Protocol Full Title interventional trial:

The PreLiFe study: Effectiveness of a mobile preconception lifestyle programme in couples undergoing fertility treatment: a multicentre randomized controlled trial

Protocol Acronym/short title:

PreLiFe-study: A mobile **Pre**conception **Li**festyle programme in couples undergoing **Fe**rtility treatment

Version and date of final protocol:

Version 1: 18/06/2018

Trial identifiers

NCT (clinicaltrials.gov): Application after EC approval

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1. Study synopsis

Title of clinical trial	The **PreLiFe** study: Effectiveness of a mobile **pre**conception **li**festyle programme in couples undergoing **fe**rtility treatment: a multicentre randomized controlled trial
Principal Investigator	Dr. Sharon Lie Fong
Medical condition or disease under investigation	Couples undergoing *in vitro* fertilisation (IVF) with or without Intracytoplasmic sperm injection (ICSI)
Purpose of clinical trial	Evaluating the added value of a mobile preconceptional lifestyle programme in comparison to care as usual in couples undergoing IVF.
Primary outcome(s)	Cumulative ongoing pregnancy rate (COPR) within 12 months after randomization (i.e. viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan) and IVF discontinuation rate.
Secondary outcome(s)	Other reproductive outcomes (e.g. implantation and clinical pregnancy), lifestyle parameters (diet, physical activity, personal wellbeing), physical health and fertility related quality of life. Partners' support, the adherence to the programme and subjective quality of the programme.
Trial Design	Multicentre randomized clinical trial
Sample Size	460 couples (230 per group)
Summary of eligibility criteria	• Infertile heterosexual couples starting a first IVF-cycle (with or without ICSI) • Women ≤ 38 years • Both partners possess a smartphone • Both partners understand and speak Dutch • Written informed consent after been informed on all aspects of the study
Intervention	A mobile preconceptional lifestyle programme (PreLiFe app) and treatment specific information in addition to care as usual for 12 months or until an ongoing pregnancy has been confirmed by ultrasound.
Control	Attention control: Care as usual + a mobile application only providing the treatment specific information of the PreLiFe app including reminders of medication and time of fertility treatment appointments for 12 months or until an ongoing pregnancy has been confirmed by ultrasound.
Maximum duration of treatment of a subject	12 months
Version and date of final protocol (and ammendements)	Version 1

2. Background and rationale

The life plan of the vast majority of people includes having children. Unfortunately many couples are faced with fertility problems (prevalence=9%) and decide to turn to fertility treatment, including *in vitro* fertilisation (IVF) with or without Intracytoplasmic Sperm Injection (ICSI)(1). Infertility and its treatment result in a considerate emotional and economic burden (2, 3). In Belgium, the IVF-success rate, i.e. a live born baby is 58.6% after 3 treatment cycles or approximately one year (4). However, during this period, 33 % of the couples prematurely discontinue IVF, with the main reason for discontinuation the perceived burden of the treatment (4, 5).

So far no lifestyle support is offered to Belgian IVF-couples although a recent guideline of the European Society of Human Reproduction (ESHRE) highlighted the importance for fertility clinics to support their patients (6) and the lack of support in fertility clinics is shown as one out in three IVF-couples seek complementary therapy on their own including lifestyle and/or psychosocial support (7, 8).

The majority of randomized controlled trials on IVF-patients evaluate medical drugs, clinical decisions (medication dose, day of embryo transfer) or laboratory procedures. Recently, some observational and interventional studies in fertility patients, have shown that improving diet, physical activity and/or personal wellbeing, is not only beneficial for patient's general health but also for their IVF-success rate and treatment burden (9-12).

Observational studies regarding lifestyle factors and fertility treatment

Couples' healthy diet, normal body mass index (BMI) and moderate physical activity are associated with increased IVF-pregnancy rates (10, 13-16). The evidence regarding the association between couples' personal wellbeing and their IVF-outcome is conflicting as highlighted by two meta-analyses with opposing conclusions (17, 18).

Interventional studies regarding lifestyle support and fertility treatment

One non-randomized controlled trial (RCT) reports improved diet and physical activity and increased pregnancy rates after IVF ($p= 0.02$) in subfertile women receiving lifestyle education on diet and physical activity (9). Regarding personal wellbeing, a recent meta-analysis concluded that psychosocial interventions for couples undergoing IVF are effective, both in reducing psychological distress ($p=0.001$) and in improving clinical pregnancy rates ($p<0.001$) (19). Mindfulness, as a psychosocial intervention, is a promising method as it is an easy access approach. A recent study showed significant improvements in the fertility related quality of life of women and in IVF-pregnancy rates after a mindfulness intervention (20).

