft uitgebracht na raadpleging van de Ethische Comités van elk centrum waarin deze studie zal worden uitgevoerd met name: Ethisch Comité UZ Antwerpen, Commissie voor Ethiek AZ Sint Jan Brugge-Oostende, Commissie voor Medische Ethiek Imeldaziekenhuis Bonheiden, Commissie voor Medisch Ethiek AZ Diest. De ethische comités hebben als taak de personen die aan klinische studies deelnemen te beschermen. Ze controleren of uw rechten als patiënt en 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. Neem de tijd om erover te praten met een vertrouwenspersoon indien u dat wenst.

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. Uw beslissing zal in geen geval uw relatie met de arts-onderzoeker beïnvloeden, noch de kwaliteit van uw verdere verzorging.

Als u aanvaardt om aan deze studie deel te nemen, ondertekent u het toestemmingsformulier. De arts-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.

Voor uw veiligheid is het wel aanbevolen om de arts-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. Alle gebruikelijke medische prestaties worden aangerekend aan de ziekteverzekering en deelnemers.

Vertrouwelijkheidsgarantie

Uw deelname aan de studie betekent dat u ermee akkoord gaat dat de arts-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 arts-onderzoeker te vragen welke gegevens hij/zij over u heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op uw huidige klinische situatie maar ook op uw medische voorgeschiedenis en op de resultaten van onderzoeken die werden uitgevoerd voor de behandeling van uw gezondheid volgens de geldende zorgstandaard. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn[1].

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

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

De arts-onderzoeker en zijn team zullen gedurende de volledige klinische studie de enige personen zijn die een verband kunnen leggen tussen de overgedragen gegevens en uw medisch 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 artsen-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, kan uw medisch dossier 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 arts-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 artsen 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.

---

[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).

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat u akkoord gaat dat uw gecodeerde medische 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 ziekte 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 arts-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, E-mail : gdpr.research@uzleuven.be.
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
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, UZ 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. UZ 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.

[4] In overeenstemming met artikel 29 van de Belgische Wet inzake experimenten op de menselijke persoon (7 mei 2004)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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
Roles and responsibilities: committees	#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)	10, 11

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
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	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, non-inferiority, exploratory)	5
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#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	7,8
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)	7
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	9

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Data collection plan	#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	7,8
Data collection plan: retention	#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	7
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	7
Statistics: outcomes	#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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

Statistics: analysis population and missing data	#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)	9
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11

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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11,13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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

BMJ Open

The effectiveness of a mobile preconception lifestyle programme in couples undergoing in vitro fertilisation (IVF): the protocol for the PreLiFe randomised controlled trial (PreLiFe-RCT)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029665.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Apr-2019
Complete List of Authors:	Boedt, Tessy; KU Leuven, Department of Chronic Diseases Metabolism and Ageing; University Hospitals Leuven, Leuven University Fertility Centre Dancet, Eline; KU Leuven, Department of Development and Regeneration ; University Hospitals Leuven, Leuven University Fertility Centre Lie Fong, Sharon; University Hospitals Leuven, Leuven University Fertility Centre Peeraer, Karen; KU Leuven, Department of Development and Regeneration; University Hospitals Leuven, Leuven University Fertility Centre De Neubourg, Diane; Antwerp University Hospital, Centre for Reproductive Medicine Pelckmans, Sofie; Imelda Hospital Bonheiden, Department of Obstetrics and Gynaecology van de Vijver, Arne; General Hospital Sint Jan Bruges-Ostend, Department of Obstetrics and Gynaecology Seghers, Jan; KU Leuven, Department of Movement Sciences Van der Gucht, Katleen; KU Leuven, Leuven Mindfulness Centre; KU Leuven, Faculty of Psychology and Educational Sciences Van Calster, Ben; KU Leuven, Department of Development and Regeneration; Leiden University Medical Centre, Department of Biomedical Data Sciences Spiessens, Carl; KU Leuven, Department of Development and Regeneration; University Hospitals Leuven, Leuven University Fertility Centre Matthys, Christophe; KU Leuven, Department of Chronic Diseases, Metabolism and Ageing; University Hospitals Leuven, Department of Endocrinology
Primary Subject Heading:	Reproductive medicine
Secondary Subject Heading:	Public health
Keywords:	Lifestyle, Infertility, Diet, Physical Activity, Mindfulness

TITLE

The effectiveness of a mobile preconception lifestyle programme in couples undergoing in vitro fertilisation (IVF): the protocol for the PreLiFe randomised controlled trial (PreLiFe-RCT)

AUTHORS

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WORD COUNT

3605

Protocol version 1 (with revisions)

ABSTRACT

Introduction: Infertility and *in vitro* fertilization (IVF; with or without intracytoplasmic sperm injection, ICSI) result in considerable emotional and financial burden. Increasing evidence suggests that lifestyle factors, including diet, physical activity and emotional wellbeing, are associated with IVF-success rates. Currently, IVF is not routinely combined with a lifestyle programme. The PreLiFe randomised controlled trial (RCT) assesses the effects of a new mobile preconception lifestyle programme (PreLiFe-programme) in couples undergoing IVF.

Methods and analysis: A multicentre RCT including 460 heterosexual couples starting IVF in Belgian fertility clinics. IVF-Couples are randomised between an attention control group or the PreLiFe-programme for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound. The attention control programme includes a mobile application with treatment information (i.e. appointments and medication instructions) in addition to standard care. The PreLiFe-programme includes a mobile application with the same treatment information in combination with a lifestyle programme. This new lifestyle programme includes tailored advice and skills training on diet, physical activity and mindfulness in combination with text messages and telephone interaction with a health care professional trained in motivational interviewing. The primary outcome of this RCT is the cumulative ongoing pregnancy rate within 12 months after randomisation. Secondary outcomes include changes in diet, physical activity, emotional distress, body mass index (BMI), waist circumference, quality of life and other reproductive outcomes including IVF-discontinuation, clinical pregnancy rate, and time to pregnancy. Additionally, partner support and the feasibility (use and acceptability) of the PreLiFe-programme will be evaluated in the intervention group. Analysis will be according to intention to treat.

Ethics and dissemination: This study has been approved by the Medical Ethical Committee of the Leuven University Hospital (Belgium) and the other recruiting clinics. The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications.

Trial registration: clinicaltrials.gov: NCT03790449

KEY WORDS

Lifestyle; infertility; fertility treatment; IVF; reproductive outcome; mHealth; diet; physical activity; mindfulness

ARTICLE SUMMARY

Strengths and Limitations of this Study

- This is an adequately powered multicentre randomised controlled trial (RCT).
- The development of the PreLiFe-programme was theory- and evidence-based.
- Both partners are included as infertility is a condition affecting couples.
- This is an open-label study, only the statistician is blinded, which can be considered a limitation.
- Due to clinical practice, there is no fixed lead in time free from IVF, leading for some couples to little time to have an effect of the PreLiFe-programme before IVF.

INTRODUCTION

Infertility, defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, affects one in ten heterosexual couples and about half of them seeks fertility treatment.[1] Infertility and its treatment, including *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), result in considerable emotional and financial burden.[2 3] In Belgium, the IVF-success rate, i.e. a live born baby is approximately 50% after one year of treatment.[4 5] However, during this period, one out of three couples discontinue IVF, mainly due to the IVF-related burden.[4 6] Improving IVF-success rates and reducing the burden of IVF are, therefore, important research priorities for reproductive medicine.[7]

