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Title:

Protocol of the Fit-For-Fertility Study: a multicentre randomized controlled trial assessing a lifestyle program targeting women with obesity and infertility

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Abstract

Introduction:

Women with obesity are at a higher risk of infertility as well as gestational and neonatal complications. Lifestyle changes are universally recommended for women with obesity seeking fertility treatments, but such intervention has only been assessed in very few robust studies. This study's objectives are therefore to assess the clinical outcomes and cost-effectiveness of an interdisciplinary lifestyle intervention (the Fit-For-Fertility Program; FFFP) targeting women with obesity and subfertility in a diverse population.

Methods and Analysis:

This pragmatic multicentre randomized controlled trial (RCT) will include 616 women with obesity (BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with polycystic ovary syndrome or at-risk ethnicities) who are evaluated at a Canadian fertility clinic for subfertility. Women will be randomized either to 1) the FFFP (experimental arm) alone for 6 months, and then in combination with usual care for infertility if not pregnant; or 2) directly to usual fertility care (control arm). Women in the intervention group benefit from the program up to 18 months or, if pregnant, up to 24 months or the end of the pregnancy (whichever comes first). Women from both groups are evaluated every 6 months for a maximum of 18 months. The primary outcome is live birth rate at 24 months. Secondary outcomes include fertility, pregnancy and neonatal outcomes; lifestyle and anthropometric measures; and cost-effectiveness. Qualitative data collected from focus groups of participants and professionals will also be analyzed.

Ethics and Dissemination:

This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universtaire de santé et des services sociaux de l'Estrie – CHUS* (research coordinating centre) on December 10, 2018, and has been or will be approved successively by each participating centers' REB. This pragmatic RCT will inform decision-makers on improving care trajectories and policies regarding fertility treatments for women with obesity and subfertility.

Trial Registration:

ClinicalTrials.gov: NCT03908099, Registered April 9, 2019.

Protocol version: 1.1, April 13, 2019

Strengths and limitations of this study

- This study has a strong design: a multicentre, two-arm, parallel pragmatic randomized-controlled trial comparing the Fit-For-Fertility program to usual fertility care, using quantitative and qualitative assessments.
- The primary study outcome of live birth rate at 24 months, and the main secondary outcomes of fertility outcomes and pregnancy or neonatal complications, are strong clinical outcomes pertinent for patients. The study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system.
- Early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations

will increase the feasibility of the trial and the potential impact and use of the findings to influence policies and priorities of institutions and governments.

- It is not possible to blind the intervention and data collection since the tested intervention is a lifestyle program, but the study primary outcome of life birth is a robust clinical outcome that is not susceptible to bias.
- Self-reported questionnaires may introduce desirability or recall biases, but the study uses tools validated in such setting and these biases should be similar in the intervention and control groups.

Keywords

Obesity, Fertility, Women, Lifestyle, Weight loss, Pregnancy, Randomized controlled trial, Live birth, Cost-Effectiveness, Polycystic ovary syndrome

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List of abbreviations

AEoSI, Adverse Events of Special Interest;

ART, assisted reproduction technology;

ALT, alanine amino transferase;

β-hCG, human chorionic gonadotropin;

BMI, body mass index;

CHUM, Centre hospitalier universitaire de Montréal;

CHUQ, Centre hospitalier universitaire de Québec;

CHUS, Centre hospitalier universitaire de Sherbrooke;

CI, confidence intervalle;

CIUSSS, Centre intégré universitaire de santé et des services sociaux;

COVID-19, Coronavirus Disease 2019;

EOSS, Edmonton Obesity Staging System;

FertiQoL, Fertility Quality of Life questionnaire;

FFQ, Food Frequency Questionnaire;

FSH, follicle stimulating hormone;

HADS, Hospital Anxiety and Depression Scale;

HbA1c, glycated hemoglobin;

HDL, high-density lipoprotein cholesterol;

ICER, incremental cost-effectiveness ratio;

IPAQ, International Physical Activity Questionnaire;

ITT, intent-to-treat;

IUSMM, Institut universitaire en santé mentale de Montréal;

IVF, *in vitro* fertilization;

LDL, low-density lipoprotein cholesterol;

LH, luteinizing hormone;

MAR, medically assisted reproduction;

OR, odd ratio;

PCOS, polycystic ovary syndrome;

PRECIS, PRagmatic-Explanatory Continuum Indicator Summary;

PRL, prolactin;

PSQI, Pittsburg Sleep Quality Index;

PV, Pregnancy visit;

QALY, Quality-Adjusted Life Years;

REDCap, Research Electronic Data Capture;

RCT, randomized controlled trial;

REB, Research Ethics Board;

SAE, Serious Adverse Events;

SF-6Dv2, Short Form-6 Dimensions – version 2;

SHBG, sex hormone-binding globulin;

SMART, Specific, Measurable, Attainable, Realistic and Timely;

TSH, thyroid-stimulating hormone;

V0, baseline research visit at time 0; and

WHO, World Health Organization.

Introduction

Women with obesity and infertility

Infertility affects approximately 10-15% of couples in Canada and the rest of North America [1]. According to the International Glossary on Infertility and Fertility Care, infertility is "a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner" [2]. For the purpose of this study, subfertility is defined as an infertility with a reasonable probability of spontaneous pregnancy without medical intervention, which excludes couples with sterility or severe infertility (such as bilateral irreversible tubal factor or severe male factor). Medically assisted reproduction (MAR), including ovulation induction, ovarian stimulation, intra-uterine insemination and assisted reproductive technology (ART) [2] are part of the current clinical management of infertility and have become more and more used and effective in helping infertile couples to achieve a pregnancy [3]. Unfortunately, these procedures are costly and carry risks for both women and infants. These risks can occur at different stages of ART: ovarian stimulation (ovarian hyperstimulation syndrome, thromboembolism, and ovarian torsion), oocyte retrieval (infection and bleeding) and early pregnancy (ectopic or heterotopic pregnancy, and multiple gestations[4]). Although these risks are rare, they can have significant consequences. Furthermore, some studies have suggested that ART procedures may have negative neonatal consequences, such as

higher frequencies of alterations in DNA methylation patterns associated with DNA imprinting disorders in children conceived through ART [5].

Obesity (defined operationally as a BMI ≥ 30 kg/m^2 [6]), is a known modifiable risk factor associated with female infertility [7] and the population affected worldwide is high enough for obesity to be recognized as a global epidemic by the World Health Organization since 2000 [8]. The prevalence of obesity has been estimated to be as high as 30% in Canadian and 38% in American populations, respectively [9]. More precisely, 21% of Canadian women of reproductive age had obesity in 2015 [10]. Women who plan to get pregnant are currently more likely to be affected by obesity [11], which can significantly affect their fertility. For instance, a very large cohort study including more than 40,000 couples estimated that women with obesity display a 78% higher risk of having infertility compared to women with a normal BMI (18.50-24.99 kg/m^2) (odd ratio [OR] with 95% confidence interval [CI]: 1.78 [1.63-1.95]) [12]. Women with obesity are also more likely to develop polycystic ovary syndrome (PCOS), which is the leading cause of anovulatory infertility, affecting 6-10% of women of childbearing age [13]. Furthermore, a higher BMI has been associated with reduced pregnancy rates even in women with ovulatory cycles, equating to a 4% decrease in pregnancy rate per kg/m^2 of BMI increase in women with a BMI ≥ 29kg/m [14].

Moreover, studies assessing MAR procedures have reported that women with obesity: i) require higher doses and a longer duration of clomiphene [15] and gonadotrophins [16-19] to achieve ovulation, ii) display a lower pregnancy rate per cycle [18], and iii) are at a higher risk of cycle cancellation [16,18] and miscarriage [20,21].

Obesity also increases the risk of complications during pregnancy, such as gestational diabetes, pre-eclampsia, caesarean section and intrauterine death [22,23]. In keeping with the Developmental Origins of Health and Disease paradigm, maternal pre-pregnancy BMI and excessive gestational weight gain are consistently associated with the early development of obesity and diabetes in the offspring [24]. Obesity in childhood is closely linked to adult obesity [25,26], perpetuating the intergenerational cycle of obesity [27-29]. Adopting a healthy lifestyle before conception and restoring of a healthy metabolic environment early during pregnancy likely represents the best approach to break the vicious circle of intergenerational propagation of obesity and diabetes.

Accordingly, targeting women with obesity prior to conception may be essential to reduce the burden of infertility and MAR costs, as well as obesity and cardiometabolic diseases in our societies.

Infertility management in women with obesity seeking fertility treatments

To prevent the adverse effects of obesity on female fertility and on gestational and neonatal health, many organizations have recommended that women with obesity should be assisted, before conception, to lose weight (5 to 10 % of their initial weight) and adopt a healthy lifestyle, and maintain that healthy lifestyle during pregnancy [30-33]. Results from a recent systematic review support lifestyle modification prior to ART in women with overweight or obesity [34]. The authors pointed out that despite the lack of RCTs in the area, pre-conception weight loss in women with overweight or obesity can help improve fertility and pregnancy outcomes. Out of the 7 RCTs assessing non-surgical methods of

weight loss, including some form of lifestyle intervention, the most methodologically rigorous study was a RCT published in the *New England Journal of Medicine* in 2016 [35]. This study compared 287 women with obesity and subfertility who were randomized to a 6-month structured lifestyle intervention (including 6 outpatient visits and 4 telephone consultations with a nurse or dietician) and 285 women assigned to prompt fertility treatments. The lifestyle intervention lasted only 6 months and was not continued during fertility treatments or pregnancy. After a follow-up of 24 months, the lifestyle program did not improve the live birth rate, but resulted in a significant increase in the rate of spontaneous pregnancies (rate ratio [95% confidence]: 1.61 [1.16-2.24]) and reduced the need for fertility treatments (rate ratio [95% confidence]: 0.78 [0.70-0.86]) [36]. In a follow-up article, the same group of authors observed, from a hospital perspective, an incremental cost-effectiveness ratio (ICER) of €15,845 per additional point of percentage in the healthy live birth rate resulting from the lifestyle program compared to usual care. The authors concluded that their intervention may be deemed as cost-effective, especially for longer follow-up timelines, in anovulatory women, women who completed the study or women ≥ 36 years of age [37].

Interestingly, in a survey asking women with obesity or overweight and considering pregnancy if they were interested in adopting a healthier lifestyle prior to conception, 91% reported their willingness to participate in a lifestyle program [38]. However, despite the patients' motivation and the international recommendations to encourage women to optimize their lifestyle before starting fertility treatments, most women with obesity do not have access to such targeted lifestyle programs integrated within their fertility care. Therefore, our objective is to give these women access to the Fit-For-Fertility Program

(FFFP), an interdisciplinary lifestyle intervention, integrated into the fertility clinic care pathway. This program supports participants in adopting sustainable healthy behaviours, in pre-conception, throughout fertility treatments, and during pregnancy. In response to the national priority to improve the quality and costs of reproductive and perinatal care established by our *Canadian network on reproductive and maternal health of women with obesity and infertility*, we will conduct a multicentre RCT assessing the FFFP in women with subfertility and obesity.

Research question and hypotheses

For this RCT, our research question is: Compared to usual care, does the FFFP cost-effectively improve i) the live birth rate and other fertility outcomes and ii) pregnancy and neonatal outcomes, in women with obesity and subfertility who seek fertility treatments. We hypothesize that in comparison to prompt initiation of usual fertility care, participation in the FFFP, alone for 6 months and then in combination with usual care for infertility, will: 1) improve the fertility of women with obesity, 2) reduce costs associated with fertility treatments, and 3) decrease the occurrence of some complications related to maternal weight during the pregnancy and for their offspring.

Study objectives

The primary objective of this study is to assess the effectiveness of the FFFP on fertility outcomes in a diverse Canadian population of women with obesity and subfertility who are seeking fertility treatments. Secondary objectives are to assess the FFFP's 1)

cost-effectiveness, primarily in terms of costs per live birth, as well as other measures of the program's costs and effectiveness measures, and 2) impacts on maternal and neonatal health.

Methods and Analysis

Study design

This study is a multicentre, two-arm, parallel pragmatic RCT comparing the FFFP to usual fertility care, using quantitative and qualitative assessments (ClinicalTrials.gov: NCT03908099). More specifically, we developed a pragmatic RCT based on the PRECIS-2 principles [39].