Mobile health (mHealth) interventions have been recognised by (inter-)national policies as a promising method for promoting healthy behavioural change of both the general population and couples trying to conceive (12, 21, 22). A recent Dutch study showed that a personalized mHealth intervention acting on diet and other lifestyle factors such as smoking and physical activity in the reproductive population improved their diet and lifestyle behaviour and enhanced pregnancy chance. This programme worked better if both partners of couples participated (22, 23). Nevertheless, no (mobile) preconceptional lifestyle programme integrating all three elements (diet, physical activity and personal wellbeing) and targeting as well subfertile men and women i.e. IVF-couples, is routinely available in the fertility setting.

3. Study objectives and design

3.1 Study objectives

Evaluate the added value of a mobile preconceptional lifestyle programme in comparison to care as usual in couples undergoing IVF.

3.2 Primary endpoints

The primary outcome is cumulative ongoing pregnancy rate (COPR) within 12 months after randomization and IVF-discontinuation rate. Ongoing pregnancy is defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan (24). All pregnancies (Spontaneous and IVF pregnancies) conceived within these 12 months are followed up until the 12 weeks ultrasound scan. IVF-discontinuation is described as couples undergoing IVF who do not return for a further IVF cycle in our fertility centres after the failure of a previous cycle. To calculate our primary endpoint, an ongoing pregnancy within 12 months after randomization is counted as a positive event, whereas IVF discontinuation and absence of pregnancy are counted as a negative event.

3.3 Secondary endpoints

The secondary outcomes are changes in other reproductive outcomes including transfer outcome, implantation and clinical pregnancy, changes in lifestyle parameters (diet, physical activity, personal wellbeing), and fertility related quality of life. Additionally, the partners' support, adherence to the programme and the subjective quality of the programme is evaluated. Data collection and analysis of this data is described below (4.4 data collection).

3.4 Study Design and setting

PreLiFe is a non-commercial multicentre randomised controlled trial in which 5 fertility centres from 3 provinces in the Flanders region of Belgium are involved: University Hospital of Leuven, University Hospital Antwerp, Imelda Hospital Bonheiden, Academic Hospital Diest and Academic Hospital Sint Jan Bruges. The intervention group will receive a mobile preconceptional lifestyle programme (PreLiFe app) and fertility treatment specific information in addition to care as usual for 12 months or until ongoing pregnancy occurs. The control group will receive care as usual and fertility treatment specific information via a mobile app. Due to the nature of the intervention participants, study nurses and PhD student are aware of allocations. Figure 1 and 2 give an overview of the study.

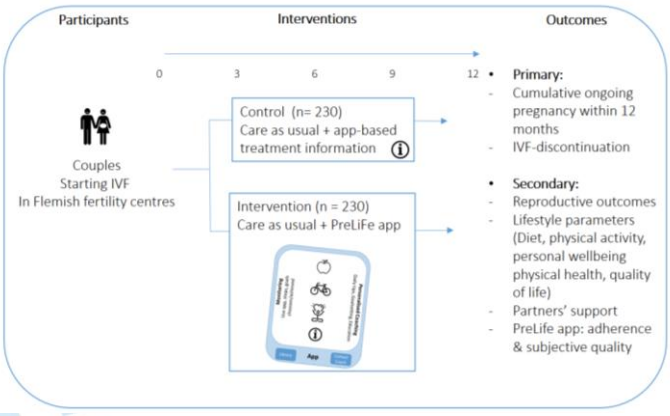

Figure 1: Study diagram

4. Methods

4.1 Study population and sample size

Eligibility criteria

The following inclusion criteria are applied:

- Infertile heterosexual couples starting a first IVF-cycle (with or without ICSI) with infertility defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse
- Women aged ≤ 38 years
- Both partners possess a smartphone
- Both partners understand and speak Dutch
- Written informed consent after been informed on all aspects of the study

The following exclusion criteria are applied:

- Couples with previous IVF/ICSI treatment cycles
- Couples where one of the partners has special dietary requirements including patients that underwent bariatric surgery, patients with Coeliac disease, renal disease, or diabetes mellitus
- Couples where one of the partners has specific movement's constraints including Cerebral Palsy, Hemiparesis…
- Couples starting IVF/ICSI with preimplantation genetic diagnosis (PGD)
- Couples using donor gametes or donor embryos

Sample size calculation

We calculated sample size for an intention-to-treat analysis of the primary endpoint. The null hypothesis is that the cumulative ongoing pregnancy rate is the same in both arms.