One potential option for improving IVF-success rates and reducing the burden of IVF is an interdisciplinary developed lifestyle programme. Observational and interventional studies have recently shown that a healthy lifestyle is not only beneficial for infertile patients' general health but also for their IVF-success rate and for reducing IVF-burden. More specifically, observational studies showed that couples' healthy diet, normal body mass index (BMI) and moderate physical activity are associated with increased IVF-pregnancy rates.[8-15] One non-randomised controlled trial (RCT) reports improved diet, physical activity and increased pregnancy rates in infertile women receiving lifestyle education on diet and physical activity in addition to IVF.[16] Regarding personal wellbeing, two meta-analyses of observational studies came to contradictory conclusions on whether couples' personal wellbeing is associated with their IVF-outcome.[17 18] A meta-analysis of interventional studies, recently concluded that psychosocial interventions for couples undergoing IVF are effective, both in reducing emotional distress and in improving IVF-pregnancy rates.[19] Psychosocial interventions focussing on mindfulness are promising as it has recently been shown to result in significant improvements in the fertility related quality of life of women and in IVF-pregnancy rates.[20] A guideline of the European Society of Human Reproduction and Embryology (ESHRE) highlighted the importance of interdisciplinary support programmes, which can be provided by all staff members during routine fertility care.[21] So far, no lifestyle programme is offered routinely to IVF-couples and this results in one out of three couples deciding for themselves to seek complementary therapy outside of the fertility clinic, including lifestyle and/or psychosocial support.[22 23]

Mobile health (mHealth) as mode of delivery of support programmes has been recognised by (inter-)national policy makers as a promising method for promoting healthy behaviour in both the general population and couples trying to conceive.[24-26] A recent Dutch study showed that a mHealth intervention, targeting amongst others diet and physical activity of the population of reproductive age, improved their lifestyle and pregnancy rate, especially if both partners participated.[14 25] Nevertheless, no mobile preconception lifestyle programme addressing both infertile men and women and integrating advice on diet and physical activity with mindfulness exercises is available in routine fertility care.

METHODS AND ANALYSIS

This protocol was based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-)guidelines.[27]

Aim

The PreLiFe-RCT aims to assess the effects of a new mobile preconception lifestyle programme for couples undergoing IVF, the PreLiFe-programme. This RCT hypothesizes that following the PreLiFe-programme results in a higher cumulative ongoing pregnancy rate within 12 months as compared to an attention control group.

Study Design, Setting and Timing

The PreLiFe-RCT is a non-commercial randomised controlled trial in which the fertility clinics of the following five Belgian hospitals are involved: University Hospitals Leuven, Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint-Jan Bruges. Eligible couples starting IVF are randomised (1:1 allocation ratio) to the PreLife-programme or to an attention control group for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age. Recruitment started in January 2019.

Recruitment

The treating gynaecologist introduces the study to eligible couples during the consultation prior to starting IVF. Couples who are interested, are referred to a researcher, who explains the PreLiFe-RCT in detail and asks the couples for written informed consent. The multicentre set-up of the study ensures that a sufficient number of participants can be included.

Inclusion Criteria

Dutch speaking infertile heterosexual couples starting a first IVF cycle (with or without ICSI; irrespective of the IVF indication), in which the women is maximally 38 years old and in which both partners have a smartphone are eligible.

Exclusion Criteria

Couples, who were previously treated with IVF and/or who need preimplantation genetic testing (PGT) or donor gametes are not eligible. In addition, couples are excluded if one of the partners has special dietary requirements due to amongst others bariatric surgery, coeliac disease or renal disease and/or has movement constraints due to amongst others cerebral palsy or hemiparesis.

Randomisation, Blinding and Treatment Allocation

Block randomisation (stratified by clinic) with a 1:1 allocation ratio of eligible, consenting couples is performed with the aid of an online password-protected programme to prevent disclosing the allocation sequence to recruiters. In view of the nature of the intervention, this is an open-label study where only the statistician is blinded.

Interventions

During the first 12 months after randomisation or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age, participating couples receive standard medical treatment, i.e. IVF with or without ICSI according to the local protocol of the participating hospital and without guidance on lifestyle.

Both partners of couples randomised to the control group additionally receive an attention control programme, which mimics the amount of attention received by the intervention group, but is thought not have a specific effect.[28] More specifically, the attention control group receives a mobile application (app) with treatment information detailing medication instructions and planned appointments.

Both partners of couples randomised to the intervention group additionally receive the new PreLiFe-programme. The PreLiFe-programme has been developed at KU Leuven, after following multiple steps for developing complex health promotion interventions in line with theory and evidence and after consulting patients and health care professionals.[29 30] The main theory followed to improve healthy lifestyle behaviour is the self-determination theory (SDT), which requires meeting participants need for autonomy, competence and relatedness.[31] The PreLiFe-programme includes a mobile application (PreLiFe-app) with treatment information and tailored advice and skills training on diet, physical activity and mindfulness in combination with (i.e. blended care) interaction with a health care professional, trained in motivational interviewing.[32 33] Regarding diet, the PreLiFe-app focusses on improving food literacy, which is described as an interrelated combination of knowledge, skills and self-efficacy on food planning, selecting foods, food preparation, eating and evaluating information about food.[34 35] Food literacy is an evidence-base model to develop a lifelong healthy, sustainable and gastronomic relationship with food. The PreLiFe-app tailors the dietary advise and skills with the aid of a limited set of questions on food literacy, resulting in tailored goals, tips and recipes. Regarding physical activity, the PreLiFe-app focusses on improving daily physical activity (at moderate intensity) and reducing sedentary behaviour as advised by the World Health Organization (WHO).[36] The physical activity advice and skills training is tailored based on a pedometer linked to the PreLiFe-app and a limited set of questions on the PreLiFe-app, resulting in tailored goals and tips. To improve emotional wellbeing, an evidence-based mindfulness program, is included in the PreLiFe-app.[37 38] The mindfulness exercises follow the format and content of mindfulness based stress reduction.[39-41] Participants are instructed to select specific guided exercises based on their own time-schedule. The advice and skills training of the different components has different formats including: movies (animation and talking heads), audio files, text supported by graphic figures and photos. Blended care is implemented by allowing couples to ask lifestyle-related questions via text messages in the PreLiFe-app and couples receive a telephone call every 3 months (1, 4, 7 and 10 months after randomisation).

Outcomes, Data Collection and Data Management

The primary outcome of this RCT is cumulative ongoing pregnancy rate within 12 months after randomisation. The secondary biomedical outcomes are: BMI, waist circumference, IVF-discontinuation, clinical pregnancy rate and time to pregnancy. The secondary outcomes in which changes are assessed with Patient Reported Outcome Measures (PROMs) are: diet, physical activity, emotional distress and quality of life. In the intervention group, partner support and the feasibility of the PreLiFe-programme (i.e. use and acceptability) are additionally evaluated. Table 1 describes outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome. Data are extracted from medical records, self-administered online questionnaires, the PreLiFe-app or additionally assessed by the researchers (i.e. BMI and waist circumference). Local researchers will enter all data in the Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, 'Castor EDC'.[42] The combination of this web-based, instantaneous electronic validation, and regular on-site monitoring safeguards quality and completeness of the data.

Participant Timeline

Figure 1 provides an overview of all PreLiFe-RCT procedures from recruitment, until the end of the study. Couples, who consented during their consultation prior to IVF, receive a PreLiFe-RCT intake on the same day of their IVF-intake. The PreLiFe-intake consists of the following elements: addressing questions of couples about the study; collecting baseline measurements, extracting patients' medical and fertility related history from medical records; randomisation and configuring the PreLiFe-programme. At baseline, 3, 6, 9 and 12 months after randomisation, the researcher sends a link with self-administered online questionnaires on lifestyle behaviour and partner support to participating couples through email and through the mobile app. The follow-up measurements of physical health including height, weight and waist circumference are planned about every 3 months, simultaneously with standard appointments during fertility treatment. Reminders are sent to participants to ensure attendance at follow-up and prevent dropout of the study. A deviation of two weeks before up to two weeks after the planned time of measurement is allowed. IVF-trajectories include two different phases. Phase one, where all couples undergo a fresh IVF cycle and phase two with possible pregnancies, follow-up frozen-thawed embryo transfer cycles (if available) and subsequent fresh cycles for which planning differs in time for all couples (see figure 1). The course and outcome of the treatment of the couples is extracted from medical records by the researcher for a period up to 12 months after randomisation. The study ends 12 months after randomisation or if an ongoing pregnancy confirmed by ultrasound (at 12 weeks of gestational age) occurs within 12 months after randomisation. All pregnancies (spontaneous and IVF pregnancies) conceived within these 12 months are followed up until the 12 weeks ultrasound scan. At the end of the study period the feasibility (use and acceptability) of the PreLiFe-programme will be assessed in the intervention group through self-administered online questionnaires. App-based tracking is used throughout the study to evaluate the use of the PreLiFe-programme. Participants can withdraw from the study at any time for any reason if they wish to do so without any consequences on their IVF trajectory.