Patient and Public Involvement

Our study relies on the early and regular involvement of knowledge users and decision-makers to ensure their appropriation of the results. Engaged patients have been implicated early in the development of this protocol to ensure that the results will be relevant for the target population and that the methods are appropriate for the participants. Following these principles increases the potential impact and use of the findings to influence policies and priorities of institutions and governments.

Setting and recruitment

The study will be conducted in seven Canadian fertility clinics from coast to coast and in an ethnically diverse population of women: Olive Fertility Centre in Vancouver (British-Columbia), with its Asian population; Mount Sinai Hospital in Toronto (Ontario) and *Centre hospitalier de l'Université de Montréal* (CHUM), with large multiethnic communities; *Centre hospitalier universitaire de Sherbrooke* (CHUS) and *Centre hospitalier universitaire de Québec de l'Université de Laval* (CHU de Quebec-UL) (Quebec), which are smaller centres with mainly a Caucasian population; and Atlantic Assisted Reproductive Therapies Clinic in Halifax (Nova Scotia) that has a Caucasian and Afro-American populations. We are also in the process of recruiting a 7th centre, ideally in the province of Manitoba.

Potentially eligible patients can be approached in one of two ways: 1) by a member within their circle of care (nurse, physician, receptionist, etc.) who then provides contact info to research staff, or 2) by responding to an advertisement indicating their interest to learn more about the study. Written informed consent is obtained individually for each patient during the baseline research visit (V0), after a full explanation of the study's protocol and answers to the patient's questions by the research staff, and before any data collection or study procedures. The following screening and baseline data are obtained during this visit: eligibility assessment (inclusion/exclusion criteria), medical history, concomitant medications, patient demographics and a baseline evaluation of study outcomes. Eligibility is confirmed by the site investigator before randomization.

Participant eligibility

Patients who meet the following inclusion criteria can participate in the study:

1) Being infertile, defined as (a) failure to achieve a clinical pregnancy after ≥12 months of regular unprotected sexual intercourse, (b) not conceiving after having attempted ≥6 months in women with irregular menstrual cycles or ≥35 years of age; or (c) women with an established cause of infertility;
2) Aged between 18 and 40 years (since initiation of fertility treatments should not be delayed in women above 40 y.o.); and
3) With obesity (BMI ≥ 30 kg/m^2 or 27 kg/m^2 for Asian and Latin American, based on WHO 2004 [40]), or with a BMI ≥ 27 kg/m^2 for women with PCOS. These women display the metabolic consequences of non-PCOS women with obesity at a lower BMI, and benefit more from lifestyle modifications.

Women presenting at least one the following exclusion criteria will not be eligible to enroll in the study:

1) Any uncontrolled medical or mental condition that contra-indicates fertility treatments, based on clinical judgment of the fertility specialist;
2) Natural conception is impossible or highly unlikely (e.g., bilateral tubal factor, severe male factor defined as a total motile sperm count < 5 million on the most recent partner's seminal analysis), where the only indicated MAR procedures are IVF or donor sperm insemination (this exclusion criteria defines subfertility, such that only subfertile couples are enrolled);
3) History of recurrent spontaneous abortions (>2 miscarriages at less than 22 weeks of gestation), with evidence of conception (such as positive β-hCG), within the last

12 months (since these women are more likely to have a defect that cannot be improved by lifestyle);

4) Previously diagnosed uncontrolled eating disorder or major depression that would contra-indicate the initiation of a lifestyle intervention;
5) A high level of depressive state, as determined by a score for depression on the Hospital Anxiety and Depression Scale (HADS) ≥ 15 [41,42], which is not a diagnostic of depression but would also contra-indicate the initiation of a lifestyle intervention;
6) Planning for or past history of bariatric surgery, which would confound the impact of the lifestyle intervention tested;
7) Planning for or engaging in another lifestyle intervention that would be similar to the intervention tested, e.g., including individual visits every 8 weeks or less, which would also confound the impact of the FFFP;
8) Inability to understand the language in which group sessions is provided in the participating centre, i.e., French in the province of Quebec and English in other provinces; and
9) Unable to attend research visits at the participating centre for the next 18 months.

Randomization

Randomization to the FFFP or control group occurs after completion of the V0 and the eligibility assessment. Group allocation is concealed using online computerized randomization using REDCap (Research Electronic Data Capture tool hosted at the Université de Sherbrooke) [43] with permuted blocks of variable block sizes (2 to 6),

stratified by centre and PCOS status (yes/no). PCOS is an important potential confounder or modifier since it decreases fertility and may affect the response to the lifestyle intervention [13]. The randomization list has been generated by an independent statistician and participants are randomized in one of two arms using a 1:1 ratio. The randomization process is initiated by the site investigator or delegate who accesses the web-based system and confirms patient's eligibility and informed consent. The patient's unique study identifier and open-label study treatment allocation is then automatically and electronically delivered to the local site investigator or delegate.

Following randomization, the research staff informs the fertility care team of the patient's allocation group. On the one hand, if the participant is randomized to the control group, the fertility care team is informed that their patient can undergo fertility treatments immediately, according to their usual care. On the other hand, if the participant is randomized to the intervention group, the fertility clinic will be notified that the patient has to postpone any MAR procedures for the following 6 months, during which the patient is enrolled in the FFFP. At the end of this first 6-month period, if the participant failed to conceive, the research staff contacts the fertility clinic team to inform them that the participant can now undergo usual fertility care, in combination with the FFFP.

Interventions

Control Arm

Participants randomized to the control group are provided immediate access to the usual fertility care, as recommended by their fertility specialist, for a maximum of 24 months. This may include lifestyle counselling by their fertility specialist and usual fertility treatments. Since this is a pragmatic trial, they may undergo any lifestyle approaches or consult any professionals they want on their own, but are discouraged to engage in a lifestyle program similar to the FFFP, as they agreed when recruited for the study, in order to avoid such an important contamination between intervention arms.

Experimental Arm

Participants randomized to the intervention group follow the FFFP alone for the first 6 months, then in combination with usual fertility care for an additional 12 months if not pregnant. After these 18 months, usual fertility care can continue to be provided alone for a maximum follow-up of 24 months. The FFFP is also provided throughout gestation for participants who achieve a successful pregnancy. Accordingly, the lifestyle program is provided for a maximum of 18 months if there is no pregnancy, or otherwise, up to the end of pregnancy or to a total study follow-up of 24 months (whichever comes first).

The FFFP was initially developed based on 2007 Canadian clinical practice guidelines [44]and the approach implemented by our group at the CHUS obesity clinic [45], and was then improved and adapted based on the experience gained from our completed pilot study [46] and focus groups with study participants. This intervention is aimed at supporting participants to implement progressive and sustainable lifestyle changes. Participants attend 30-minutes individual sessions with a dietitian and a

kinesiologist, respectively, every 6 weeks for the first 6 months, then every 8 weeks for the following 6 months, and then every 12 weeks until the end of the treatment period. These individual meetings take place in person with the participant, or virtually using an authorized system of telemedicine in the event that face-to-face meetings are not possible (e.g., due to public health rules such as during the COVID-19 pandemic). Personal remote contact (e.g., by phone, e-mail) is offered between in-person meetings. Patients are guided by the dietitian and kinesiologist to formulate SMART goals (Specific, Measurable, Attainable, Realistic and Timely) [47]. These professionals are trained in evidence-based motivational communication skills [48], with emphasis placed on how to arm women with the knowledge, motivation, and skills to achieve sustainable lifestyle changes. To ensure equitable delivery of the intervention, we will implement an internal quality control and training process. Therefore, after receiving training in motivational communication by our leading expert (KLL), each professional will audio-record their first three individual meetings. These recordings will be evaluated by an expert in motivational communication using a coding scheme to verify fidelity. Feedback regarding the professional's application of motivational communication techniques will be provided as needed, and additional recordings may be necessary based on the trainer's assessment. After 6 and 12 months, three more individual sessions are recorded and used to analyze the quality and fidelity of the intervention from a research perspective. Consent for recording individual meetings is a specific question in the informed consent form and participants have the opportunity to revoke their agreement at any time during the course of their participation in the study.

Participants also benefit from weekly group sessions divided into 2 parts of 45 minutes each [46] (see Table 1 for group sessions' topics): 1) Workshops that cover 8

different topics addressing nutritional aspects and relevant healthy lifestyle habits (alcohol, tobacco and motivational issues) and 2) Supervised classes of physical activity where one of 8 different types of exercise are practiced. Women are invited to participate in group sessions every week throughout the study, but are required to attend all 8 different sessions within the first 6 months. The spouses of participants are highly encouraged to participate in all activities, as lifestyle modification is also important for the partner to improve a couple's fertility [49,50].

Table 1. Topics of the Fit-For-Fertility's Interactive workshops and physical activity sessions.

Sessions	Interactive workshops (45 min)	Physical activity sessions (45 min)
1	"Let's get going! Follow the Guide!"	"A step in the right direction!"
	→ *Introduction to the Canadian Food Guide*	→ *Walking for fitness [outdoors]*
2	"Finding balance"	"Stay active… even at home!"
	→ *Changes that pay off*	→ *Weight training exercises at home*
3	"Taking charge of your environment"	"Step-by-Step!"
	→ *The act of eating*	→ *Step aerobics class*
4	"Listening to your body…"	"Bulk up your health!"
	→ *Feeling hungry and feeling full*	→ *Muscle building with an elastic band and exercise ball*
5	"The label says it all"	"Stay Zen!"
	→ *Food labels*	→ *Initiation to yoga*
6	"Planning is the key!"	"Cardio-muscular" walking!"
	→ *Meal planning*	→ *Combined weight training and walking [outdoors]*
7	"Thinking about it isn't enough!"	"Short circuit!"
	→ *Change process and motivation*	→ *Circuit fitness*
8	"Breathe in, breathe out!"	"Groove it out!"
	→ *Sleep, alcohol and tobacco*	→ *Zumba Class*

For women with a confirmed pregnancy, our team schedules a meeting to set new lifestyle objectives specific to pregnancy to promote, a healthy pregnancy, including optimal gestational weight gain based on the Institute of Medicine guidelines [51]. This meeting can take place during a regular intervention meeting or during the first research pregnancy visit (PV1), whichever comes first.

Data collection

As illustrated in Figure 1, research evaluation visits take place in both groups at baseline and every 6 months for a total of 18 months if no pregnancy occurs. Women who become pregnant ***within*** the first 18 months of follow-up are met at the beginning of their pregnancy (PV1) and at 24-28 weeks of pregnancy (PV2) for measures (see Figure 1). Women who become pregnant ***after*** 18 months of follow-up do not undergo research visits during their pregnancy. Data collection and measures during these research visits are detailed in Table 2.

Table 2. Research visits and data collected.

	V0	V6	V12	V18	PV1	**PV2**
Informed consent	●					
Physical exam (anthropometry, blood pressure and heart rate)	●	●	●	●	●	●
Concomitant medications	●	●	●	●	●	●
Blood sample						
Fasting levels of sex steroids	●	●	●	●		
FSH, LH	●	●	●	●		
TSH	●	●	●	●	●	●

Prolactin		●	●	●	●		
β-hCG		●	●	●	●	●	
ALT		●	●	●	●	●	●
HbA1c		●	●	●	●	●	●
Glucose		●	●	●	●	●	●
Lipids		●	●	●	●		
Creatinine		●					
Extra samples shipped to the coordinating site (Sherb., QC)		●	●	●	●	●	●
Initial Medical Questionnaire		●					
Actual Health Status Questionnaire			●	●	●	●	●
FertiQoL		●	●	●	●		
HADS		●	●	●	●	●	●
IPAQ		●	●	●	●	●	●
Readiness to Change Questionnaire		●	●	●	●	●	●
PSQI		●	●	●	●	●	●
Socio-demographic Questionnaire		●					
Patient's Costs Questionnaire			●	●	●	●	●
SF-6D.v2		●	●	●	●	●	●
FFQ web		●	●	●	●	●	●
Fitbit & Fitbit Journal		●	●	●	●	●	●
6 minutes walking test		●	●	●	●	●	
Participant's Satisfaction Questionnaire					●		●
AEoSI and SAE review		●	●	●	●	●	●

Abbreviations: AEoSI: adverse events of special interest; ALT: alanine amino transferase; β-hCG: human chorionic gonadotropin; FertiQoL: Fertility Quality of Life questionnaire; FFQ: Food Frequency Questionnaire; FSH: follicle stimulating hormone; HADS: Hospital Anxiety and Depression Scale; HbA1c: glycated hemoglobin; IPAQ: International Physical Activity Questionnaire; LH: luteinizing hormone; PSQI: Pittsburgh Sleep Quality Index; PV1: first pregnancy research visit (beginning of pregnancy); PV2: pregnancy research visit at 24-28 weeks of gestation; SAE: serious adverse events; SF-6D-v2: Short Form-6 Dimensions – version 2; TSH: thyroid-stimulating hormone; V0: baseline research visit; V6, V12, V18: research visits at 6, 12 and 18 months post-randomization, respectfully.