Calculations were performed in collaboration with a statistician from KU Leuven based on literature from the field of reproductive medicine regarding: (i) the cumulative IVF-pregnancy rates in Belgium (4), (ii) the IVF-discontinuation rates in Belgium (4), (iii) data on the impact of a preconception lifestyle intervention on ongoing pregnancy rates (9) and (iv) data on the impact of a self-administered psychosocial intervention on IVF-discontinuation rates(25).

In Belgium, the cumulative pregnancy rate is 58.6 % after 3 cycles or approximately one year. However, during this period, 33 % of the couples prematurely discontinue IVF(4). These assumptions result in expecting the cumulative ongoing pregnancy rate to be 39 % in the control arm: (1-0.33)*0.586 = 0.39. For the intervention arm, we assume a cumulative pregnancy rate of 61.9% (9) and IVF discontinuation rate of 15% (25). Hence, we assume that the intervention will mainly influence the likelihood that couples continue treatment rather than the true pregnancy rate. Further, in this arm we assume that 20% will stop with the intervention but continue with IVF (26). In such cases, we assume that the cumulative pregnancy rate is 58.6 instead of 61.9%. These assumptions result in expecting the cumulative ongoing pregnancy rate to be 52% in the intervention arm: (1-0.15)*(0.2*0.586+0.8*0.619) = 0.52.

Assuming the primary outcome to be 39% in the control arm and 52% in the intervention arm, we need 230 couples per arm to have 80% power at 5% alpha for comparing success rates with a likelihood ratio chi-squared test. Calculations were performed using PASS14 software.

Feasibility

The multicentre set-up of the study will ensure that a sufficient number of participants can be included. In LUFC and AZ Diest on average 250 couples/year are starting IVF. In the University Hospital of Antwerp there are 200 couples/year, In Imelda hospital Bonheiden 80 couples/year and in the hospital of Bruges there are 200 couples/year starting IVF. Estimating that at least 60% of the couples will agree to participate in the trial our recruitment will take maximum 15 months. The follow up of our study consist of approximately 12 months + 12 weeks until ongoing pregnancy. We expect many couples undergoing IVF to take part in our intervention since this population is highly motivated to achieve a healthy pregnancy and child.

4.2 Interventions (treatment of participants)

Care as usual/ control group

The care as usual serving as control for this intervention is fertility treatment i.e. IVF with or without ICSI according to local protocols for infertility patients. This means no guidance on lifestyle. However, the control group will receive treatment specific information, including reminders of injection of human Chorionic Gonadotropin (hCG) and time of fertility treatment appointments through a mobile application for 12 months or until an ongoing pregnancy has been confirmed by ultrasound. We will give them this information through our PreLiFe app to have attention control.

Investigational treatment/ intervention group

The intervention group will receive a mobile preconceptional lifestyle programme (PreLiFe app) in addition to care as usual for 12 months or until an ongoing pregnancy has been confirmed by ultrasound. This novel PreLiFe app will provide information, feedback through monitoring and skills training on diet, physical activity and personal wellbeing. As in the control group, treatment specific information will also be provided through the PreLiFe app to the intervention group, to enhance adherence. This includes reminders of injection of hCG and time of fertility treatment appointments

Theoretical framework of the PreLiFe app

The intervention will be based on concepts of patient-centredness and the self-determination theory (SDT) and designed according to the intervention taxonomy (27). The concept of patient-centred care in our intervention is implemented by applying human-centred design meaning the end-user, patient in the current situation, is put first in every step of the design and development process (28). This work is conducted by the user experience research group of KU Leuven, specialized in human-centred design. The SDT is a theory of human motivation to induce healthy lifestyle behaviour. The SDT proposes that when the basic psychological needs of autonomy, competence and relatedness are met, an individual's inherent activity will be supported, optimal motivation will be promoted, and positive psychological and behavioural outcomes will be obtained (29). Autonomy deals with peoples' perception of the extent to which they can decide for themselves whether or not to behave in a certain way. To promote autonomy, participants can choose themselves on which lifestyle topic they want to work in the PreLiFe app. Competence refers to the confidence people have in their knowledge and skills, necessary to show the right behaviours. Therefore, our intervention will focus on improving confidence and self-efficacy by providing education and exercises on lifestyle factors. Relatedness pertains the feeling of connectedness with others, of belonging, therefore we focus on couples in our intervention. Both partners will receive the PreLiFe app to enhance partner involvement and relatedness.