Table 1: Outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome.

Outcomes	Definitions/Methods of assessment	Timing of assessments					
		Baseline	3 months	6 Months	9 months	12 months	Continuously
Patient Reported Outcome Measures	**Questionnaire name (abbreviation)** - **Content of questions** - **Details on evaluation, subscales and scoring**						
Background and General Lifestyle Behaviour	Questions on Background and General Lifestyle Behaviour. - Questions on smoking, alcohol use, supplement intake and complementary therapy. - Descriptive evaluation.	x	X	x	X	X	
Diet	Food Frequency Questionnaire (FFQ).[43] - Questions on frequency and portion size of consumption of foods and beverages. - Evaluation of dietary pattern and diet quality (index to reflect compliance with food based dietary guidelines[44]). Diet quality score: 0-100 (the higher, the better diet quality).	x	X	x	X	X	
Physical Activity	International Physical Activity Questionnaire Short Form (IPAQ-SF).[45] - Questions on duration and frequency of different intensities of physical activity. - Evaluation based on WHO recommendations[36].	x	X	x	X	X	
Personal Wellbeing	Depression, Anxiety and Stress Scale (DASS-21).[46 47] - Questions on symptoms of stress, anxiety and depression (emotional distress). - Stress, anxiety and depression subscales, overall score: 0-126 (the higher, the more emotional distress).	x	X	x	X	X	
Quality of Life (QOL)	Fertility Quality of Life Tool (FertiQOL).[48 49] - Questions on fertility related quality of life. - Emotional, mind-body, relational and social subscales, overall score: 0-100 (the higher, the better quality of life).	x	X	x	X	X	
Partner support *	Questionnaire based on the social support for diet and exercise scales.[50] - Questions on partner support for diet, physical activity and mindfulness. - Support for diet (0-15), physical activity (0-15), and mindfulness (0-10) subscales (the higher, the better partner support).		x	x	X	X	
Acceptability of PreLiFe-programme *	A short version of the subjective quality subscale of the Mobile App Rating Scale (MARS).[51] - Questions on the acceptability and subjective quality of the PreLiFe-programme. - Descriptive evaluation + subjective quality: 0-10 (the higher the better subjective quality of the PreLiFe-programme).					X	
Outcomes collected from PreLiFe-app	**Definition/Specification**						
Use of PreLiFe-programme *	App-based-tracking to evaluate the percentage of participants (couples) using the PreLiFe-programme in combination with a question on their motivation of (not) using the PreLiFe-programme.		x	x	X	X	
Outcomes extracted from medical records	**Definition/Specification**						
Socio-demographic background	Age; Ethnicity; Level of education; Profession.	x					
Medical history	Current and resolved medical conditions; Current medication use.	x					
Fertility history	Duration of self-reported infertility; Indication of infertility: male, female or mixed factor infertility; Primary or secondary infertility.	x					
Course of IVF treatment	Details on fresh and frozen-thawed IVF/ICSI cycles such as date and type of stimulation, date of aspiration, number of oocytes, total motile sperm count, date of fresh embryo transfer, date of frozen-thawed embryo transfer, in case of a cancelled cycle, date and reason of cancellation; outcome of the cycle (detection of hCG) and any adverse events.						x
Clinical pregnancy	A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy.[52]						x
Time to (clinical) pregnancy	The time taken to establish a pregnancy, measured in months.[52]						x
Ongoing pregnancy	A viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan.[53]						x
IVF-discontinuation	Couples who had quit IVF before the achievement of a pregnancy.[54]						x
Outcomes measured by the researcher	**Definition/Specification**						
Body Mass Index	To estimate nutritional status. BMI is defined as a person's weight in kilograms divided by the square of the person's height in metres (kg/m^2). Weight is measured when wearing light clothes and no shoes on a calibrated scale Height is measured without shoes on a stadiometer.	x	x	x	X	x	
Waist circumference	To estimate abdominal fat. Waist circumference is measured with a waist circumference measuring tape according to international Standards for Anthropometric Assessment.	x	x	x	X	x	
*Only Measured in the intervention group							

Sample Size

A sample size for an intention-to-treat analysis of the primary outcome (cumulative ongoing pregnancy rate) was calculated, in collaboration with a statistician from KU Leuven. The calculations were based on literature from the field of reproductive medicine regarding: (i) the optimistic, realistic and pessimistic cumulative IVF-success rates in Belgium[4 5], (ii) the IVF-discontinuation rates in Belgium[4], (iii) data on the impact of a preconception lifestyle intervention on IVF-success rates[16] (iv) data on the impact of a psychosocial intervention on IVF-discontinuation rates[55] and (v) data on withdrawal of fertility patients from lifestyle interventions.[55 56] Assuming a cumulative ongoing pregnancy rate of 50% in the control group[4 5] and 63% in the intervention group dictates a sample size of 230 couples per group or 460 couples in total (two-sided test; power of 80% and alpha of 5%). The 13% increase in cumulative ongoing pregnancy rate within the first 12 months after starting IVF is partly expected by assuming improved IVF-success rates and partly by assuming decreased IVF-discontinuation rates. More specifically, a preconception lifestyle programme targeting physical activity, diet and stress-management increased the clinical pregnancy rates of one IVF-cycle from 19.2% to 46.1%.[16] Regarding decreasing IVF-discontinuation-rates, a cognitive coping and relaxation programme had a tendency to decrease the IVF-discontinuation rate within 12 months from 15.2% to 5.5%.[55] Calculations were performed using PASS14 software.[57]

Data Analysis

Analysis will be according to the intention-to-treat. Descriptive statistics for baseline characteristics in the two arms will be presented and the withdrawal rate from the study will be assessed and compared between the two arms. The primary outcome is cumulative ongoing pregnancy rate (COPR) within 12 months after randomization. To calculate this, an ongoing pregnancy conceived within 12 months after randomization will be counted as a positive event, whereas IVF-discontinuation and absence of pregnancy will be counted as a negative event. The COPR in both groups will be compared using multivariate logistic regression models with controlling for potential confounders such as age and BMI. Odds ratios with 95% confidence intervals will be reported. A p-value <0.05 will be used to determine statistical significance for the intervention. Furthermore, cumulative incidences of ongoing pregnancy and IVF-discontinuation in the intervention and control group will be described. Similar analysis will be performed for binary secondary outcomes such as clinical pregnancy. Additionally we will evaluate changes in lifestyle parameters including changes in the diet, physical activity, emotional distress, BMI, waist circumference and fertility related quality of life over time and we will evaluate the differences between the intervention and control group in these parameters. Mixed models for repeated measurements (MMRM) will be used to evaluate treatment, time and interactive effects on these secondary outcomes. The determination of statistical significance will not be central to the analysis of secondary endpoints, yet nominal p-values may be reported. Descriptive analysis will be conducted on additional parameters measured only in the intervention group, more specifically: partner

support and feasibility of the PreLiFe-programme. Regarding missing data, MMRM is used which is consistent under the 'missing at random' assumption and in line with the intention-to-treat principle.[58] For the primary outcome we do not expect missing data.

Harms

Throughout the PreLiFe-RCT, all solicited and spontaneously reported adverse events and other unintended effects of the PreLiFe-programme or RCT will be collected, assessed, reported and managed according to good clinical practice (GCP).

Patient and Public Involvement

For the development of the PreLiFe-programme and the PreLife-RCT, we applied a human-centred design, consulting both patients and health care professionals. Additionally, an advisory committee has been installed from the start of the development of the project and includes representatives of the Belgian patient association 'De Verdwaalde Ooievaar' and of the 'Belgian Society for Reproductive Medicine' (BSRM).

ETHICS AND DISSEMINATION

This study has been approved by the Medical Ethical Committee of the University Hospitals Leuven (Belgium) and the local ethics committees of the participating clinics (i.e. Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint Jan Bruges)(s61596). If any protocol amendments would have to be made, they will be reported and submitted to all medical ethical committees.