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Participants are instructed to contact the study team between visits or phone calls if they become pregnant or if any relevant situations occur (e.g., miscarriage, accident, moving, changing phone number). Importantly, all clinical outcomes are ascertained with participants and their medical records 24 months after participants' randomization, regardless of the timing of their last research visit and the occurrence of a pregnancy. Pregnancy and neonatal outcomes occurring 24 months after randomization will not be included in the primary analysis of the primary outcome, but are recorded for secondary analyses.

Outcome measures and their assessment

Fertility outcomes: The primary outcome is the cumulative incidence of live birth at 24 months. Secondary fertility outcomes are also collected from medical records at 24 months and include: the rate of biochemical pregnancy (confirmed by a positive serum β-hCG), ongoing confirmed pregnancy (viable pregnancy at ≥10 weeks of gestation), spontaneous miscarriage of a confirmed pregnancy (<22 gestational weeks), multiple gestation, spontaneous pregnancy, pregnancy following MAR procedures, doses of fertility medications, number of MAR and/or ART cycles, number of embryo transfers, and complications due to MAR procedures.

Pregnancy outcomes (all secondary outcomes): Total gestational weight gain, calculated by subtracting weight at the research visit closest to the onset of pregnancy from the last weight available in the antenatal record. Weekly gestational weight gain, calculated by dividing total weight gestational gain by the number of weeks between the

first and last measure of weight. Pregnancy complications, which are retrieved from medical records, include gestational diabetes, gestational hypertensive disorders, thromboembolism, preterm birth, late fetal loss, stillbirth and post-partum hospital stay >7 days.

Neonatal outcomes (all secondary outcomes): Birth weight, Apgar scores, hypoglycemic episodes, hyperbilirubinemia, birth trauma, admission to neonatal intensive care unit and neonatal death (up to 28 days of life), which are retrieved from medical records.

Anthropometric measures and vital signs (all secondary outcomes): Anthropometric measures are collected at each research visit. Weight is measured with a standard calibrated scale and height is measured with a stadiometer, based on the models available at each centre. Foot-to-foot bioelectrical impedance analysis technology is used to estimate the percentage of fat mass and fat free mass [52] in most, but not all centres (models depend on each centre). Waist circumference measurement is done with a measuring tape according to the National Institutes of Health [53]. Heart rate and blood pressure are measured after a five-minute rest period in a sitting position. Two measurements are taken for waist circumference and vital signs, with the average being used for analyses.

Endocrine and metabolic blood markers (all secondary outcomes): A blood sample is taken at each research visit to measure different hormonal and metabolic biological markers: luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid-stimulating

hormone (TSH), prolactin (PRL), human chorionic gonadotropin (β-hCG), serum progesterone, androstenedione, estradiol, total and calculated free testosterone, sex hormone-binding globulin (SHBG), glycated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), cholesterol ratio, glucose, alanine amino transferase (ALT) and creatinine (at initial research visit only). All markers are assessed at local laboratories, since they are clinically indicated. Additional plasma samples are shipped to CHUS and stored for future analyses relevant to this study's objectives, when further funding becomes available.

Lifestyle outcomes (all secondary outcomes): Lifestyle outcomes are assessed at each research visit. Nutritional intake is evaluated using the validated web version of the Food Frequency Questionnaire (FFQ web), referring to the patient's nutritional consumption of the last month. This questionnaire enables to extract data on specific food groups and micro- or macronutrients. This questionnaire has been shown to have a moderate validity and a good reproducibility for assessing nutrient intakes in healthy adults [54]. Participants complete the questionnaire at the research centre at their first research visit to ensure good understanding of the questions. For subsequent research visits, participants have the possibility to receive a link to complete the FFQ web electronically from home. Sleep duration and quality are evaluated by the Pittsburg Sleep Quality Index (PSQI) questionnaire, which has been shown to have a strong reliability and validity, as well as a moderate structural validity in the context of screening for sleep dysfunction [55]. The International Physical Activity Questionnaire (IPAQ) – short version – is used to assess physical activity practice over the past 7 days: it was shown to have a good

repeatability of data and is as reliable as other self-administered physical activity questionnaires [56]. Furthermore, participants are asked to wear after the research visit a Fitbit© Flex 2 monitor during 7 consecutive days, 24 hours/day, in order to objectively assess physical activity levels (energy expenditure, number of steps, distance walked, time spent being inactive, lightly active, active and very active), as well as sleep data (minutes spent asleep, awake and restless (when moving while sleeping)). Fitbit© devices have been shown to accurately estimate the daily number of steps and the time spent in bed and sleeping, while overestimating the time spent doing highly intense activities [57]. However, data extracted will be mainly used to assess the change of physical activity levels and sleep over time and not whether physical activity recommendations are met. This estimation bias should be consistent at each measurement time point and will be adjusted for baseline measures. The participant's physical fitness level is assessed using the 6-minute walk test (6mWT), which has shown to be a simple, safe and low-cost test to assess the effect of an intervention on the physical performance and walk capacity beyond weight loss [58]. Other lifestyle habits, such as alcohol, tobacco and drugs consumption, are measured by a study-specific self-reported questionnaire.

Quality of life (secondary outcome): Participants' quality of life specifically related to infertility and its treatments are assessed using the Fertility Quality of Life questionnaire (FertiQoL) [59]. Moreover, the Short Form-6 Dimensions – version 2 (SF-6Dv2) is used to determine Quality-Adjusted Life Years (QALY), which is an important variable for the economic evaluation of the intervention, and to assess the general quality of life of our participants, as well as the impact of our intervention on dimensions of quality of life.

Patients' perceptions and satisfaction (all secondary outcomes): Based on experience from previous studies [46,60,61], we will evaluate the expectations, perceptions and satisfaction towards care provided for fertility and weight management in all participants with a questionnaire, and will further assess these aspects in a small sample (from both groups) using focus groups. The satisfaction questionnaire is given at the 18-month research visit (V18) or at the second pregnancy research visit (PV2) if pregnant. Focus groups will take place at 2 time points: 1) after completion of the study by half of the participants and 2) close to the end of the trial. A total of 168 patients (27% of all participants) will participate in the focus groups across all 7 centres, each centre evaluating two separate sub-groups of 6 patients from the intervention and control groups. The number of participants for the second series of focus groups may be adjusted to reach data saturation. See bellow under "Methodology and analyses of qualitative substudy" for more details.

Health-related costs (secondary outcomes): Data is collected from both the patient and the health care system perspectives for each mother/child dyad. Costs of interest include costs related to the FFFP, fertility treatments, adverse events or complications, pregnancy-related visits and hospital admissions, and patient out-of-pocket expenses. Data collection for this component will be done through patient questionnaires, charts reviews, administrative data, and interviews with healthcare providers and fertility clinic staff for the description of care procedures.

Medical history and physical health (all secondary outcomes): A study-specific self-administered questionnaire will be used to evaluate participant's relevant medical history,

use of medications or natural products, and physical health during daily activities. It will be possible with the data of this questionnaire to use the Edmonton Obesity Staging System (EOSS), which has been shown to be an effective classification tool for obesity risk assessment, including in the context of obesity and infertility [62].

Data management, monitoring and quality assessment

Research measures and outcomes are recorded through printed or online versions of the questionnaires and paper Case Report Forms at each relevant timepoint. These are checked for integrity by each site's research assistant before being entered into the centralized web-based database REDCap.

The central coordinator at the CHUS is responsible for training of the research staff and health professionals (dietitians and kinesiologists), and the monitoring at all centres. The central coordinator is also responsible for ensuring that patient safety, study procedures and data collection are performed at each centre according to the research protocol and Good Clinical Practice guidelines [63]. The central coordinator sends regular queries to site coordinators to resolve discrepancies identified in the database and performs regular onsite visits. These visits will begin after the site research teams have recruited their first 35 participants (corresponding to one-third of participants to be recruited per sites). Then they will be held at every 6-month intervals to assess protocol adherence, intervention standardization, as well as data completeness and quality. During onsite monitoring visits, approximately 10% of participants' records will be reviewed. Concordance with the original data entered by the site will be assessed using the Cohen's

kappa statistics. A kappa coefficient below 0.60 for one site at the time of a visit, which is considered as less than a moderate concordance [64], will require repeating the training of research staff at this site and, if necessary, revising of all records of participants who completed the study at this site, if possible.

The trial steering committee of this projects includes JPB, RB, AG, EG, WK, BCM, ASM, CKN, MHP, BT, and their key research team members. An advisory committee is also in place and includes JPB, WF, FG, MFL, KL, TP, ASM, SNR, KA, NC, PS, SL, Becky Attenborough, now retired from the Reproductive Care Program of Nova Scotia, Celine Braun, president of the *Association des couples infertiles du Québec*, Rahda Chari, now retired from the Maternal Newborn Child & Youth Strategic Clinical Network, Alberta, Anne Hayes from the Ministry of Health and Long-Term Care of Ontario, Tamil Kendall, past provincial executive director of perinatal services BC, Martine Pageau, *Directrice du sport, du loisir et de l'activité physique* at *Ministère de l'Éducation et de l'Enseignement supérieur du Québec*, Daniel Riverin, past director of Mother-Child Services of Quebec Ministry of Health and Danielle Xavier, past president of Conceivable Dream. The steering and advisory committees meet periodically to support the coordination of the FFF study, and their implication had already started at the protocol design stage.

Safety measurement

Due to the relatively short duration of recruitment and follow-up of participants, it will not be relevant to perform formal interim efficacy analyses for futility or superiority and interim safety analyses. Furthermore, it is very unlikely that the proposed lifestyle

intervention, which is already recommended during preconception and pregnancy in women with obesity, would cause any safety issues. For these reasons, a Data and Safety Monitoring Board (DSMB) will not be required for this trial, and no interim analyses will be performed. However, Adverse Events of Special Interest (AEoSI) and Serious Adverse Events (SAE) will be closely monitored throughout the study (see Table 3). These potential events will be evaluated according to their causality and severity. Furthermore, after randomization of the first 50 patients, the trial's steering committee will produce a quarterly blinded report of AEoSI and SAE for each treatment group, including the grades of causality with the intervention. If SAE occur, these events will be reported to the coordination centre and local Research Ethics Board (REB), as well as the central REB of the Province of Quebec.