Lifestyle content of the PreLiFe app

The content of the PreLiFe app will focus on diet, physical activity and personal wellbeing as these parameters can as well affect general and reproductive health. Additionally treatment specific information is included.

Following the principle of autonomy, subjects can choose themselves on which of these lifestyle topics they want to work.

Diet:
In this part we want to improve food literacy by promoting healthy eating which leads to an overall improved dietary quality. Food literacy is an evidence-based model to promote healthy eating, based on developing a lifelong healthy relation to food based on four broad domains: food planning, selecting the right foods, food preparation and eating (30, 31).Our research team included as well a fifth domain, which is about information gathering and interpretation about food. Eating healthy is not just about what you eat or how to cook, but also about knowing how to make the right choices, and knowing that planning your food intake can lead to healthier choices. This part is guided by experienced members of the Nutrition research group (CEE). Food literacy and diet quality will be monitored at baseline using a Food Frequency Questionnaire (FFQ) and questions on food literacy. Based on these results participants will receive tailored advice, tips and recipes to improve their food literacy and diet quality.

Physical activity:
The aim of our physical activity part is to stimulate physical activity and reduce sedentary behaviour as advised in the WHO Global recommendations on physical activity for health (63). This part is guided by experienced members of the Physical Activity, Sport & Health research group (PASH) of the KU Leuven. Daily steps will be monitored using a pedometer (via their own wearable device or via smartphone pedometer applications) and structured physical activity will be monitored using a questionnaire and physical activity log. Participants will receive a tailored movement plan and tips to improve their daily and moderate physical activity level.

Personal well-being:
To improve personal wellbeing, short mindfulness based exercises guided by Dr. Edel Maex (Psychiatrist and expert in mindfulness) and based on the book “Mindfulness. In de maalstroom van je leven” (62) will be provided to participants using audio files and videos. This part is guided by experienced members of the psychology research group (Psycho).

Workflow of PreLiFe app
The PreLiFe app includes a backend server, a secure login and messaging module and a dashboard for the health care providers. It consist of a monitoring and a coaching/feedback module. The monitoring module will collect information through questionnaires, and will collect information regarding the use of the app. Physical activity will be measured via their own wearable device or via a smartphone pedometer application. Together with the data from the assessments, it will be send to a backend server and mined to derive personal profiles of the participants. Based on these profiles, personalized advice and feedback is offered in the form of tips/tricks, education, exercises and personalised goals. The coaching will be offered by using the latest insights in user interface and interaction design. A conversational interface will be used to structure the content in the app. This type of interface presents the data in a dialogue with the user, like the user is having a conversation with the system. This user interface design pattern allows high levels of context awareness and personalisation, which is beneficial for long-term engagement and thus adherence.

Coaching with the PreLife app
The coaching or feedback module of the PreLife app consists of the following features:

- Individual goal setting on one or more of our topics. The patients can prioritize goals themselves through the application.

- Automatically generation of personal recommendations, exercises or tips via e.g. pop-up messages based on the monitoring.
- Library with links to relevant information, recipes, exercises and FAQ's in related topics.

Additionally, a PhD student, who will be trained in motivational interviewing prior to the study will guide the patients in the intervention group during the study. In general, this PhD student will contact the couples by telephone once every 3 months (1, 4 ,7 and 10 months after randomization). During this contact, along the principles of motivational interviewing the participants will be questioned about the lifestyle programme. Motivational interviewing is a method of communication, designed to facilitate natural change (stimulate the patient's intrinsic motivation) (32). We will start with a general open question on their experience with the lifestyle programme. If patients want, we can provide feedback on their personal lifestyle parameters, tackle perceived barriers and address benefits associated with the PreLife app. Additionally we will provide 'just in time coaching' when the patients are in need for additional support. The couples can contact the coach via the "contact coach button" in the application and write a short text message. The responsible PhD student will reply to this text message through the app within 72 hours (if necessary after consultation of the expert (medical doctor, dietician, psychologist…). Only lifestyle related questions will be answered. For fertility treatment related questions, the participants are referred to the treating fertility centre.