Confidentiality of the participant's data is ensured by using participant IDs rather than identifiable information in the data set (i.e. coding) and by storing the document linking the IDs to the identifiable information separately. Only researchers from the study have access to the coded data.

The findings of this RCT will be disseminated through presentations at international scientific meetings and in peer-reviewed publications in accordance with academic standards. The participating sites are not allowed to publish any data or results from the study prior the multicentre publication. Authorship to publications will be in accordance with the requirements published by the International Committee of medical Journal Editors, in accordance with the requirements of the respective medical journal and according to the KU Leuven Publication Policy. We do not intend to collaborate with a medical writer.

DISCUSSION

The PreLiFe-RCT examines a novel preconception lifestyle programme for couples undergoing IVF, including tailored advice and skills training on diet, physical activity and mindfulness, in a mHealth format combined with motivational interviewing via text messages and telephone interaction. This PreLife-programme is theory- and evidence-based and has been developed systematically.[30 59] Besides examining a novel lifestyle intervention for couples undergoing IVF, with the potential of low-cost widespread implementation, this RCT has several strengths. First, this RCT has adequate power, which is enabled by the multicentre setting. Second, This RCT includes couples rather than individuals in the light of the evidence that addressing couples in lifestyle interventions provides extra support and maximises compliance.[25 60] Third, this RCT has an attention control condition rather than standard care.[28] This RCT has also some potential limitations. A limitation, which is inevitable due to the nature of the intervention, is that this is an open-label study where only the statistician could be blinded. A second potential limitation is that due to clinical practice, the PreLiFe-programme is offered right before the start of IVF without a fixed lead in time free from IVF. This leads for some couples to little time to follow the PreLiFe-programme and improve their lifestyle before their first IVF cycle. However, we will capture the time between offering the PreLiFe-programme and start of IVF. Finally, publishing this protocol outlines our effort to limit the risk of bias in our RCT.

With this RCT, we expect to demonstrate the added value of a mobile preconception lifestyle programme for reproductive and lifestyle outcomes in couples undergoing IVF. If this RCT proves that our lifestyle programme is effective, lifestyle support programmes should be implemented in standard care in each fertility clinic.

Author Contributions

TB, ED, KVDG, JS, BVC, CS and CM designed the trial, developed the protocol and applied for funding. TB, KP, DDN, SP, AVDV and SLF applied for ethical approval and implemented the logistics of the trial. All authors read, revised and approved the final manuscript.

Funding Statement

This work was supported by the Research foundation Flanders (Belgium).
(FWO-TBM; reference: T005417N).

Competing Interests

The authors declare to have no financial or non-financial conflicts of interest.

Acknowledgements

We acknowledge Barbara Weyn and Steve De Backer for the technical development of the PreLiFe-programme; Roos Voorend and Jan Derboven for contributing to the human centred design of the PreLiFe-programme, as well as all the patients, midwives and gynaecologists participating in the human centred design research; Edel Maex, Filip Raes, and Peter Kuppens for contributing to the development of the mindfulness part of our PreLiFe-programme; An Bogaerts for contributing to the development of the physical activity part of our PreLiFe-programme and the Nutrition Unit of University Hospitals Leuven for contributing to the development of the diet part of our PreLiFe-programme. Additionally we want to acknowledge our advisory committee of our FWO-TBM project and all clinics who are contributing to patient recruitment or are preparing to do so.

Other declarations

The following other declarations are not applicable to this manuscript: consent for publication, availability of data and material and endnotes.

List of abbreviations

BSRM: Belgian Society for Reproductive Medicine; BMI: body mass index; COPR: cumulative ongoing pregnancy rate; DASS21: depression, anxiety and stress scale; EDC: electronic data capture; ESHRE: European Society of Human Reproduction and Embryology; ET: embryo transfer; FertiQOL: fertility related quality of life questionnaire; FFQ: food frequency questionnaire; GCP: good clinical practice; hCG: human chorionic gonadotropin ICSI: intracytoplasmic sperm injection; IPAQ: international physical activity questionnaire; IVF: in vitro fertilization; MARS: mobile app rating scale; MMRM: mixed models for repeated measurements; PGT: preimplantation genetic testing; PROMs: patient reported outcome measures; QOL: quality of life; RCT: randomised controlled trial; SPIRIT: standard protocol items recommendations for interventional trials; WHO: World Health Organization.

Availability of data and material

All data is stored in a Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, i.e. Castor EDC. A link to the study protocol, secured EDC platform and other study documents can be found on the study website. Upon completion of the data collection, this RCT will be analyzed by the PreLiFe research team. This PreLiFe research team will facilitate data-sharing with other interested research groups wishing to perform additional analysis.

Figures

Figure 1: Overview of PreLiFe-RCT

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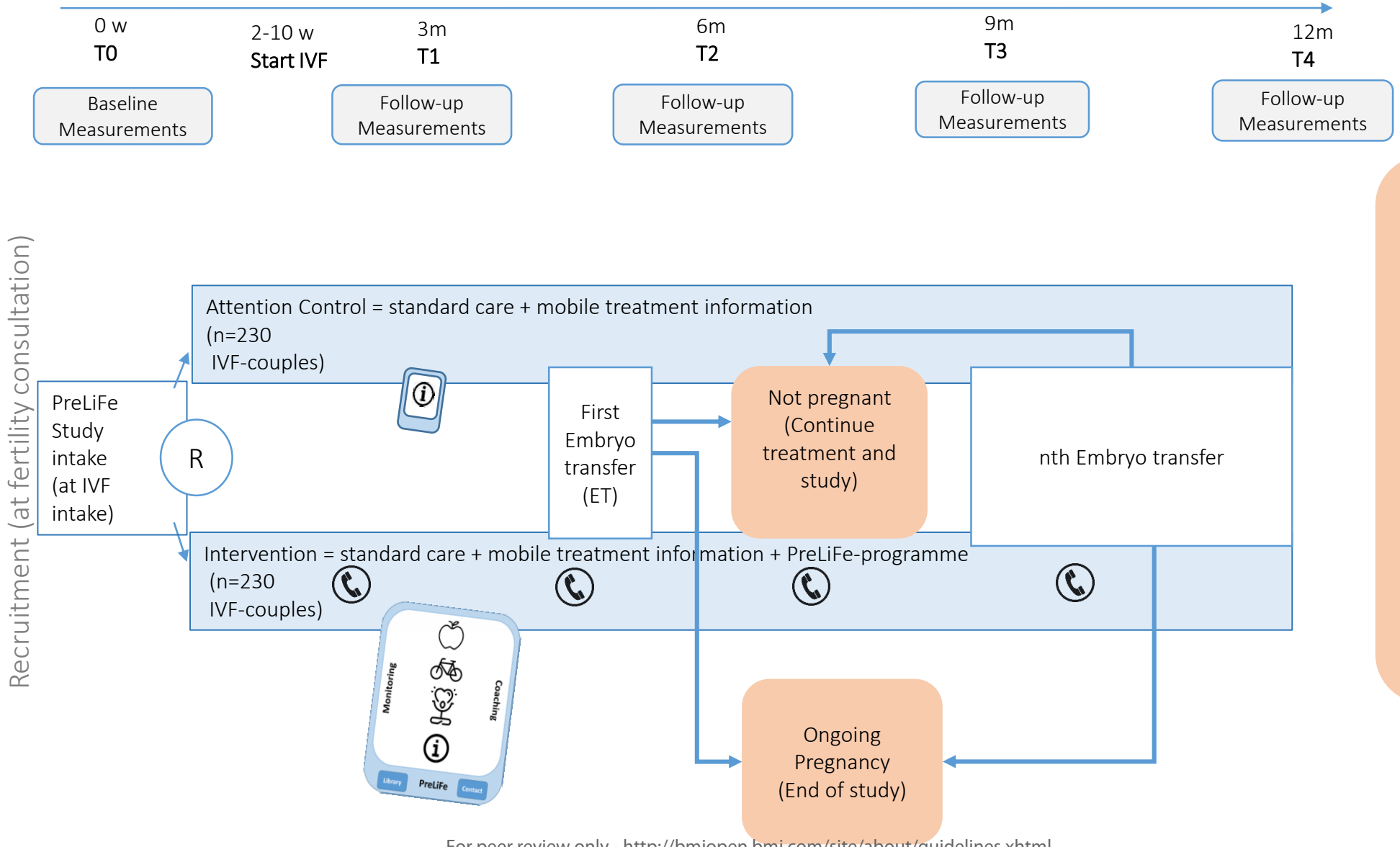
Participants