Table 3. Adverse Events of Special Interest (AEoSI) and Serious Adverse Events (SAE) monitored during the study

AEoSI
Clinically significant injury (requiring consultation or limiting activities) occurring during exercise, i.e. a planned physical activity with the purpose to improve or maintain physical fitness
Spontaneous miscarriage (spontaneous loss of a pregnancy before 22 weeks of gestation)
Ovarian hyperstimulation syndrome
Multiple gestation
Gestational diabetes requiring pharmacologic treatment, usually insulin
Gestational hypertensive disorder (gestational hypertension, pre-eclampsia or eclampsia)
Thromboembolic clinical event during pregnancy
Preterm birth (occurring after 22 weeks and before 37 weeks of gestational age)
Newborn small for gestational age (birth weight <10th percentile of the sex-specific birth weight for gestational age reference)

Newborn large for gestational (birth weight >90th percentile of the sex-specific birth weight for gestational age reference)
SAE
Antenatal clinically significant uterine bleeding (requiring admission or blood transfusion)
Late fetal loss, i.e. fetal death between 22 and 28 weeks of gestational age.
Stillbirth (>28 weeks of gestational age)
Neonatal death (between childbirth and before 28 days of life)
Newborn with severe congenital malformation (causing a functional handicap)
Admission of newborn to the neonatal intensive care unit
A medical complication that prolongs mother's post-partum hospital stay >7 days

Statistical analyses and sample size

Sample size calculation

Experts from our *Canadian network on reproductive and maternal health of women with obesity and infertility* agreed that for a study using a lifestyle intervention and following intent-to-treat (ITT) principles, the minimal clinically important difference (MCID) in the trial primary outcome, i.e., cumulative life birth rates, would be 15% between groups. Therefore, a sample size of 293 women per group is required to detect a 15% absolute difference between groups, with a power of 95% and alpha level of 5%, from an estimated live birth rate of 35% in the control group (based on our previous pilot RCT [46]) to 50% in the intervention group (nQuery avisor 4.0). Assuming a withdrawal rate of 5% (eligibility criteria violation and loss to follow up), the total recruitment target is 616 women. A 95% power is sufficient for most of our secondary outcome analyses. To recruit a total of 616 participants in 18 months, the two clinics with smaller practices (CHUS and CHUQ) will need to recruit 53 participants (i.e., 39 per year), and the other 5 clinics will have to recruit

102 participants (i.e., 68 per year). These recruitment rates are feasible given the data from our pre-trial survey of participating fertility clinics that showed that smaller practices (CHUS, CHUQ) evaluate 80 to 315 new women with obesity per year, and larger practices, between 265 and 810.

Statistical analyses of quantitative data

The primary outcome is 24-month live birth cumulative incidence and the primary analyses of interest will be ITT, including all randomized participants with available data and no violation of eligibility criteria. The ITT analyses will be supplemented by per-protocol analyses that will exclude women who dropped out of the study during their first 6 months in both groups, i.e. who signified their desire to stop participating in the study and/or intervention visits, or were unreachable from that period up to the end of the trial. The per-protocol analyses will keep all women who persevered in the study for at least 6 months and were therefore appropriately exposed to the intervention (intervention group) and adherent to the 6-month study visit (both group). The 24-month cumulative incidence of live birth will be compared between the two arms using the Mantel-Haenszel test with stratification by centre and PCOS status. This analysis will be supplemented by a survival analysis (log rank test) where the time to live birth will be used. Randomized groups will be examined at baseline to ensure demographic and clinical data are comparable. If substantial imbalance is found, which is very unlikely, additional analyses will be carried out to assess the potential confounding effects of this imbalance, using multiple logistic regression and Cox proportional hazards model. Similar analyses will be used for the other clinical outcome variables that are categorical. Continuous outcome

variables will also be compared between groups based on either ITT or per-protocol analyses, using linear mixed models with repeated measures.

We will also analyze the impact of the FFFP on lifestyle and anthropometric outcomes, as well as other outcomes measured during a research visit, at 6 months (including research visits occurring 6 ± 1 months after randomization), as frequently reported in previous and similar trials. For these analyses, continuous variables will be compared between groups using unpaired *t* tests and categorical variables will be examined using chi-square tests. Missing data due to missed research visits or incomplete data collection will not be imputed, due to the relatively small sample size, such that these analyses might be subjected to non-random missing data differing between groups. Therefore, these tests will be corrected for potential baseline imbalances and confounding effects as mentioned above. Variables that are not normally distributed will be mathematically transformed to fit a normal distribution allowing their use in these models. Subgroup analyses will be performed for all outcomes based on baseline age, level of obesity (BMI ≥ 35 vs < 35 kg/m^2), ethnic origins, socio-economic status, the cause of subfertility and polycystic ovary syndrome status. A 5% level of significance will be used for all analyses.

Economic evaluation

The economic evaluation of the FFFP represents the second objective of this study. The primary economic analysis will be based on the incremental cost-effectiveness ratio (ICER), using live birth as the primary effectiveness outcome. As a secondary measure of cost-effectiveness, QALYs will be calculated from the SF-6Dv2 [65,66], using the algorithm developed by Mulhern et al [67]. QALYs will help in considering the aspect of

health related quality of life affected by weight reduction, healthy lifestyle and psychological impacts of subfertility. A 1.5% discount rate will be considered for periods higher than one year and sensitivity analysis will be performed [68]. To estimate the confidence interval on the difference in costs, we will perform non-parametric analyses with 5,000 bootstrap replications. We will also perform cost-effectiveness acceptability curves to compare the cost-effectiveness thresholds for different costs per unit gain [68,69].

Methodology and analyses of qualitative substudy

In addition to the simple satisfaction questionnaire, an in-depth, qualitative iterative exploration of patient's perceptions of the FFFP and medical care will be performed. Purposive sampling will be used to create the two sub-groups in each clinic, based on the technique of critical incidents using patients' characteristics (levels of satisfaction with their care based on questionnaires, fertility or pregnancy outcomes, loss or gain of weight during follow-up, ethnic group, etc.). A semi-structured interview guide will be used for the focus groups, tailored to each trial group, with open-ended questions adapted from results of previous studies on similar topics [70].The 90-minute focus group meetings will be led by a facilitator who will encourage participation and discussions [71,72]. An experienced observer from our research group will participate remotely from Sherbrooke: he will take notes and support the facilitator, by asking follow-up questions for example. Data will be analyzed as soon as possible by a member of the research team, using Miles, Huberman & Saldana's method. The analysis of the content of the focus groups as they are conducted will help enrich the subsequent focus groups (iterative approach) [73]. A

preliminary analysis grid with various categories based on our previous work will be used, to which emerging categories will be added successively. Regular discussions with the research team will take place during the analysis process to promote a comprehensive understanding of the material collected.

After the trial completion, health professionals' perceptions, self-efficacy, inter-professional collaboration, and satisfaction toward obesity management will be evaluated through a taped-recorded semi-structured focus group interviews in each clinic, as we have previously done [46,60,74]. Discussions among physicians, nurses, dietitians, kinesiologists, clinic administrative personnel, and directors will be encouraged. These focus groups will be performed and analyzed using the same methods as described above for patients.

Discussion

In this paper, we present the research protocol for a multicentre pragmatic RCT assessing clinical and economic outcomes of an interdisciplinary lifestyle intervention targeting women with subfertility and obesity (the Fit-For-Fertility program) that takes place 6 months before initiating fertility treatments and, for the first time, continues in combination with usual fertility care as well as during pregnancy. This study will highlight on important aspects related to the effectiveness, cost-effectiveness and transferability of such a program in a diverse population.

Obesity has been shown to negatively impact on women's reproductive capacity by reducing chances of pregnancy, with or without the help of fertility treatments [12,16,18,19]. Women with obesity are also at a higher risk of complications during pregnancy. Interventions supporting changes in lifestyle habits and a moderate weight loss of 5-10% of the initial weight are highly recommended for women who are trying to conceive [31-33]. Unfortunately, there is little evidence from large and of good quality RCTs in this population supporting this recommendation. To our knowledge, there is only one published RCT (the LIFESTYLE study) evaluating the impacts of a 6-month lifestyle intervention on fertility outcomes among a general population of women with obesity and subfertility, not specifically affected with PCOS [35]. Although the authors did not observe an improvement in their primary outcome (vaginal birth of a healthy singleton) with their lifestyle intervention as compared to usual care, they reported a higher proportion of women in the intervention group achieving a spontaneous pregnancy (26.1% vs 16.2%, RR [95% CI: 1.61 [1.16-2.24]) and a reduced total number of treatment cycles. Our trial

will therefore contribute significantly to the actual knowledge and levels of evidence in the literature.

Although this study uses a robust methodology, as all studies, it has a few limitations. First, data collection is done mainly using self-reported questionnaires that can result in a desirability bias. However, most of the questionnaires used have been validated and used in previous studies, and the bias should be similar in the intervention and control groups. Additionally, self-reported questionnaires may introduce a recall bias when patients have to report on previous events (e.g., costs, nutritional intake in the last month). In that perspective, clear and detailed instructions are given to patients at each research visit to assist them in completing the questionnaires to the best of their ability. Fourth, there may be a degree of diversity in the FFFP delivery due to the multicentre nature of the study. In the context of a pragmatic RCT, this diversity would in fact, reflect the real-world reality of program implementation in different fertility clinics. While we consider this aspect to be a strength contributing to the generalizability of the results, it could also result in a variability in the efficacy of the intervention at each centre. To mitigate this concern, formal training is provided to all health professionals regarding motivational interviewing techniques, with coaching for the first meetings with participants until the professional masters these skills appropriately. Fidelity of the proper use of motivational communication in real clinical settings will be monitored throughout the study and corrective measures will be initially suggested to professionals, if needed. Furthermore, some standardization in administering the core concepts of the FFFP is provided to health professionals beforehand to ensure that the interventions are as effective as possible.

Despite its limitations, this study is highly relevant and uses a robust study design. The multicentre setting allows our work to be more generalizable, because of the diversity in the sub-populations and healthcare systems enrolled. The slight differences in provincial healthcare systems in Canada will allow us to examine the potential of the FFFP to be implemented in various health care contexts. The proposed study relies on early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations, which will increase the potential impact and use of the findings to influence policies and priorities of institutions and governments. The results of our multicentre RCT will have major scientific impact since they will provide important data on the importance of a lifestyle program supporting women with obesity seeking fertility treatments. We believe our work will promote better fertility outcomes and response to ART as well as contribute in achieving a healthy pregnancy and giving birth to a healthy baby. This study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system. Therefore, the FIT-For-Fertility study has the potential to improve the care trajectory of women with subfertility and obesity seeking fertility treatments, and do so at an acceptable cost both for patients and government-funded providers.

Ethics approval and consent to participate

This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universtaire de santé et des services sociaux de l'Estrie – CHUS* (*CIUSSS de l'Estrie – CHUS*) (research coordinating centre) on December 10, 2018 (reference number: MP-31-2019-2802). The central REB of *CIUSSS de l'Estrie – CHUS* acts as the central REB for centres in the Province of Quebec and individual ethics approval has been obtained for all participating centres in the other provinces, and will be obtained for the 7th centre to be recruited. Ethics approval will be maintained annually. Informed consent is obtained from participants before beginning any research procedure and supported throughout their participation in the trial. The participant may withdraw at any time during the study without impact on their regular medical care. If the study participant decides to leave the study, the information that was collected will still be available in order to help answer study research questions unless the participant provides written documentation of their wish to have the data removed. All personal health information will be treated in a confidential manner with respect to its collection, use and disclosure. Participant names or potentially identifying personal health information will not leave the institution. A master list that links participant identifiers to their unique participant number will be maintained at all study sites, stored separately from all other study records according to local institutional policies, and locked by key or password.

Consent for publication

Not applicable.

Trial status

Due to the widespread public health rules and restrictions implemented in the province of Quebec from March 2020 due to the COVID-19 pandemic, the RCT has experienced considerable delays in the initiation of the study in each centre. Furthermore, one centre located in the province of Alberta had to withdraw from the trial for considerations related to the pandemic. Recruitment has begun in Sherbrooke, Quebec, with its first randomization in May 2019 (n=33 as of November 2021), Québec city, Quebec, in February 2020 (n=14), Toronto, Ontario, in May 2021 (n=1), and in Montreal, Quebec, in November 2021 (n=1). The centre in Halifax has not yet begun recruiting because of COVID-19 restrictions in its province. Other centres are ready and allowed to start recruiting at this time. We are also in the process of recruiting a 7th centre in the province of Manitoba.

Availability of data and material

Not applicable.

Competing interests

Ferring Inc. has provided an unrestricted grant for the trial, without influencing the design or conduct of the trial, or the analysis or dissemination of the study's results.

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Authors' contributions

JPB is the senior author of the manuscript, he designed the study and obtained funding as principal investigator of the trial; and MB wrote the first draft of the manuscript in collaboration with MG, FJD and JPB. Authors have made substantial contributions to the conception or design of the trial (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP, FJD, RB, MS , BT, NC), contribute or will likely contribute to the acquisition of data for the study (JPB, MG, BCM, ASM, FG, MHP, FJD, RB, AG, EG, CKN, WK, SL, BT), and/or will likely contribute to analysis or interpretation of future data (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP, RB, WF, EG, CKN, MS, BT). All authors revised critically this manuscript for intellectual content, approved the version to be published and agreed to be accountable for all aspects of the work.