4.3 Study procedures

Participant timeline

Figure 2 gives an overview of the study procedure from recruitment, study intake and randomisation till end of follow-up period. Due to the nature of the fertility treatment process our study will consist of 2 different phases. Phase 1, where all patients are undergoing a fresh IVF cycle and phase 2 with possible pregnancies, follow-up cryo cycles (if embryos are available after freezing/thawing) and next fresh cycles which differs in time for all couples (see figure 2).

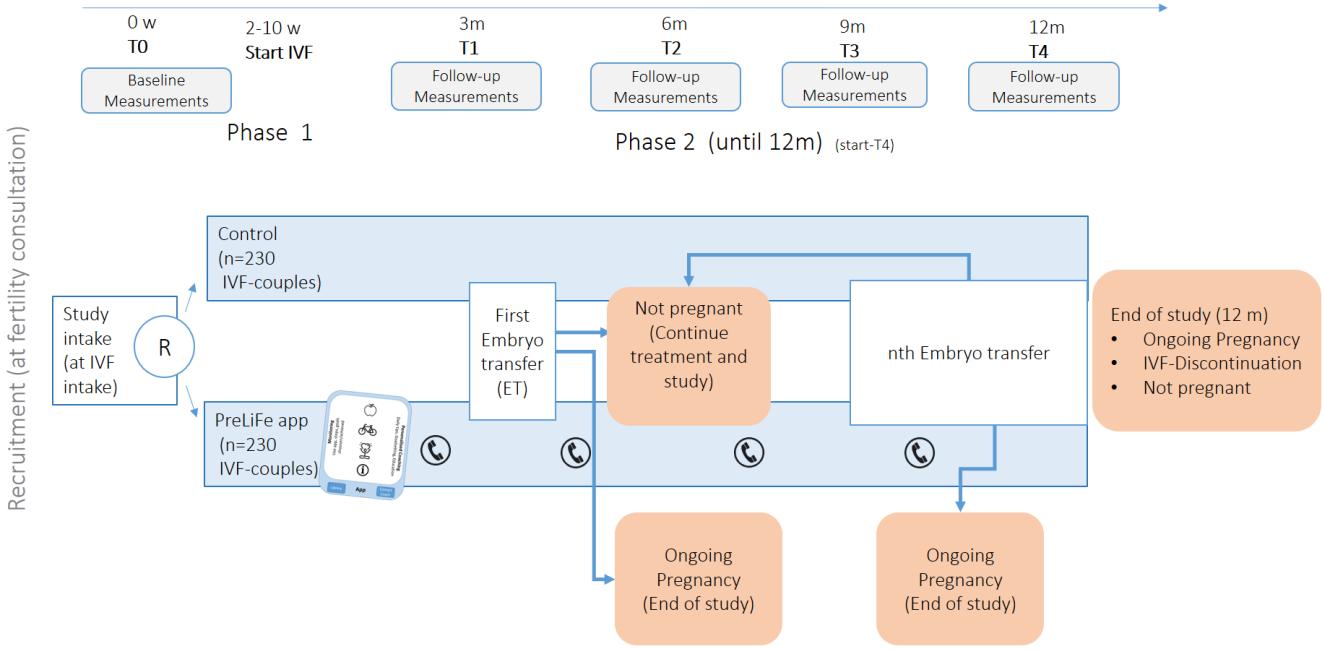

Figure 2: Time line of PreLiFe study

Selection and recruitment of participants

The treating physician will introduce the study to eligible couples at the fertility consultation. If couples are interested to participate they are referred to an experienced study nurse present at the fertility consultation. This recruiter will explain the PreLiFe study more in depth and provide the couples with an informed consent.

Study intake & baseline measurements (T0)

Consenting couples are invited for study intake. The timing of this intake session is fitted in the conventional appointment prior to start of an IVF to enable easy access. During this standard appointment, couples will receive practical information on their IVF treatment including the use of the medication. The study intake will be conducted by an experienced study nurse. The study intake consists of the following elements:

- Addressing additional questions of couples on the study.
-Collecting baseline measurements (see data collection).
- Retrieving patient's medical and fertility related history from medical records.
-Randomization
-Installing and explaining PreLiFe app.