Groups (Control & Intervention) and measurements moments

Outcomes



Primary:

- Cumulative ongoing pregnancy within 12 months

Secondary:

- Lifestyle parameters (Diet, Physical Activity, Emotional Distress, BMI, Waist Circumference & QOL)
- Partners' Support
- Feasibility of PreLiFe-programme
- IVF and Reproductive outcomes

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
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

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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
Roles and responsibilities: committees	#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)	10, 11

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
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	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, non-inferiority, exploratory)	5
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#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	7,8
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)	7
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	9

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Data collection plan	#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	7,8
Data collection plan: retention	#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	7
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	7
Statistics: outcomes	#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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

Statistics: analysis population and missing data	#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)	9
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11

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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11,13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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

BMJ Open

The effectiveness of a mobile preconception lifestyle programme in couples undergoing in vitro fertilisation (IVF): the protocol for the PreLiFe randomised controlled trial (PreLiFe-RCT)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029665.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Jun-2019
Complete List of Authors:	Boedt, Tessy; KU Leuven, Department of Chronic Diseases Metabolism and Ageing; University Hospitals Leuven, Leuven University Fertility Centre Dancet, Eline; KU Leuven, Department of Development and Regeneration ; University Hospitals Leuven, Leuven University Fertility Centre Lie Fong, Sharon; University Hospitals Leuven, Leuven University Fertility Centre Peeraer, Karen; KU Leuven, Department of Development and Regeneration; University Hospitals Leuven, Leuven University Fertility Centre De Neubourg, Diane; Antwerp University Hospital, Centre for Reproductive Medicine Pelckmans, Sofie; Imelda Hospital Bonheiden, Department of Obstetrics and Gynaecology van de Vijver, Arne; General Hospital Sint Jan Bruges-Ostend, Department of Obstetrics and Gynaecology Seghers, Jan; KU Leuven, Department of Movement Sciences Van der Gucht, Katleen; KU Leuven, Leuven Mindfulness Centre; KU Leuven, Faculty of Psychology and Educational Sciences Van Calster, Ben; KU Leuven, Department of Development and Regeneration; Leiden University Medical Centre, Department of Biomedical Data Sciences Spiessens, Carl; KU Leuven, Department of Development and Regeneration; University Hospitals Leuven, Leuven University Fertility Centre Matthys, Christophe; KU Leuven, Department of Chronic Diseases, Metabolism and Ageing; University Hospitals Leuven, Department of Endocrinology
Primary Subject Heading:	Reproductive medicine
Secondary Subject Heading:	Public health
Keywords:	Lifestyle, Infertility, Diet, Physical Activity, Mindfulness

TITLE

The effectiveness of a mobile preconception lifestyle programme in couples undergoing in vitro fertilisation (IVF): the protocol for the PreLiFe randomised controlled trial (PreLiFe-RCT)

AUTHORS

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WORD COUNT

3606

Protocol version 1 (2nd revision)

ABSTRACT

Introduction: Infertility and *in vitro* fertilization (IVF; with or without intracytoplasmic sperm injection, ICSI) result in considerable emotional and financial burden. Increasing evidence suggests that lifestyle factors, including diet, physical activity and emotional wellbeing, are associated with IVF-success rates. Currently, IVF is not routinely combined with a lifestyle programme. The PreLiFe randomised controlled trial (RCT) assesses the effects of a new mobile preconception lifestyle programme (PreLiFe-programme) in couples undergoing IVF.

Methods and analysis: A multicentre RCT including 460 heterosexual couples starting IVF in Belgian fertility clinics. IVF-Couples are randomised between an attention control group or the PreLiFe-programme for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound. The attention control programme includes a mobile application with treatment information (i.e. appointments and medication instructions) in addition to standard care. The PreLiFe-programme includes a mobile application with the same treatment information in combination with a lifestyle programme. This new lifestyle programme includes tailored advice and skills training on diet, physical activity and mindfulness in combination with text messages and telephone interaction with a health care professional trained in motivational interviewing. The primary outcome of this RCT is the cumulative ongoing pregnancy rate within 12 months after randomisation. Secondary outcomes include changes in diet, physical activity, emotional distress, body mass index (BMI), waist circumference, quality of life and other reproductive outcomes including IVF-discontinuation, clinical pregnancy rate, and time to pregnancy. Additionally, partner support and the feasibility (use and acceptability) of the PreLiFe-programme will be evaluated in the intervention group. Analysis will be according to intention to treat.

Ethics and dissemination: This study has been approved by the Medical Ethical Committee of the Leuven University Hospital (Belgium) and the other recruiting clinics. The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications.

Trial registration: clinicaltrials.gov: NCT03790449

KEY WORDS

Lifestyle; infertility; fertility treatment; IVF; reproductive outcome; mHealth; diet; physical activity; mindfulness

ARTICLE SUMMARY

Strengths and Limitations of this Study

- This is an adequately powered multicentre randomised controlled trial (RCT).
- The development of the PreLiFe-programme was theory- and evidence-based.
- Both partners are included as infertility is a condition affecting couples.
- This is an open-label study, only the statistician is blinded, which can be considered a limitation.
- Due to clinical practice, there is no fixed lead in time free from IVF, leading for some couples to little time to have an effect of the PreLiFe-programme before IVF.

INTRODUCTION

Infertility, defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, affects one in ten heterosexual couples and about half of them seeks fertility treatment.[1] Infertility and its treatment, including *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), result in considerable emotional and financial burden.[2 3] In Belgium, the IVF-success rate, i.e. a live born baby is approximately 50% after one year of treatment.[4 5] However, during this period, one out of three couples discontinue IVF, mainly due to the IVF-related burden.[4 6] Improving IVF-success rates and reducing the burden of IVF are, therefore, important research priorities for reproductive medicine.[7]

One potential option for improving IVF-success rates and reducing the burden of IVF is an interdisciplinary developed lifestyle programme. Observational and interventional studies have recently shown that a healthy lifestyle is not only beneficial for infertile patients' general health but also for their IVF-success rate and for reducing IVF-burden. More specifically, observational studies showed that couples' healthy diet, normal body mass index (BMI) and moderate physical activity are associated with increased IVF-pregnancy rates.[8-15] One non-randomised controlled trial (RCT) reports improved diet, physical activity and increased pregnancy rates in infertile women receiving lifestyle education on diet and physical activity in addition to IVF.[16] Regarding personal wellbeing, two meta-analyses of observational studies came to contradictory conclusions on whether couples' personal wellbeing is associated with their IVF-outcome.[17 18] A meta-analysis of interventional studies, recently concluded that psychosocial interventions for couples undergoing IVF are effective, both in reducing emotional distress and in improving IVF-pregnancy rates.[19] Psychosocial interventions focussing on mindfulness are promising as it has recently been shown to result in significant improvements in the fertility related quality of life of women and in IVF-pregnancy rates.[20] A guideline of the European Society of Human Reproduction and Embryology (ESHRE) highlighted the importance of interdisciplinary support programmes, which can be provided by all staff members during routine fertility care.[21] So far, no lifestyle programme is offered routinely to IVF-couples and this results in one out of three couples deciding for themselves to seek complementary therapy outside of the fertility clinic, including lifestyle and/or psychosocial support.[22 23]

Mobile health (mHealth) as mode of delivery of support programmes has been recognised by (inter-)national policy makers as a promising method for promoting healthy behaviour in both the general population and couples trying to conceive.[24-26] A recent Dutch study showed that a mHealth intervention, targeting amongst others diet and physical activity of the population of reproductive age, improved their lifestyle and pregnancy rate, especially if both partners participated.[14 25] Nevertheless, no mobile preconception lifestyle programme addressing both infertile men and women and integrating advice on diet and physical activity with mindfulness exercises is available in routine fertility care.