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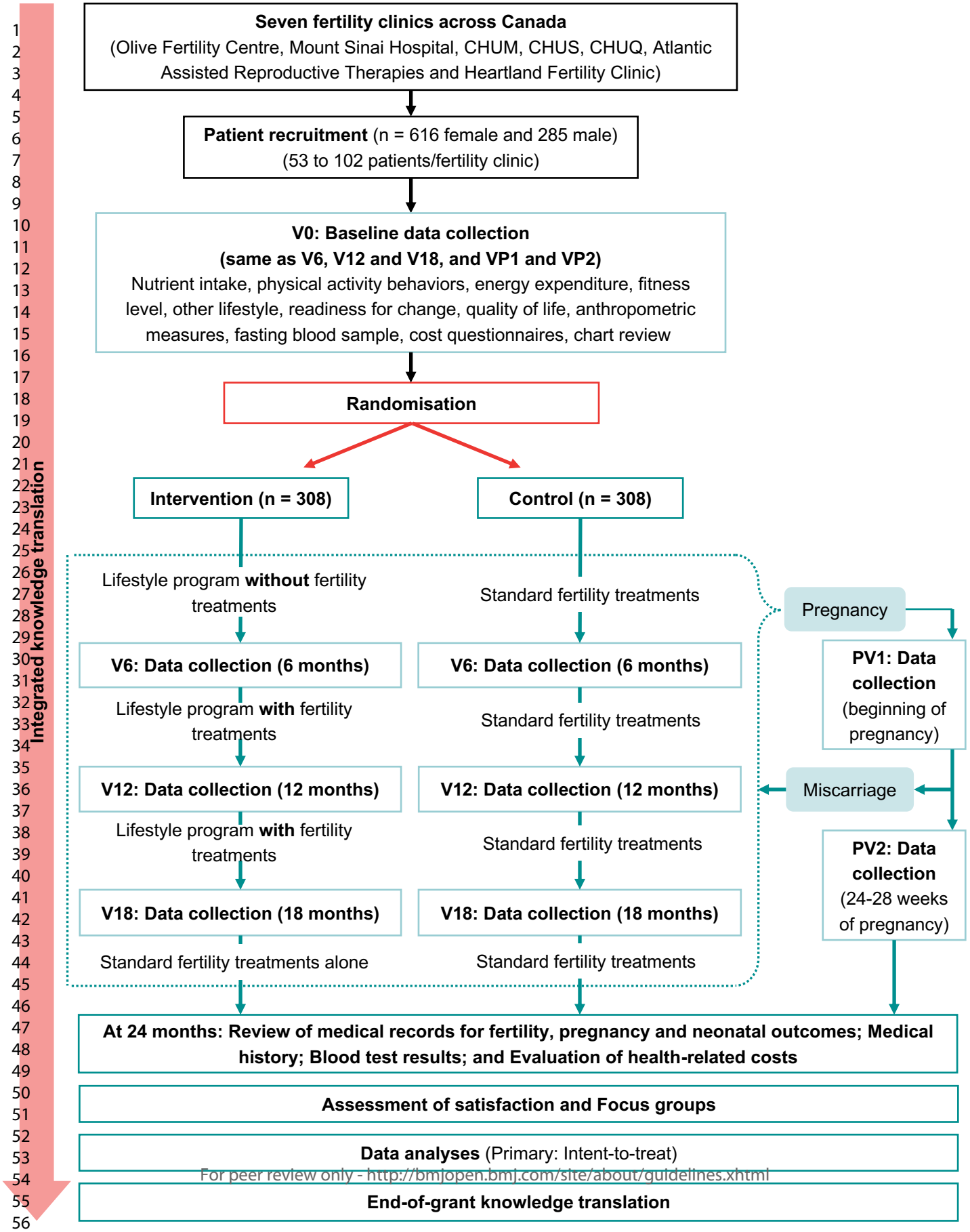
Figure legend:

Figure 1 – Fit-For-Fertility's Study Flowchart.

Figure 1. Fit-For-Fertility's Study Flowchart.



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	41
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2 and 42
	5b	Name and contact information for the trial sponsor	2
	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	40
	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)	30-31

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-12
	6b	Explanation for choice of comparators	16-18
Objectives	7	Specific objectives or hypotheses	12-13
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	13-21
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14
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)	15-16
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	17-21
	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)	31-32
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	30
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18
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	21-32
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)	18-22 + Figure 1

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	32-33
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	32-33
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16-17
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	16-17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16-17
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	21-31
	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	33-34

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	29-31
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	33-36
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	33-36
	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)	34
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	29-31
	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	31
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	31-32
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	31
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	39
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)	30-31

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	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	39
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	40-41
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
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	31
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	26

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

BMJ Open

Protocol of the Fit-For-Fertility Study: a multicentre randomized controlled trial assessing a lifestyle program targeting women with obesity and infertility

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	< HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Protocol of the Fit-For-Fertility Study: a multicentre randomized controlled trial assessing a lifestyle program targeting women with obesity and infertility

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Protocol date and version: October 14th, 2021 (version 1)

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03908099
Date of registration in primary registry	April 9, 2019
Secondary identifying numbers	MP-31-2019-2802, #1025047, H18-03597, 19-0317-A
Source(s) of monetary or material support	Canadian Institutes of Health Research *Université de Sherbrooke* *Centre hospitalier universitaire de Québec* Ferring Inc.
Primary sponsor	Canadian Institutes of Health Research
Secondary sponsor(s)	*Université de Sherbrooke* *Centre hospitalier universitaire de Québec* Ferring Inc.
Contact for public queries	Jean-Patrice Baillargeon [Jean-Patrice.Baillargeon@USherbrooke.ca]
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Public title	Protocol for the Fit-For-Fertility Study
Scientific title	Protocol of the Fit-For-Fertility Study: a multicentre randomized controlled trial assessing a lifestyle program targeting women with obesity and infertility
Countries of recruitment	Canada
Health condition(s) or problem(s) studied	Obesity and infertility
Intervention(s)	Usual fertility care (control arm)
	Fit-For-Fertility intervention (lifestyle intervention program) alone for 6 months, and in combination with usual fertility care in not pregnant (experimental arm)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years and < 40 years Sexes eligible for study: women
	Inclusion criteria: infertile women with obesity (BMI ≥ 30 kg/m^2 or 27 kg/m^2 for Asian and Latin American, based on WHO 2004), or with a BMI ≥ 27 kg/m^2 for women with PCOS
	Exclusion criteria: uncontrolled medical or mental condition contra-indicating fertility treatments, only indicated medically assisted reproductive technology is

Data category	Information
	IVF or donor insemination, history of recurrent spontaneous abortion, previously diagnosed uncontrolled eating disorder or major depression, high-level of depressive state according to the HADS (score ≥ 15), planning for or past history of bariatric surgery, planning for or engaged in another lifestyle intervention, inability to understand French or English, unable to attend research visits.
Study type	Interventional
	Allocation: randomized intervention model (1:1), with stratification for cent
Date of first enrolment	May 2019
Target sample size	616
Recruitment status	Recruiting
Primary outcome(s)	24-month live birth cumulative incidence (intention-to-treat analysis)
Key secondary outcomes	Fertility, pregnancy and neonatal outcomes; lifestyle and anthropometric measures, cost-effectiveness and qualitative data.

50

Abstract

Introduction:

Women with obesity are at a higher risk of infertility as well as gestational and neonatal complications. Lifestyle changes are universally recommended for women with obesity seeking fertility treatments, but such intervention has only been assessed in very few robust studies. This study's objectives are therefore to assess the clinical outcomes and cost-effectiveness of an interdisciplinary lifestyle intervention (the Fit-For-Fertility Program; FFFP) targeting women with obesity and subfertility in a diverse population.

Methods and Analysis:

This pragmatic multicentre randomized controlled trial (RCT) will include 616 women with obesity (BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with polycystic ovary syndrome or at-risk ethnicities) who are evaluated at a Canadian fertility clinic for subfertility. Women will be randomized either to 1) the FFFP (experimental arm) alone for 6 months, and then in combination with usual care for infertility if not pregnant; or 2) directly to usual fertility care (control arm). Women in the intervention group benefit from the program up to 18 months or, if pregnant, up to 24 months or the end of the pregnancy (whichever comes first). Women from both groups are evaluated every 6 months for a maximum of 18 months. The primary outcome is live birth rate at 24 months. Secondary outcomes include fertility, pregnancy and neonatal outcomes; lifestyle and anthropometric measures; and cost-effectiveness. Qualitative data collected from focus groups of participants and professionals will also be analyzed.

Ethics and Dissemination:

This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universtaire de santé et des services sociaux de l'Estrie – CHUS* (research coordinating centre) on December 10, 2018, and has been or will be approved successively by each participating centres' REB. This pragmatic RCT will inform decision-makers on improving care trajectories and policies regarding fertility treatments for women with obesity and subfertility.

Trial Registration:

ClinicalTrials.gov: NCT03908099, Registered April 9, 2019.

Protocol version: 1.1, April 13, 2019

Strengths and limitations of this study

- This study has a strong design: a multicentre, two-arm, parallel pragmatic randomized-controlled trial comparing the Fit-For-Fertility program to usual fertility care, using quantitative and qualitative assessments.
- The primary study outcome of live birth rate at 24 months, and the main secondary outcomes of fertility outcomes and pregnancy or neonatal complications, are strong clinical outcomes pertinent for patients. The study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system.
- Early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations

will increase the feasibility of the trial and the potential impact and use of the findings to influence policies and priorities of institutions and governments.

- It is not possible to blind the intervention and data collection since the tested intervention is a lifestyle program, but the study primary outcome of life birth is a robust clinical outcome that is not susceptible to bias.
- Self-reported questionnaires may introduce desirability or recall biases, but the study uses tools validated in such setting and these biases should be similar in the intervention and control groups.

Keywords

Obesity, Fertility, Women, Lifestyle, Weight loss, Pregnancy, Randomized controlled trial, Live birth, Cost-Effectiveness, Polycystic ovary syndrome

Word Count: 8,029

Number of **tables**: 3; and **figures**: 1

List of abbreviations

AEoSI, Adverse Events of Special Interest;

ART, assisted reproduction technology;

ALT, alanine amino transferase;

β-hCG, human chorionic gonadotropin;

BMI, body mass index;

CHUM, Centre hospitalier universitaire de Montréal;

CHUQ, Centre hospitalier universitaire de Québec;

CHUS, Centre hospitalier universitaire de Sherbrooke;

CI, confidence intervalle;

CIUSSS, Centre intégré universitaire de santé et des services sociaux;

COVID-19, Coronavirus Disease 2019;

EOSS, Edmonton Obesity Staging System;

FertiQoL, Fertility Quality of Life questionnaire;

FFQ, Food Frequency Questionnaire;

FSH, follicle stimulating hormone;

HADS, Hospital Anxiety and Depression Scale;

HbA1c, glycated hemoglobin;

HDL, high-density lipoprotein cholesterol;

ICER, incremental cost-effectiveness ratio;

IPAQ, International Physical Activity Questionnaire;

ITT, intent-to-treat;

IUSMM, Institut universitaire en santé mentale de Montréal;

IVF, *in vitro* fertilization;

LDL, low-density lipoprotein cholesterol;

LH, luteinizing hormone;

MAR, medically assisted reproduction;

OR, odd ratio;

PCOS, polycystic ovary syndrome;

PRECIS, PRagmatic-Explanatory Continuum Indicator Summary;

PRL, prolactin;

PSQI, Pittsburg Sleep Quality Index;

PV, Pregnancy visit;

QALY, Quality-Adjusted Life Years;

REDCap, Research Electronic Data Capture;

RCT, randomized controlled trial;

REB, Research Ethics Board;

SAE, Serious Adverse Events;

SF-6Dv2, Short Form-6 Dimensions – version 2;

SHBG, sex hormone-binding globulin;

SMART, Specific, Measurable, Attainable, Realistic and Timely;

TSH, thyroid-stimulating hormone;

V0, baseline research visit at time 0; and

WHO, World Health Organization.