Randomisation procedure, blinding and treatment allocation

The randomization of couples will take place after eligibility check and informed consent approval. For the randomisation, a computer generated randomisation procedure via a password-protected website will be used. The computer generated randomisation scheme is 1:1 by trial arm and stratified by centre. In view of the nature of the intervention, participants, study nurses and the PhD student are aware of allocations. In this RCT only the statistician will be blinded.

Follow-up measurements of participants (T1-T4)

At baseline and 3, 6, 9 and 12 months after randomisation, the study nurse performs the follow up measurements which consists of web-based questionnaires on lifestyle behaviour and measurements of physical health including weight and waist circumference (see data collection and table 1). The follow-up measurements are planned simultaneously with regular appointments during the fertility treatment. In our group, we are used to measure these outcomes, to work with validated instruments and scales. The study nurses are trained by experienced researchers to adequately measure these parameters; nevertheless, Standard Operating Procedures (SOP) will be available. Reminders will be sent to participants to ensure attendance at the follow-up study days and prevent drop-out of the study. Moreover, the study nurse will register fertility treatment and the course and outcome of subsequent pregnancies for a period up to 12 months after randomization.

End of study

The study ends 12 months after randomization or if an ongoing pregnancy occurs within 12 months after randomization (i.e. viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan). All pregnancies occurring within these 12 months are followed up until the 12 weeks ultrasound scan. At the end of the study we will perform a post study measurement, were we will measure changes in lifestyle behaviour since the last measurement and the subjective quality of the app in the intervention group.

Withdrawal of participants

Participants can withdraw from the study at any time for any reason if they wish to do so without any consequences. Patients who drop out of the study will be treated according to local protocols for infertility patients.

4.4 Data collection and data management

Data collection

Table 1 gives an overview of the different measurements and time points during the study.
Data will be collected from medical records, web-based questionnaires, physical assessments and the PreLiFe app itself. All questionnaires can be found in appendix 1.

Table 1: Measurements and time points of PreLiFe Study

Measurements		Method or sample used	Phase 1 Baseline	3	Phase 2 6	9	12	Every
Lifestyle parameters								
General Lifestyle	Supplement use, smoking, complementary therapy use	Questions (Q)	x	x	x	x	x	
Diet	Diet (quality)	FFQ (Q)	x	x	x	x	x	
	Physical activity (self reported)	IPAQ (Q)	x	x	x	x	x	
Physical activity	Physical activity (objective) **	Pedometer in app	x	x	x	x	x	x
Personal Wellbeing	Stress, depression and anxiety	DASS-21 (Q)	x	x	x	x	x	
QOL	Fertility related QOL	FERTIQOL (Q)	x	x	x	x	x	
Fertility treatment and reproductive outcomes								
	Fertility treatment	Medical records	x	x	x	x	x	x
	Pregnancy follow-up	Medical records		x	x	x	x	x
IVF-success	IVF-discontinuation	Medical records		x	x	x	x	x
Physical examinations								
	Weight	Scale (twice)	x	x	x	x	x	
	Height	Stadiometer (twice)	x					
Physical Health	Waist circumference	Tape (twice)	x	x	x	x	x	
Other								
	Socio-demographic data	Questionnaire/Medical records	x					
Baseline data	Past/current medical and fertility history	Medical records	x					
Support	Partners support **	Q		x	x	x	x	
Adherence	Adherence to the programme **	Q + app data		x	x	x	x	
Quality	Subjective quality of the application * **	MARS subscale (Q)					x	
* Measured at the end of the study ** Only measured in intervention group								

Data collected at baseline:

Socio-demographic data (age, ethnicity, level of education and work situation), medical history and fertility related history (indication, type and duration of infertility). These data are obtained from questionnaires and medical records and will be transferred immediately to the eCRF.

Data collected at baseline and follow-up every 3 months:

General Lifestyle behaviour: a web-based questionnaire based on the questionnaires of the INTERACT study is used to evaluate if the couples smoke, drink alcohol, take supplements or follow other complementary therapy (33).