METHODS AND ANALYSIS

This protocol was based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-)guidelines.[27]

Aim

The PreLiFe-RCT aims to assess the effects of a new mobile preconception lifestyle programme for couples undergoing IVF, the PreLiFe-programme. This RCT hypothesizes that following the PreLiFe-programme results in a higher cumulative ongoing pregnancy rate within 12 months as compared to an attention control group.

Study Design, Setting and Timing

The PreLiFe-RCT is a non-commercial randomised controlled trial in which the fertility clinics of the following five Belgian hospitals are involved: University Hospitals Leuven, Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint-Jan Bruges. Eligible couples starting IVF are randomised (1:1 allocation ratio) to the PreLife-programme or to an attention control group for a period of 12 months or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age. Recruitment started in January 2019.

Recruitment

The treating gynaecologist introduces the study to eligible couples during the consultation prior to starting IVF. Couples who are interested, are referred to a researcher, who explains the PreLiFe-RCT in detail and asks the couples for written informed consent. The multicentre set-up of the study ensures that a sufficient number of participants can be included.

Inclusion Criteria

Dutch speaking infertile heterosexual couples starting a first IVF cycle (with or without ICSI; irrespective of the IVF indication), in which the women is maximally 38 years old and in which both partners have a smartphone are eligible.

Exclusion Criteria

Couples, who were previously treated with IVF and/or who need preimplantation genetic testing (PGT) or donor gametes are not eligible. In addition, couples are excluded if one of the partners has special dietary requirements due to amongst others bariatric surgery, coeliac disease or renal disease and/or has movement constraints due to amongst others cerebral palsy or hemiparesis.

Randomisation, Blinding and Treatment Allocation

Block randomisation (stratified by clinic) with a 1:1 allocation ratio of eligible, consenting couples is performed with the aid of an online password-protected programme to prevent disclosing the allocation sequence to recruiters. In view of the nature of the intervention, this is an open-label study where only the statistician is blinded.

Interventions

During the first 12 months after randomisation or until an ongoing pregnancy is confirmed by ultrasound at 12 weeks of gestational age, participating couples receive standard medical treatment, i.e. IVF with or without ICSI according to the local protocol of the participating hospital and without guidance on lifestyle.

Both partners of couples randomised to the control group additionally receive an attention control programme, which mimics the amount of attention received by the intervention group, but is thought not have a specific effect.[28] More specifically, the attention control group receives a mobile application (app) with treatment information detailing medication instructions and planned appointments.

Both partners of couples randomised to the intervention group additionally receive the new PreLiFe-programme. The PreLiFe-programme has been developed at KU Leuven, after following multiple steps for developing complex health promotion interventions in line with theory and evidence and after consulting patients and health care professionals.[29 30] The main theory followed to improve healthy lifestyle behaviour is the self-determination theory (SDT), which requires meeting participants need for autonomy, competence and relatedness.[31] The PreLiFe-programme includes a mobile application (PreLiFe-app) with treatment information and tailored advice and skills training on diet, physical activity and mindfulness in combination with (i.e. blended care) interaction with a health care professional, trained in motivational interviewing.[32 33] Regarding diet, the PreLiFe-app focusses on improving food literacy, which is described as an interrelated combination of knowledge, skills and self-efficacy on food planning, selecting foods, food preparation, eating and evaluating information about food.[34 35] Food literacy is an evidence-base model to develop a lifelong healthy, sustainable and gastronomic relationship with food. The PreLiFe-app tailors the dietary advise and skills with the aid of a limited set of questions on food literacy, resulting in tailored goals, tips and recipes. Regarding physical activity, the PreLiFe-app focusses on improving daily physical activity (at moderate intensity) and reducing sedentary behaviour as advised by the World Health Organization (WHO).[36] The physical activity advice and skills training is tailored based on a pedometer linked to the PreLiFe-app and a limited set of questions on the PreLiFe-app, resulting in tailored goals and tips. To improve emotional wellbeing, an evidence-based mindfulness program, is included in the PreLiFe-app.[37 38] The mindfulness exercises follow the format and content of mindfulness based stress reduction.[39-41] Participants are instructed to select specific guided exercises based on their own time-schedule. The advice and skills training of the different components has different formats including: movies (animation and talking heads), audio files, text supported by graphic figures and photos. Blended care is implemented by allowing couples to ask lifestyle-related questions via text messages in the PreLiFe-app and couples receive a telephone call every 3 months (1, 4, 7 and 10 months after randomisation).

Outcomes, Data Collection and Data Management

The primary outcome of this RCT is cumulative ongoing pregnancy rate within 12 months after randomisation. The secondary biomedical outcomes are: BMI, waist circumference, IVF-discontinuation, clinical pregnancy rate and time to pregnancy. The secondary outcomes in which changes are assessed with Patient Reported Outcome Measures (PROMs) are: diet, physical activity, emotional distress and quality of life. In the intervention group, partner support and the feasibility of the PreLiFe-programme (i.e. use and acceptability) are additionally evaluated. Table 1 describes outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome. Data are extracted from medical records, self-administered online questionnaires, the PreLiFe-app or additionally assessed by the researchers (i.e. BMI and waist circumference). Local researchers will enter all data in the Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, 'Castor EDC'.[42] The combination of this web-based, instantaneous electronic validation, and regular on-site monitoring safeguards quality and completeness of the data.

Participant Timeline

Figure 1 provides an overview of all PreLiFe-RCT procedures from recruitment, until the end of the study. Couples, who consented during their consultation prior to IVF, receive a PreLiFe-RCT intake on the same day of their IVF-intake. The PreLiFe-intake consists of the following elements: addressing questions of couples about the study; collecting baseline measurements, extracting patients' medical and fertility related history from medical records; randomisation and configuring the PreLiFe-programme. At baseline, 3, 6, 9 and 12 months after randomisation, the researcher sends a link with self-administered online questionnaires on lifestyle behaviour and partner support to participating couples through email and through the mobile app. The follow-up measurements of physical health including height, weight and waist circumference are planned about every 3 months, simultaneously with standard appointments during fertility treatment. Reminders are sent to participants to ensure attendance at follow-up and prevent dropout of the study. A deviation of two weeks before and up to two weeks after the planned time of measurement is allowed. IVF-trajectories include two different phases. Phase one, where all couples undergo a fresh IVF cycle and phase two with possible pregnancies, follow-up frozen-thawed embryo transfer cycles (if available) and subsequent fresh cycles for which planning differs in time for all couples (see figure 1). The course and outcome of the treatment of the couples is extracted from medical records by the researcher for a period up to 12 months after randomisation. The study ends 12 months after randomisation or if an ongoing pregnancy confirmed by ultrasound (at 12 weeks of gestational age) occurs within 12 months after randomisation. All pregnancies (spontaneous and IVF pregnancies) conceived within these 12 months are followed up until the 12 weeks ultrasound scan. At the end of the study period the feasibility (use and acceptability) of the PreLiFe-programme will be assessed in the intervention group through self-administered online questionnaires. App-based tracking is used throughout the study to evaluate the use of the PreLiFe-programme. Participants can withdraw from the study at any time for any reason if they wish to do so without any consequences on their IVF trajectory.

Table 1: Outcomes, definitions of outcomes, methods of assessment and timings of assessments for each outcome.