Introduction

Women with obesity and infertility

Infertility affects approximately 10-15% of couples in Canada and the rest of North America [1]. According to the International Glossary on Infertility and Fertility Care, infertility is "a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner" [2]. For the purpose of this study, subfertility is defined as an infertility with a reasonable probability of spontaneous pregnancy without medical intervention, which excludes couples with sterility or severe infertility (such as bilateral irreversible tubal factor or severe male factor). Medically assisted reproduction (MAR), including ovulation induction, ovarian stimulation, intra-uterine insemination and assisted reproductive technology (ART) [2] are part of the current clinical management of infertility and have become more and more used and effective in helping infertile couples to achieve a pregnancy [3]. Unfortunately, these procedures are costly and carry risks for both women and infants. These risks can occur at different stages of ART: ovarian stimulation (ovarian hyperstimulation syndrome, thromboembolism, and ovarian torsion), oocyte retrieval (infection and bleeding) and early pregnancy (ectopic or heterotopic pregnancy, and multiple gestations[4]). Although these risks are rare, they can have significant consequences. Furthermore, some studies have suggested that ART procedures may have negative neonatal consequences, such as

higher frequencies of alterations in DNA methylation patterns associated with DNA imprinting disorders in children conceived through ART [5].

Obesity (defined operationally as a BMI ≥ 30 kg/m^2 [6]), is a known modifiable risk factor associated with female infertility [7] and the population affected worldwide is high enough for obesity to be recognized as a global epidemic by the World Health Organization since 2000 [8]. The prevalence of obesity has been estimated to be as high as 30% in Canadian and 38% in American populations, respectively [9]. More precisely, 21% of Canadian women of reproductive age had obesity in 2015 [10]. Women who plan to get pregnant are currently more likely to be affected by obesity [11], which can significantly affect their fertility. For instance, a very large cohort study including more than 40,000 couples estimated that women with obesity display a 78% higher risk of having infertility compared to women with a normal BMI (18.50-24.99 kg/m^2) (odd ratio [OR] with 95% confidence interval [CI]: 1.78 [1.63-1.95]) [12]. Women with obesity are also more likely to develop polycystic ovary syndrome (PCOS), which is the leading cause of anovulatory infertility, affecting 6-10% of women of childbearing age [13]. Furthermore, a higher BMI has been associated with reduced pregnancy rates even in women with ovulatory cycles, equating to a 4% decrease in pregnancy rate per kg/m^2 of BMI increase in women with a BMI ≥ 29kg/m [14].

Moreover, studies assessing MAR procedures have reported that women with obesity: i) require higher doses and a longer duration of clomiphene [15] and gonadotrophins [16-19] to achieve ovulation, ii) display a lower pregnancy rate per cycle [18], and iii) are at a higher risk of cycle cancellation [16,18] and miscarriage [20,21].

Obesity also increases the risk of complications during pregnancy, such as gestational diabetes, pre-eclampsia, caesarean section and intrauterine death [22,23]. In keeping with the Developmental Origins of Health and Disease paradigm, maternal pre-pregnancy BMI and excessive gestational weight gain are consistently associated with the early development of obesity and diabetes in the offspring [24]. Obesity in childhood is closely linked to adult obesity [25,26], perpetuating the intergenerational cycle of obesity [27-29]. Adopting a healthy lifestyle before conception and restoring of a healthy metabolic environment early during pregnancy likely represents the best approach to break the vicious circle of intergenerational propagation of obesity and diabetes.

Accordingly, targeting women with obesity prior to conception may be essential to reduce the burden of infertility and MAR costs, as well as obesity and cardiometabolic diseases in our societies.

Infertility management in women with obesity seeking fertility treatments

To prevent the adverse effects of obesity on female fertility and on gestational and neonatal health, many organizations have recommended that women with obesity should be assisted, before conception, to lose weight (5 to 10 % of their initial weight) and adopt a healthy lifestyle, and maintain that healthy lifestyle during pregnancy [30-33]. Results from a recent systematic review support lifestyle modification prior to ART in women with overweight or obesity [34]. The authors pointed out that despite the lack of RCTs in the area, pre-conception weight loss in women with overweight or obesity can help improve fertility and pregnancy outcomes. Out of the 7 RCTs assessing non-surgical methods of

weight loss, including some form of lifestyle intervention, the most methodologically rigorous study was a RCT published in the *New England Journal of Medicine* in 2016 [35]. This study compared 287 women with obesity and subfertility who were randomized to a 6-month structured lifestyle intervention (including 6 outpatient visits and 4 telephone consultations with a nurse or dietician) and 285 women assigned to prompt fertility treatments. The lifestyle intervention lasted only 6 months and was not continued during fertility treatments or pregnancy. After a follow-up of 24 months, the lifestyle program did not improve the live birth rate, but resulted in a significant increase in the rate of spontaneous pregnancies (rate ratio [95% confidence]: 1.61 [1.16-2.24]) and reduced the need for fertility treatments (rate ratio [95% confidence]: 0.78 [0.70-0.86]) [36]. In a follow-up article, the same group of authors observed, from a hospital perspective, an incremental cost-effectiveness ratio (ICER) of €15,845 per additional point of percentage in the healthy live birth rate resulting from the lifestyle program compared to usual care. The authors concluded that their intervention may be deemed as cost-effective, especially for longer follow-up timelines, in anovulatory women, women who completed the study or women ≥ 36 years of age [37].

Interestingly, in a survey asking women with obesity or overweight and considering pregnancy if they were interested in adopting a healthier lifestyle prior to conception, 91% reported their willingness to participate in a lifestyle program [38]. However, despite the patients' motivation and the international recommendations to encourage women to optimize their lifestyle before starting fertility treatments, most women with obesity do not have access to such targeted lifestyle programs integrated within their fertility care. Therefore, our objective is to give these women access to the Fit-For-Fertility Program

(FFFP), an interdisciplinary lifestyle intervention, integrated into the fertility clinic care pathway. This program supports participants in adopting sustainable healthy behaviours, in pre-conception, throughout fertility treatments, and during pregnancy. In response to the national priority to improve the quality and costs of reproductive and perinatal care established by our *Canadian network on reproductive and maternal health of women with obesity and infertility*, we will conduct a multicentre RCT assessing the FFFP in women with subfertility and obesity.

Research question and hypotheses

For this RCT, our research question is: Compared to usual care, does the FFFP cost-effectively improve i) the live birth rate and other fertility outcomes and ii) pregnancy and neonatal outcomes, in women with obesity and subfertility who seek fertility treatments. We hypothesize that in comparison to prompt initiation of usual fertility care, participation in the FFFP, alone for 6 months and then in combination with usual care for infertility, will: 1) improve the fertility of women with obesity, 2) reduce costs associated with fertility treatments, and 3) decrease the occurrence of some complications related to maternal weight during the pregnancy and for their offspring.

Study objectives

The primary objective of this study is to assess the effectiveness of the FFFP on fertility outcomes in a diverse Canadian population of women with obesity and subfertility who are seeking fertility treatments. Secondary objectives are to assess the FFFP's 1)

cost-effectiveness, primarily in terms of costs per live birth, as well as other measures of the program's costs and effectiveness measures, and 2) impacts on maternal and neonatal health.

Methods and Analysis

Study design

This study is a multicentre, two-arm, parallel pragmatic RCT comparing the FFFP to usual fertility care, using quantitative and qualitative assessments (ClinicalTrials.gov: NCT03908099). More specifically, we developed a pragmatic RCT based on the PRECIS-2 principles [39].

Patient and Public Involvement

Our study relies on the early and regular involvement of engaged patients, knowledge users and decision-makers to ensure their appropriation of the results. Policy-makers and professional or patient organizations of all relevant provinces provided their support to the project and partnered with the research team to facilitate the feasibility of the trial and dissemination of the results. Importantly, three patient organizations partnered with our team and provided strong support letters: Obesity Canada, the *Association des couples infertiles du Québec* and Conceivable Dreams. Engaged patients have been implicated early in the development of this protocol to ensure that the results will be relevant for the target population and that the methods are appropriate for the

participants. Two previous participants from the pilot study conducted in Sherbrooke are actively acting as engaged participants and have participated to each step of the trial development. Before submission of the grant proposal to the funding agency, they approved the research question and general objectives of the study, as well as the acceptability of intervention and research visits' burden. Thereafter, they were regularly consulted by the Sherbrooke research team, and they partnered with the team during dedicated research meetings. Among other contributions, they have given precious input on recruitment approaches, data collection's tools and timing, intervention upgrades from the pilot study, as well as participants' newsletters. Other fertility clinics have committed to include 1 or 2 engaged patients, who will participate at research meetings at each site.

Engaged patients and patient organizations will also be instrumental to disseminate the results of the trial to the public, in particular young women with obesity and infertility. This will be performed through patient organizations' network, social media, as well as lay public press conferences and "*Café scientifique*"-like activities in which our engaged patients will be implicated. Such involvement of decision makers and patients increases the potential impact on the public and scientific community, and use of the findings to influence policies and priorities of institutions and governments.

Setting and recruitment

The study will be conducted in seven Canadian fertility clinics from coast to coast and in an ethnically diverse population of women: Olive Fertility Centre in Vancouver (British-Columbia), with its Asian population; Mount Sinai Hospital in Toronto (Ontario) and *Centre hospitalier de l'Université de Montréal* (CHUM), with large multiethnic

communities; *Centre hospitalier universitaire de Sherbrooke* (CHUS) and *Centre hospitalier universitaire de Québec de l'Université de Laval* (CHU de Quebec-UL) (Quebec), which are smaller centres with mainly a Caucasian population; and Atlantic Assisted Reproductive Therapies Clinic in Halifax (Nova Scotia) that has a Caucasian and Afro-American populations. We are also in the process of recruiting a 7th centre, ideally in the province of Manitoba.

Potentially eligible patients can be approached in one of two ways: 1) by a member within their circle of care (nurse, physician, receptionist, etc.) who then provides contact info to research staff, or 2) by responding to an advertisement indicating their interest to learn more about the study. Written informed consent (see supplemental material) is obtained individually for each patient during the baseline research visit (V0), after a full explanation of the study's protocol and answers to the patient's questions by the research staff, and before any data collection or study procedures. The following screening and baseline data are obtained during this visit: eligibility assessment (inclusion/exclusion criteria), medical history, concomitant medications, patient demographics and a baseline evaluation of study outcomes. Eligibility is confirmed by the site investigator before randomization.

Participant eligibility

Patients who meet the following inclusion criteria can participate in the study:

1) Being infertile, defined as (a) failure to achieve a clinical pregnancy after ≥12 months of regular unprotected sexual intercourse, (b) not conceiving after having

attempted ≥6 months in women with irregular menstrual cycles or ≥35 years of age; or (c) women with an established cause of infertility;

2) Aged between 18 and 40 years (since initiation of fertility treatments should not be delayed in women above 40 y.o.); and
3) With obesity (BMI ≥ 30 kg/m^2 or 27 kg/m^2 for Asian and Latin American, based on WHO 2004 [40]), or with a BMI ≥ 27 kg/m^2 for women with PCOS. These women display the metabolic consequences of non-PCOS women with obesity at a lower BMI, and benefit more from lifestyle modifications.

Women presenting at least one the following exclusion criteria will not be eligible to enroll in the study:

1) Any uncontrolled medical or mental condition that contra-indicates fertility treatments, based on clinical judgment of the fertility specialist;
2) Natural conception is impossible or highly unlikely (e.g., bilateral tubal factor, severe male factor defined as a total motile sperm count < 5 million on the most recent partner's seminal analysis), where the only indicated MAR procedures are IVF or donor sperm insemination (this exclusion criteria defines subfertility, such that only subfertile couples are enrolled);
3) History of recurrent spontaneous abortions (>2 miscarriages at less than 22 weeks of gestation), with evidence of conception (such as positive β-hCG), within the last 12 months (since these women are more likely to have a defect that cannot be improved by lifestyle);
4) Previously diagnosed uncontrolled eating disorder or major depression that would contra-indicate the initiation of a lifestyle intervention;

5) A high level of depressive state, as determined by a score for depression on the Hospital Anxiety and Depression Scale (HADS) ≥ 15 [41,42], which is not a diagnostic of depression but would also contra-indicate the initiation of a lifestyle intervention;
6) Planning for or past history of bariatric surgery, which would confound the impact of the lifestyle intervention tested;
7) Planning for or engaging in another lifestyle intervention that would be similar to the intervention tested, e.g., including individual visits every 8 weeks or less, which would also confound the impact of the FFFP;
8) Inability to understand the language in which group sessions is provided in the participating centre, i.e., French in the province of Quebec and English in other provinces; and
9) Unable to attend research visits at the participating centre for the next 18 months.