Diet (quality): A validated food frequency questionnaire (FFQ) with questions on frequency and portion size of food items is used to evaluate dietary pattern and diet quality (34). Diet quality is an index to reflect compliance with the food based dietary guidelines based on the dietary guidelines of the Belgian Superior Health Council (35).

Physical activity: Self-reported physical activity is measured and classified as low, moderate or high physically active, using the International Physical Activity Questionnaire (IPAQ). The IPAQ is a reliable and validated instrument for monitoring physical activity in population health surveillance systems (36). In the intervention group, via a pedometer in the PreLife app, the daily steps are monitored as well.

Personal wellbeing: The Depression, anxiety and stress scale (DASS-21) is a validated and reliable scale to measure symptoms of emotional distress, anxiety and depression (37).

Fertility related quality of life will be measured using the FertiQOL. This is a reliable and valid tool in measuring QOL in couples facing infertility (38).

Physical health will be assessed by measuring the following parameters:

Weight and height is measured to calculate the body mass index of couples (BMI). Couples are weighted wearing light clothes and no shoes on a calibrated scale. The height is measured without shoes on a stadiometer. The measurement of height is only performed at baseline.

Waist circumference: Measured according to the International Standards for Anthropometric Assessment with a SECA measuring tape to estimate abdominal fat.

Data on fertility treatment and reproductive outcomes are obtained from medical records. The study nurse will register fertility treatment and the course and outcome of subsequent IVF and spontaneous pregnancies for a period up to 15 months after randomization. Following data is collected:

- Self-reported start time of active pregnancy wish
- Number and type of fertility treatment (i.e. IVF/ICSI)
- Date of stimulation, aspiration, thawing and embryo transfer (or if cancelled, date and reason of cancellation)
- Transfer outcome (Detection of hCG)
- Implantation defined as the presence of a gestational sac (intra and extra uterine gestational sac) (39).
- Clinical pregnancy with fetal heart beat defines as a pregnancy diagnosed by ultrasound or clinical documentation of at least one fetus with a discernible heartbeat (39).
- Ongoing pregnancy defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan (24).
- IVF-discontinuation described as couples undergoing IVF who do not return for a further IVF cycle in our fertility centres after the failure of a previous cycle (40).

At the follow-up moments in the intervention group, we additionally collect data on:
Adherence to the programme by evaluating the % of patients using the PreLife app in combination with a question on their motivation of (not) using the PreLife app.
Social support: a short questionnaire to evaluate if they feel supported by their partner in maintaining a healthy lifestyle (41).

Data collected at the end of the study:
Next to fertility treatment and follow-up of pregnancy data, data on the subjective quality of the PreLiFe app is collected at the end of the study in the intervention group.
Subjective quality of the application is assessed with a shortened version of the subjective quality subscale of the Mobile App Rating Scale (MARS) (40).

Data management

Medical record data, and anthropometric data will be entered and stored by the study nurse in a good clinical practice compliant Electronic Data Capturing (eCRF) system developed by our IT-specialist, Steve De Backer, ESAT, KU Leuven. In case of no database access, data will be entered on paper CRF and subsequently entered into the data system when access is possible. Data from questionnaires will be collected using Qualtrics, a secure website. A link to the questionnaires will be sent by email to the participants at baseline at 3, 6,9,12 months after randomization and at the end of the study. Deviation of 2 weeks before and after the planned time point is allowed. Questionnaire data will be exported and stored in the eCRF. The data from the mobile application (i.e. use of application and physical activity from pedometer) can be retrieved from the secured website of PreLiFe of which only the research team and the participants have access.

5. Statistical analyses

Descriptive statistics for baseline values in the two arms will be presented. There will be no tests of statistical significance for differences between the two arms as these are randomised groups.The statistical analysis will be performed according to the intention-to-treat principle. This implies that couples will be analysed according to the arm to which they were randomized, and that patients who withdraw from the study or discontinue IVF treatment will be included. The withdrawal rate of the study will be assessed and compared between the two arms.

Primary study parameters

The primary outcome is cumulative ongoing pregnancy rate (COPR) within 12 months after randomization (i.e. viable intrauterine pregnancy of at least 12 weeks duration confirmed on ultrasound scan) and IVF discontinuation rate. To calculate this, an ongoing pregnancy conceived within 12 months after randomization is counted as a positive event, whereas IVF discontinuation and absence of pregnancy are counted as a negative event. The COPR in both groups will be compared using logisitic regression models that allow to control for predictive variables including both partners' BMI and age. Analysis will be according to intention to treat. Odds ratios with 95% confidence intervals will be reported. A p-value <0.05 will be used to determine statistical significance for the intervention. Additionally, Cumulative incidences of ongoing pregnancy and IVF discontinuation will be described in the intervention and control group.