Outcomes	Definitions/Methods of assessment	Timing of assessments					
		Baseline	3 months	6 Months	9 months	12 months	Continuously
Patient Reported Outcome Measures	**Questionnaire name (abbreviation)** - **Content of questions** - **Details on evaluation, subscales and scoring**						
Background and General Lifestyle Behaviour	Questions on Background and General Lifestyle Behaviour. - Questions on smoking, alcohol use, supplement intake and complementary therapy. - Descriptive evaluation.	x	X	x	X	X	
Diet	Food Frequency Questionnaire (FFQ).[43] - Questions on frequency and portion size of consumption of foods and beverages. - Evaluation of dietary pattern and diet quality (index to reflect compliance with food based dietary guidelines[44]). Diet quality score: 0-100 (the higher, the better diet quality).	x	X	x	X	X	
Physical Activity	International Physical Activity Questionnaire Short Form (IPAQ-SF).[45] - Questions on duration and frequency of different intensities of physical activity. - Evaluation based on WHO recommendations[36].	x	X	x	X	X	
Personal Wellbeing	Depression, Anxiety and Stress Scale (DASS-21).[46 47] - Questions on symptoms of stress, anxiety and depression (emotional distress). - Stress, anxiety and depression subscales, overall score: 0-126 (the higher, the more emotional distress).	x	X	x	X	X	
Quality of Life (QOL)	Fertility Quality of Life Tool (FertiQOL).[48 49] - Questions on fertility related quality of life. - Emotional, mind-body, relational and social subscales, overall score: 0-100 (the higher, the better quality of life).	x	X	x	X	X	
Partner support *	Questionnaire based on the social support for diet and exercise scales.[50] - Questions on partner support for diet, physical activity and mindfulness. - Support for diet (0-15), physical activity (0-15), and mindfulness (0-10) subscales (the higher, the better partner support).		x	x	X	X	
Acceptability of PreLiFe-programme *	A short version of the subjective quality subscale of the Mobile App Rating Scale (MARS).[51] - Questions on the acceptability and subjective quality of the PreLiFe-programme. - Descriptive evaluation + subjective quality: 0-10 (the higher the better subjective quality of the PreLiFe-programme).					X	
Outcomes collected from PreLiFe-app	**Definition/Specification**						
Use of PreLiFe-programme *	App-based-tracking to evaluate the percentage of participants (couples) using the PreLiFe-programme in combination with a question on their motivation of (not) using the PreLiFe-programme.		x	x	X	X	
Outcomes extracted from medical records	**Definition/Specification**						
Socio-demographic background	Age; Ethnicity; Level of education; Profession.	x					
Medical history	Current and resolved medical conditions; Current medication use.	x					
Fertility history	Duration of self-reported infertility; Indication of infertility: male, female or mixed factor infertility; Primary or secondary infertility.	x					
Course of IVF treatment	Details on fresh and frozen-thawed IVF/ICSI cycles such as date and type of stimulation, date of aspiration, number of oocytes, total motile sperm count, date of fresh embryo transfer, date of frozen-thawed embryo transfer, in case of a cancelled cycle, date and reason of cancellation; outcome of the cycle (detection of hCG) and any adverse events.						x
Clinical pregnancy	A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy.[52]						x
Time to (clinical) pregnancy	The time taken to establish a pregnancy, measured in months.[52]						x
Ongoing pregnancy	A viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan.[53]						x
IVF-discontinuation	Couples who had quit IVF before the achievement of a pregnancy.[54]						x
Outcomes measured by the researcher	**Definition/Specification**						
Body Mass Index	To estimate nutritional status. BMI is defined as a person's weight in kilograms divided by the square of the person's height in metres (kg/m^2). Weight is measured when wearing light clothes and no shoes on a calibrated scale Height is measured without shoes on a stadiometer.	x	x	x	X	x	
Waist circumference	To estimate abdominal fat. Waist circumference is measured with a waist circumference measuring tape according to international Standards for Anthropometric Assessment.	x	x	x	X	x	
*Only Measured in the intervention group							

Sample Size

A sample size for an intention-to-treat analysis of the primary outcome (cumulative ongoing pregnancy rate) was calculated, in collaboration with a statistician from KU Leuven. The calculations were based on literature from the field of reproductive medicine regarding: (i) the optimistic, realistic and pessimistic cumulative IVF-success rates in Belgium[4 5], (ii) the IVF-discontinuation rates in Belgium[4], (iii) data on the impact of a preconception lifestyle intervention on IVF-success rates[16] (iv) data on the impact of a psychosocial intervention on IVF-discontinuation rates[55] and (v) data on withdrawal of fertility patients from lifestyle interventions.[55 56] Assuming a cumulative ongoing pregnancy rate of 50% in the control group[4 5] and 63% in the intervention group dictates a sample size of 230 couples per group or 460 couples in total (two-sided test; power of 80% and alpha of 5%). The 13% increase in cumulative ongoing pregnancy rate within the first 12 months after starting IVF is partly expected by assuming improved IVF-success rates and partly by assuming decreased IVF-discontinuation rates. More specifically, a preconception lifestyle programme targeting physical activity, diet and stress-management increased the clinical pregnancy rates of one IVF-cycle from 19.2% to 46.1%.[16] Regarding decreasing IVF-discontinuation-rates, a cognitive coping and relaxation programme had a tendency to decrease the IVF-discontinuation rate within 12 months from 15.2% to 5.5%.[55] Calculations were performed using PASS14 software.[57]

Data Analysis

Analysis will be according to the intention-to-treat. Descriptive statistics for baseline characteristics in the two arms will be presented and the withdrawal rate from the study will be assessed and compared between the two arms. The primary outcome is cumulative ongoing pregnancy rate (COPR) within 12 months after randomization. To calculate this, an ongoing pregnancy conceived within 12 months after randomization will be counted as a positive event, whereas IVF-discontinuation and absence of pregnancy will be counted as a negative event. The COPR in both groups will be compared using multivariate logistic regression models with controlling for potential confounders such as age and BMI. Odds ratios with 95% confidence intervals will be reported. A p-value <0.05 will be used to determine statistical significance for the intervention. Furthermore, cumulative incidences of ongoing pregnancy and IVF-discontinuation in the intervention and control group will be described. Similar analysis will be performed for binary secondary outcomes such as clinical pregnancy. Additionally we will evaluate changes in lifestyle parameters including changes in the diet, physical activity, emotional distress, BMI, waist circumference and fertility related quality of life over time and we will evaluate the differences between the intervention and control group in these parameters. Mixed models for repeated measurements (MMRM) will be used to evaluate treatment, time and interactive effects on these secondary outcomes. The determination of statistical significance will not be central to the analysis of secondary endpoints, yet nominal p-values may be reported. Descriptive analysis will be conducted on additional parameters measured only in the intervention group, more specifically: partner

support and feasibility of the PreLiFe-programme. Regarding missing data, MMRM is used which is consistent under the 'missing at random' assumption and in line with the intention-to-treat principle.[58] For the primary outcome we do not expect missing data.

Harms

Throughout the PreLiFe-RCT, all solicited and spontaneously reported adverse events and other unintended effects of the PreLiFe-programme or RCT will be collected, assessed, reported and managed according to good clinical practice (GCP).

Patient and Public Involvement

For the development of the PreLiFe-programme and the PreLife-RCT, we applied a human-centred design, consulting both patients and health care professionals. Additionally, an advisory committee has been installed from the start of the development of the project and includes representatives of the Belgian patient association 'De Verdwaalde Ooievaar' and of the 'Belgian Society for Reproductive Medicine' (BSRM).

ETHICS AND DISSEMINATION

This study has been approved by the Medical Ethical Committee of the University Hospitals Leuven (Belgium) and the local ethics committees of the participating clinics (i.e. Antwerp University Hospital, Imelda Hospital Bonheiden, General Hospital Diest and General Hospital Sint Jan Bruges)(s61596). If any protocol amendments would have to be made, they will be reported and submitted to all medical ethical committees.

Confidentiality of the participant's data is ensured by using participant IDs rather than identifiable information in the data set (i.e. coding) and by storing the document linking the IDs to the identifiable information separately. Only researchers from the study have access to the coded data.

The findings of this RCT will be disseminated through presentations at international scientific meetings and in peer-reviewed publications in accordance with academic standards. The participating sites are not allowed to publish any data or results from the study prior the multicentre publication. Authorship to publications will be in accordance with the requirements published by the International Committee of medical Journal Editors, in accordance with the requirements of the respective medical journal and according to the KU Leuven Publication Policy. We do not intend to collaborate with a medical writer.