Randomization

Randomization to the FFFP or control group occurs after completion of the V0 and the eligibility assessment. Group allocation is concealed using online computerized randomization using REDCap (Research Electronic Data Capture tool hosted at the Université de Sherbrooke) [43] with permuted blocks of variable block sizes (2 to 6), stratified by centre and PCOS status (yes/no). PCOS is an important potential confounder or modifier since it decreases fertility and may affect the response to the lifestyle intervention [13]. The randomization list has been generated by an independent statistician and participants are randomized in one of two arms using a 1:1 ratio. The

randomization process is initiated by the site investigator or delegate who accesses the web-based system and confirms patient's eligibility and informed consent. The patient's unique study identifier and open-label study treatment allocation is then automatically and electronically delivered to the local site investigator or delegate.

Following randomization, the research staff informs the fertility care team of the patient's allocation group. On the one hand, if the participant is randomized to the control group, the fertility care team is informed that their patient can undergo fertility treatments immediately, according to their usual care. On the other hand, if the participant is randomized to the intervention group, the fertility clinic will be notified that the patient has to postpone any MAR procedures for the following 6 months, during which the patient is enrolled in the FFFP. At the end of this first 6-month period, if the participant failed to conceive, the research staff contacts the fertility clinic team to inform them that the participant can now undergo usual fertility care, in combination with the FFFP.

Interventions

Control Arm

Participants randomized to the control group are provided immediate access to the usual fertility care, as recommended by their fertility specialist, for a maximum of 24 months. This may include lifestyle counselling by their fertility specialist and usual fertility treatments. Since this is a pragmatic trial, they may undergo any lifestyle approaches or consult any professionals they want on their own, but are discouraged to

engage in a lifestyle program similar to the FFFP, as they agreed when recruited for the study, in order to avoid such an important contamination between intervention arms.

Experimental Arm

Participants randomized to the intervention group follow the FFFP alone for the first 6 months, then in combination with usual fertility care for an additional 12 months if not pregnant. After these 18 months, usual fertility care can continue to be provided alone for a maximum follow-up of 24 months. The FFFP is also provided throughout gestation for participants who achieve a successful pregnancy. Accordingly, the lifestyle program is provided for a maximum of 18 months if there is no pregnancy, or otherwise, up to the end of pregnancy or to a total study follow-up of 24 months (whichever comes first).

The FFFP was initially developed based on 2007 Canadian clinical practice guidelines [44]and the approach implemented by our group at the CHUS obesity clinic [45], and was then improved and adapted based on the experience gained from our completed pilot study [46] and focus groups with study participants. This intervention is aimed at supporting participants to implement progressive and sustainable lifestyle changes. Participants attend 30-minutes individual sessions with a dietitian and a kinesiologist, respectively, every 6 weeks for the first 6 months, then every 8 weeks for the following 6 months, and then every 12 weeks until the end of the treatment period. These individual meetings take place in person with the participant, or virtually using an authorized system of telemedicine in the event that face-to-face meetings are not possible (e.g., due to public health rules such as during the COVID-19 pandemic). Personal remote

contact (e.g., by phone, e-mail) is offered between in-person meetings. Patients are guided by the dietitian and kinesiologist to formulate SMART goals (Specific, Measurable, Attainable, Realistic and Timely) [47]. These professionals are trained in evidence-based motivational communication skills [48], with emphasis placed on how to arm women with the knowledge, motivation, and skills to achieve sustainable lifestyle changes. To ensure equitable delivery of the intervention, we will implement an internal quality control and training process. Therefore, after receiving training in motivational communication by our leading expert (KLL), each professional will audio-record their first three individual meetings. These recordings will be evaluated by an expert in motivational communication using a coding scheme to verify fidelity. Feedback regarding the professional's application of motivational communication techniques will be provided as needed, and additional recordings may be necessary based on the trainer's assessment. After 6 and 12 months, three more individual sessions are recorded and used to analyze the quality and fidelity of the intervention from a research perspective. Consent for recording individual meetings is a specific question in the informed consent form and participants have the opportunity to revoke their agreement at any time during the course of their participation in the study.

Participants also benefit from weekly group sessions divided into 2 parts of 45 minutes each [46] (see Table 1 for group sessions' topics): 1) Workshops that cover 8 different topics addressing nutritional aspects and relevant healthy lifestyle habits (alcohol, tobacco and motivational issues) and 2) Supervised classes of physical activity where one of 8 different types of exercise are practiced. Women are invited to participate in group sessions every week throughout the study, but are required to attend all 8 different sessions within the first 6 months. The spouses of participants are highly

encouraged to participate in all activities, as lifestyle modification is also important for the partner to improve a couple's fertility [49,50].

Table 1. Topics of the Fit-For-Fertility's Interactive workshops and physical activity sessions.

Sessions	Interactive workshops (45 min)	Physical activity sessions (45 min)
1	"Let's get going! Follow the Guide!"	"A step in the right direction!"
	→ *Introduction to the Canadian Food Guide*	→ *Walking for fitness [outdoors]*
2	"Finding balance"	"Stay active… even at home!"
	→ *Changes that pay off*	→ *Weight training exercises at home*
3	"Taking charge of your environment"	"Step-by-Step!"
	→ *The act of eating*	→ *Step aerobics class*
4	"Listening to your body…"	"Bulk up your health!"
	→ *Feeling hungry and feeling full*	→ *Muscle building with an elastic band and exercise ball*
5	"The label says it all"	"Stay Zen!"
	→ *Food labels*	→ *Initiation to yoga*
6	"Planning is the key!"	"Cardio-muscular" walking!"
	→ *Meal planning*	→ *Combined weight training and walking [outdoors]*
7	"Thinking about it isn't enough!"	"Short circuit!"
	→ *Change process and motivation*	→ *Circuit fitness*
8	"Breathe in, breathe out!"	"Groove it out!"
	→ *Sleep, alcohol and tobacco*	→ *Zumba Class*

For women with a confirmed pregnancy, our team schedules a meeting to set new lifestyle objectives specific to pregnancy to promote, a healthy pregnancy, including optimal gestational weight gain based on the Institute of Medicine guidelines [51]. This meeting can take place during a regular intervention meeting or during the first research pregnancy visit (PV1), whichever comes first.

Data collection

As illustrated in Figure 1, research evaluation visits take place in both groups at baseline and every 6 months for a total of 18 months if no pregnancy occurs. Women who become pregnant ***within*** the first 18 months of follow-up are met at the beginning of their pregnancy (PV1) and at 24-28 weeks of pregnancy (PV2) for measures (see Figure 1). Women who become pregnant ***after*** 18 months of follow-up do not undergo research visits during their pregnancy. Data collection and measures during these research visits are detailed in Table 2.

Table 2. Research visits and data collected.

	V0	V6	V12	V18	PV1	**PV2**
Informed consent	●					
Physical exam (anthropometry, blood pressure and heart rate)	●	●	●	●	●	●
Concomitant medications	●	●	●	●	●	●
Blood sample						
Fasting levels of sex steroids	●	●	●	●		
FSH, LH	●	●	●	●		
TSH	●	●	●	●	●	●
Prolactin	●	●	●	●		
β-hCG	●	●	●	●	●	
ALT	●	●	●	●	●	●
HbA1c	●	●	●	●	●	●
Glucose	●	●	●	●	●	●
Lipids	●	●	●	●		
Creatinine	●					
Extra samples shipped to	●	●	●	●	●	●

the coordinating site (Sherb., QC)							
Initial Medical Questionnaire		●					
Actual Health Status Questionnaire			●	●	●	●	●
FertiQoL		●	●	●	●		
HADS		●	●	●	●	●	●
IPAQ		●	●	●	●	●	●
Readiness to Change Questionnaire		●	●	●	●	●	●
PSQI		●	●	●	●	●	●
Socio-demographic Questionnaire		●					
Patient's Costs Questionnaire			●	●	●	●	●
SF-6D.v2		●	●	●	●	●	●
FFQ web		●	●	●	●	●	●
Fitbit & Fitbit Journal		●	●	●	●	●	●
6 minutes walking test		●	●	●	●	●	
Participant's Satisfaction Questionnaire					●		●
AEoSI and SAE review		●	●	●	●	●	●

Abbreviations: AEoSI: adverse events of special interest; ALT: alanine amino transferase; β-hCG: human chorionic gonadotropin; FertiQoL: Fertility Quality of Life questionnaire; FFQ: Food Frequency Questionnaire; FSH: follicle stimulating hormone; HADS: Hospital Anxiety and Depression Scale; HbA1c: glycated hemoglobin; IPAQ: International Physical Activity Questionnaire; LH: luteinizing hormone; PSQI: Pittsburgh Sleep Quality Index; PV1: first pregnancy research visit (beginning of pregnancy); PV2: pregnancy research visit at 24-28 weeks of gestation; SAE: serious adverse events; SF-6D-v2: Short Form-6 Dimensions – version 2; TSH: thyroid-stimulating hormone; V0: baseline research visit; V6, V12, V18: research visits at 6, 12 and 18 months post-randomization, respectfully.

Participants are instructed to contact the study team between visits or phone calls if they become pregnant or if any relevant situations occur (e.g., miscarriage, accident, moving, changing phone number). Importantly, all clinical outcomes are ascertained with participants and their medical records 24 months after participants' randomization, regardless of the timing of their last research visit and the occurrence of a pregnancy.

Pregnancy and neonatal outcomes occurring 24 months after randomization will not be included in the primary analysis of the primary outcome, but are recorded for secondary analyses.

Outcome measures and their assessment

Fertility outcomes: The primary outcome is the cumulative incidence of live birth at 24 months. Secondary fertility outcomes are also collected from medical records at 24 months and include: the rate of biochemical pregnancy (confirmed by a positive serum β-hCG), ongoing confirmed pregnancy (viable pregnancy at ≥10 weeks of gestation), spontaneous miscarriage of a confirmed pregnancy (<22 gestational weeks), multiple gestation, spontaneous pregnancy, pregnancy following MAR procedures, doses of fertility medications, number of MAR and/or ART cycles, number of embryo transfers, and complications due to MAR procedures.

Pregnancy outcomes (all secondary outcomes): Total gestational weight gain, calculated by subtracting weight at the research visit closest to the onset of pregnancy from the last weight available in the antenatal record. Weekly gestational weight gain, calculated by dividing total weight gestational gain by the number of weeks between the first and last measure of weight. Pregnancy complications, which are retrieved from medical records, include gestational diabetes, gestational hypertensive disorders, thromboembolism, preterm birth, late fetal loss, stillbirth and post-partum hospital stay >7 days.

Neonatal outcomes (all secondary outcomes): Birth weight, Apgar scores, hypoglycemic episodes, hyperbilirubinemia, birth trauma, admission to neonatal intensive care unit and neonatal death (up to 28 days of life), which are retrieved from medical records.

Anthropometric measures and vital signs (all secondary outcomes): Anthropometric measures are collected at each research visit. Weight is measured with a standard calibrated scale and height is measured with a stadiometer, based on the models available at each centre. Foot-to-foot bioelectrical impedance analysis technology is used to estimate the percentage of fat mass and fat free mass [52] in most, but not all centres (models depend on each centre). Waist circumference measurement is done with a measuring tape according to the National Institutes of Health [53]. Heart rate and blood pressure are measured after a five-minute rest period in a sitting position. Two measurements are taken for waist circumference and vital signs, with the average being used for analyses.

Endocrine and metabolic blood markers (all secondary outcomes): A blood sample is taken at each research visit to measure different hormonal and metabolic biological markers: luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid-stimulating hormone (TSH), prolactin (PRL), human chorionic gonadotropin (β-hCG), serum progesterone, androstenedione, estradiol, total and calculated free testosterone, sex hormone-binding globulin (SHBG), glycated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), cholesterol ratio, glucose, alanine amino transferase (ALT) and

creatinine (at initial research visit only). All markers are assessed at local laboratories, since they are clinically indicated. Additional plasma samples are shipped to CHUS and stored for future analyses relevant to this study's objectives, when further funding becomes available.