Secondary study parameters

Binary secondary outcomes are differences in other fertility and pregnancy outcomes such as implantation and clinical pregnancy between the intervention and control group. These require similar analyses as the primary outcome. Additionally we will evaluate changes in lifestyle parameters including changes in the dietary pattern, physical activity level, personal wellbeing, physical health and fertility related quality of life over time and we will evaluate the differences between the intervention and control group in these parameters. Self-reported questionnaires will be processed according to the standard for that test. Mixed models for repeated measurements (MMRM) will be used to evaluate treatment, time and interactive effects on continuous secondary outcomes. The determination of statistical significance is not central to the analysis of secondary endpoints, yet nominal p-values may be reported.

Additional parameters measured in the intervention group are the partner's support, the adherence to the programme and subjective quality of the application. Descriptive analysis will be conducted on these parameters.

Missing data

For the primary endpoint, we do not expect missing data. For the binary secondary endpoints, the same argument applies. For continuous secondary endpoints, MMRM is used which is consistent under the 'missing at random' assumption and in line with the intention-to-treat principle (42).

A fully statistical analysis plan will be written in collaboration with the statistician prior to any analysis being undertaken.

6. Harms: safety reporting

Throughout the whole PreLiFe study, participant's health and safety will be warranted. All solicited and spontaneously reported adverse events and other unintended effects of the PreLiFe study will be collected, assessed, reported and managed according to good clinical practice guidelines (GCP). The investigator shall report all serious adverse events immediately, after first knowledge to the sponsor. If necessary, the immediate report shall be followed by detailed, written reports. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigators. For reported deaths of a subject, which is highly unlikely in this study, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.
Regarding follow-up of those adverse events and serious adverse reactions the principal investigator will take all reasonable measures, in consultation with the sponsor, to protect subjects at risk following the occurrence of such events.

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize the participant's health or safety. The study will be suspended pending further review by the accredited EC. The investigator will take care that all study participants are kept informed.

7. Quality assurance

Standard operating procedures (SOP's) on all the previously mentioned procedures will be available to maintain quality assurance.

8. Direct access to source data and documents

The investigator(s) will permit study related monitoring, EC review and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. study visit checklists, SOP's etc.).

9. Ethics and regulatory approvals

9.1 Regulation statement

The PreLiFe study will be conducted in compliance with the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), the principles of GCP and in accordance with all applicable regulatory requirements.
The study protocol and all other study-related information will be submitted to the Ethics Committees of the Participating sites and the national competent authorities where applicable, in order to obtain prior approval before the study is initiated, unless such submission to the Ethics Committee is not required by applicable national legislation or in the event of a waiver for submission has been granted. Any subsequent protocol amendments will be submitted to the appropriate Ethics Committees and national Regulatory Authorities for approval.

The study can and will be conducted only on the basis of prior informed consent by the participants, to participate in the Study. The participating sites shall obtain a signed informed consent form (ICF) for all participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The participating sites shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigators and the participating sites will treat all information and data relating to the study disclosed to participating sites and/or investigators in this study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study.

The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

The data will be coded, which means that there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research team according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the subject.

9.2 Recruitment and ICF

Eligible patients will be informed about the study by the gynaecologist, the attending resident or the fertility doctor. These patients will be invited for additional counselling by a research nurse, to ensure that they are fully informed on the nature of the study by means of both oral and written information. Patients who agree to participate will be asked to sign a written informed consent of which they will receive a copy. The partner of the patient will also be asked to sign the written informed consent. Randomisation will only be performed after receiving informed consent.

10. Publication Policy

It is anticipated that the results of the overall study shall be published in an international peer reviewed journal. The parties agree that publications or presentations of any of the results from the study shall be in accordance with accepted scientific practice, academic standards and customs. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

11. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, the sponsor shall assume, even without fault, the responsibility of any damages incurred by a study participant and linked directly or indirectly to the participation to the study. The sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by the Belgian study participants.

12. Financial Aspects

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