DISCUSSION

The PreLiFe-RCT examines a novel preconception lifestyle programme for couples undergoing IVF, including tailored advice and skills training on diet, physical activity and mindfulness, in a mHealth format combined with motivational interviewing via text messages and telephone interaction. This PreLife-programme is theory- and evidence-based and has been developed systematically.[30 59] Besides examining a novel lifestyle intervention for couples undergoing IVF, with the potential of low-cost widespread implementation, this RCT has several strengths. First, this RCT has adequate power, which is enabled by the multicentre setting. Second, This RCT includes couples rather than individuals in the light of the evidence that addressing couples in lifestyle interventions provides extra support and maximises compliance.[25 60] Third, this RCT has an attention control condition rather than standard care.[28] This RCT has also some potential limitations. A limitation, which is inevitable due to the nature of the intervention, is that this is an open-label study where only the statistician could be blinded. A second potential limitation is that due to clinical practice, the PreLiFe-programme is offered right before the start of IVF without a fixed lead in time free from IVF. This leads for some couples to little time to follow the PreLiFe-programme and improve their lifestyle before their first IVF cycle. However, we will capture the time between offering the PreLiFe-programme and start of IVF. Finally, publishing this protocol outlines our effort to limit the risk of bias in our RCT.

With this RCT, we expect to demonstrate the added value of a mobile preconception lifestyle programme for reproductive and lifestyle outcomes in couples undergoing IVF. If this RCT proves that our lifestyle programme is effective, lifestyle support programmes should be implemented in standard care in each fertility clinic.

Author Contributions

TB, ED, KVDG, JS, BVC, CS and CM designed the trial, developed the protocol and applied for funding. TB, KP, DDN, SP, AVDV and SLF applied for ethical approval and implemented the logistics of the trial. All authors read, revised and approved the final manuscript.

Funding Statement

This work was supported by the Research foundation Flanders (Belgium).
(FWO-TBM; reference: T005417N).

Competing Interests

The authors declare to have no financial or non-financial conflicts of interest.

Acknowledgements

We acknowledge Barbara Weyn and Steve De Backer for the technical development of the PreLiFe-programme; Roos Voorend and Jan Derboven for contributing to the human centred design of the PreLiFe-programme, as well as all the patients, midwives and gynaecologists participating in the human centred design research; Edel Maex, Filip Raes, and Peter Kuppens for contributing to the development of the mindfulness part of our PreLiFe-programme; An Bogaerts for contributing to the development of the physical activity part of our PreLiFe-programme and the Nutrition Unit of University Hospitals Leuven for contributing to the development of the diet part of our PreLiFe-programme. Additionally we want to acknowledge our advisory committee of our FWO-TBM project and all clinics who are contributing to patient recruitment or are preparing to do so.

Other declarations

The following other declarations are not applicable to this manuscript: consent for publication, availability of data and material and endnotes.

List of abbreviations

BSRM: Belgian Society for Reproductive Medicine; BMI: body mass index; COPR: cumulative ongoing pregnancy rate; DASS21: depression, anxiety and stress scale; EDC: electronic data capture; ESHRE: European Society of Human Reproduction and Embryology; ET: embryo transfer; FertiQOL: fertility related quality of life questionnaire; FFQ: food frequency questionnaire; GCP: good clinical practice; hCG: human chorionic gonadotropin ICSI: intracytoplasmic sperm injection; IPAQ: international physical activity questionnaire; IVF: in vitro fertilization; MARS: mobile app rating scale; MMRM: mixed models for repeated measurements; PGT: preimplantation genetic testing; PROMs: patient reported outcome measures; QOL: quality of life; RCT: randomised controlled trial; SPIRIT: standard protocol items recommendations for interventional trials; WHO: World Health Organization.

Availability of data and material

All data is stored in a Good Clinical Practice (GCP) compliant Electronic Data Capture (EDC) platform, i.e. Castor EDC. Upon completion of the data collection, this RCT will be analysed by the PreLiFe research team. Data from this RCT will be made available on reasonable request once the results are published. This PreLiFe research team will facilitate this data-sharing.

Figures

Figure 1: Overview of PreLiFe-RCT

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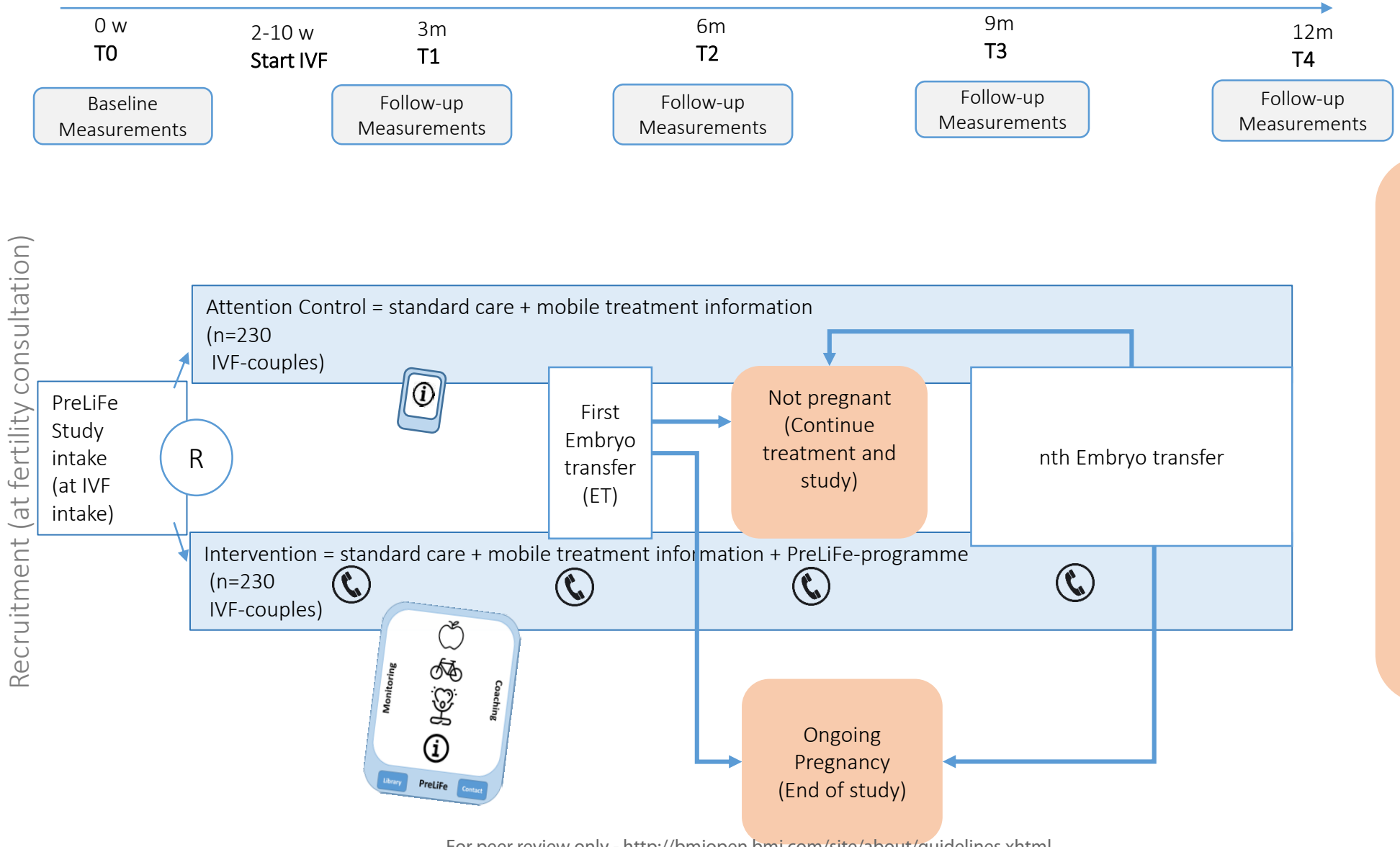
Participants

Groups (Control & Intervention) and measurements moments

Outcomes



Primary:

- Cumulative ongoing pregnancy within 12 months

Secondary:

- Lifestyle parameters (Diet, Physical Activity, Emotional Distress, BMI, Waist Circumference & QOL)
- Partners' Support
- Feasibility of PreLiFe-programme
- IVF and Reproductive outcomes

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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
Roles and responsibilities: committees	#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)	10, 11

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
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	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, non-inferiority, exploratory)	5
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#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	7,8
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)	7
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	9

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Data collection plan	#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	7,8
Data collection plan: retention	#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	7
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	7
Statistics: outcomes	#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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

Statistics: analysis population and missing data	#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)	9
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11

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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11,13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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