Lifestyle outcomes (all secondary outcomes): Lifestyle outcomes are assessed at each research visit. Nutritional intake is evaluated using the validated web version of the Food Frequency Questionnaire (FFQ web), referring to the patient's nutritional consumption of the last month. This questionnaire enables to extract data on specific food groups and micro- or macronutrients. This questionnaire has been shown to have a moderate validity and a good reproducibility for assessing nutrient intakes in healthy adults [54]. Participants complete the questionnaire at the research centre at their first research visit to ensure good understanding of the questions. For subsequent research visits, participants have the possibility to receive a link to complete the FFQ web electronically from home. Sleep duration and quality are evaluated by the Pittsburg Sleep Quality Index (PSQI) questionnaire, which has been shown to have a strong reliability and validity, as well as a moderate structural validity in the context of screening for sleep dysfunction [55]. The International Physical Activity Questionnaire (IPAQ) – short version – is used to assess physical activity practice over the past 7 days: it was shown to have a good repeatability of data and is as reliable as other self-administered physical activity questionnaires [56]. Furthermore, participants are asked to wear after the research visit a Fitbit© Flex 2 monitor during 7 consecutive days, 24 hours/day, in order to objectively assess physical activity levels (energy expenditure, number of steps, distance walked, time spent being inactive, lightly active, active and very active), as well as sleep data

(minutes spent asleep, awake and restless (when moving while sleeping)). Fitbit© devices have been shown to accurately estimate the daily number of steps and the time spent in bed and sleeping, while overestimating the time spent doing highly intense activities [57]. However, data extracted will be mainly used to assess the change of physical activity levels and sleep over time and not whether physical activity recommendations are met. This estimation bias should be consistent at each measurement time point and will be adjusted for baseline measures. The participant's physical fitness level is assessed using the 6-minute walk test (6mWT), which has shown to be a simple, safe and low-cost test to assess the effect of an intervention on the physical performance and walk capacity beyond weight loss [58]. Other lifestyle habits, such as alcohol, tobacco and drugs consumption, are measured by a study-specific self-reported questionnaire.

Quality of life (secondary outcome): Participants' quality of life specifically related to infertility and its treatments are assessed using the Fertility Quality of Life questionnaire (FertiQoL) [59]. Moreover, the Short Form-6 Dimensions – version 2 (SF-6Dv2) is used to determine Quality-Adjusted Life Years (QALY), which is an important variable for the economic evaluation of the intervention, and to assess the general quality of life of our participants, as well as the impact of our intervention on dimensions of quality of life.

Patients' perceptions and satisfaction (all secondary outcomes): Based on experience from previous studies [46,60,61], we will evaluate the expectations, perceptions and satisfaction towards care provided for fertility and weight management in all participants with a questionnaire, and will further assess these aspects in a small sample (from both groups) using focus groups. The satisfaction questionnaire is given at

the 18-month research visit (V18) or at the second pregnancy research visit (PV2) if pregnant. Focus groups will take place at 2 time points: 1) after completion of the study by half of the participants and 2) close to the end of the trial. A total of 168 patients (27% of all participants) will participate in the focus groups across all 7 centres, each centre evaluating two separate sub-groups of 6 patients from the intervention and control groups. The number of participants for the second series of focus groups may be adjusted to reach data saturation. See bellow under “Methodology and analyses of qualitative substudy” for more details.

Health-related costs (secondary outcomes): Data is collected from both the patient and the health care system perspectives for each mother/child dyad. Costs of interest include costs related to the FFFP, fertility treatments, adverse events or complications, pregnancy-related visits and hospital admissions, and patient out-of-pocket expenses. Data collection for this component will be done through patient questionnaires, charts reviews, administrative data, and interviews with healthcare providers and fertility clinic staff for the description of care procedures.

Medical history and physical health (all secondary outcomes): A study-specific self-administered questionnaire will be used to evaluate participant’s relevant medical history, use of medications or natural products, and physical health during daily activities. It will be possible with the data of this questionnaire to use the Edmonton Obesity Staging System (EOSS), which has been shown to be an effective classification tool for obesity risk assessment, including in the context of obesity and infertility [62].

Data management, monitoring and quality assessment

Research measures and outcomes are recorded through printed or online versions of the questionnaires and paper Case Report Forms at each relevant timepoint. These are checked for integrity by each site's research assistant before being entered into the centralized web-based database REDCap.

The central coordinator at the CHUS is responsible for training of the research staff and health professionals (dietitians and kinesiologists), and the monitoring at all centres. The central coordinator is also responsible for ensuring that patient safety, study procedures and data collection are performed at each centre according to the research protocol and Good Clinical Practice guidelines [63]. The central coordinator sends regular queries to site coordinators to resolve discrepancies identified in the database and performs regular onsite visits. These visits will begin after the site research teams have recruited their first 35 participants (corresponding to one-third of participants to be recruited per sites). Then they will be held at every 6-month intervals to assess protocol adherence, intervention standardization, as well as data completeness and quality. During onsite monitoring visits, approximately 10% of participants' records will be reviewed. Concordance with the original data entered by the site will be assessed using the Cohen's kappa statistics. A kappa coefficient below 0.60 for one site at the time of a visit, which is considered as less than a moderate concordance [64], will require repeating the training of research staff at this site and, if necessary, revising of all records of participants who completed the study at this site, if possible.

The trial steering committee of this projects includes JPB, RB, AG, EG, WK, BCM, ASM, CKN, MHP, BT, and their key research team members. An advisory committee is also in place and includes JPB, WF, FG, MFL, KL, TP, ASM, SNR, KA, NC, PS, SL, Becky Attenborough, now retired from the Reproductive Care Program of Nova Scotia, Celine Braun, president of the *Association des couples infertiles du Québec*, Rahda Chari, now retired from the Maternal Newborn Child & Youth Strategic Clinical Network, Alberta, Anne Hayes from the Ministry of Health and Long-Term Care of Ontario, Tamil Kendall, past provincial executive director of perinatal services BC, Martine Pageau, *Directrice du sport, du loisir et de l'activité physique* at *Ministère de l'Éducation et de l'Enseignement supérieur du Québec*, Daniel Riverin, past director of Mother-Child Services of Quebec Ministry of Health and Danielle Xavier, past president of Conceivable Dream. The steering and advisory committees meet periodically to support the coordination of the FFF study, and their implication had already started at the protocol design stage.

Safety measurement

Due to the relatively short duration of recruitment and follow-up of participants, it will not be relevant to perform formal interim efficacy analyses for futility or superiority and interim safety analyses. Furthermore, it is very unlikely that the proposed lifestyle intervention, which is already recommended during preconception and pregnancy in women with obesity, would cause any safety issues. For these reasons, a Data and Safety Monitoring Board (DSMB) will not be required for this trial, and no interim analyses will be performed. However, Adverse Events of Special Interest (AEoSI) and Serious Adverse Events (SAE) will be closely monitored throughout the study (see Table 3). These potential

events will be evaluated according to their causality and severity. Furthermore, after randomization of the first 50 patients, the trial's steering committee will produce a quarterly blinded report of AEoSI and SAE for each treatment group, including the grades of causality with the intervention. If SAE occur, these events will be reported to the coordination centre and local Research Ethics Board (REB), as well as the central REB of the Province of Quebec.

Table 3. Adverse Events of Special Interest (AEoSI) and Serious Adverse Events (SAE) monitored during the study

AEoSI
Clinically significant injury (requiring consultation or limiting activities) occurring during exercise, i.e. a planned physical activity with the purpose to improve or maintain physical fitness
Spontaneous miscarriage (spontaneous loss of a pregnancy before 22 weeks of gestation)
Ovarian hyperstimulation syndrome
Multiple gestation
Gestational diabetes requiring pharmacologic treatment, usually insulin
Gestational hypertensive disorder (gestational hypertension, pre-eclampsia or eclampsia)
Thromboembolic clinical event during pregnancy
Preterm birth (occurring after 22 weeks and before 37 weeks of gestational age)
Newborn small for gestational age (birth weight <10th percentile of the sex-specific birth weight for gestational age reference)
Newborn large for gestational (birth weight >90th percentile of the sex-specific birth weight for gestational age reference)
SAE
Antenatal clinically significant uterine bleeding (requiring admission or blood transfusion)
Late fetal loss, i.e. fetal death between 22 and 28 weeks of gestational age.
Stillbirth (>28 weeks of gestational age)
Neonatal death (between childbirth and before 28 days of life)

Newborn with severe congenital malformation (causing a functional handicap)
Admission of newborn to the neonatal intensive care unit
A medical complication that prolongs mother's post-partum hospital stay >7 days

Statistical analyses and sample size

Sample size calculation

Experts from our *Canadian network on reproductive and maternal health of women with obesity and infertility* agreed that for a study using a lifestyle intervention and following intent-to-treat (ITT) principles, the minimal clinically important difference (MCID) in the trial primary outcome, i.e., cumulative life birth rates, would be 15% between groups. Therefore, a sample size of 293 women per group is required to detect a 15% absolute difference between groups, with a power of 95% and alpha level of 5%, from an estimated live birth rate of 35% in the control group (based on our previous pilot RCT [46]) to 50% in the intervention group (nQuery avisor 4.0). Assuming a withdrawal rate of 5% (eligibility criteria violation and loss to follow up), the total recruitment target is 616 women. A 95% power is sufficient for most of our secondary outcome analyses. To recruit a total of 616 participants in 18 months, the two clinics with smaller practices (CHUS and CHUQ) will need to recruit 53 participants (i.e., 39 per year), and the other 5 clinics will have to recruit 102 participants (i.e., 68 per year). These recruitment rates are feasible given the data from our pre-trial survey of participating fertility clinics that showed that smaller practices (CHUS, CHUQ) evaluate 80 to 315 new women with obesity per year, and larger practices, between 265 and 810.

Statistical analyses of quantitative data

The primary outcome is 24-month live birth cumulative incidence and the primary analyses of interest will be ITT, including all randomized participants with available data and no violation of eligibility criteria. The ITT analyses will be supplemented by per-protocol analyses that will exclude women who dropped out of the study during their first 6 months in both groups, i.e. who signified their desire to stop participating in the study and/or intervention visits, or were unreachable from that period up to the end of the trial. The per-protocol analyses will keep all women who persevered in the study for at least 6 months and were therefore appropriately exposed to the intervention (intervention group) and adherent to the 6-month study visit (both group). The 24-month cumulative incidence of live birth will be compared between the two arms using the Mantel-Haenszel test with stratification by centre and PCOS status. This analysis will be supplemented by a survival analysis (log rank test) where the time to live birth will be used. Randomized groups will be examined at baseline to ensure demographic and clinical data are comparable. If substantial imbalance is found, which is very unlikely, additional analyses will be carried out to assess the potential confounding effects of this imbalance, using multiple logistic regression and Cox proportional hazards model. Similar analyses will be used for the other clinical outcome variables that are categorical. Continuous outcome variables will also be compared between groups based on either ITT or per-protocol analyses, using linear mixed models with repeated measures.

We will also analyze the impact of the FFFP on lifestyle and anthropometric outcomes, as well as other outcomes measured during a research visit, at 6 months (including research visits occurring 6 ± 1 months after randomization), as frequently

reported in previous and similar trials. For these analyses, continuous variables will be compared between groups using unpaired *t* tests and categorical variables will be examined using chi-square tests. Missing data due to missed research visits or incomplete data collection will not be imputed, due to the relatively small sample size, such that these analyses might be subjected to non-random missing data differing between groups. Therefore, these tests will be corrected for potential baseline imbalances and confounding effects as mentioned above. Variables that are not normally distributed will be mathematically transformed to fit a normal distribution allowing their use in these models. Subgroup analyses will be performed for all outcomes based on baseline age, level of obesity (BMI ≥ 35 vs < 35 kg/m^2), ethnic origins, socio-economic status, the cause of subfertility and polycystic ovary syndrome status. A 5% level of significance will be used for all analyses.

Economic evaluation

The economic evaluation of the FFFP represents the second objective of this study. The primary economic analysis will be based on the incremental cost-effectiveness ratio (ICER), using live birth as the primary effectiveness outcome. As a secondary measure of cost-effectiveness, QALYs will be calculated from the SF-6Dv2 [65,66], using the algorithm developed by Mulhern et al [67]. QALYs will help in considering the aspect of health-related quality of life affected by weight reduction, healthy lifestyle and psychological impacts of subfertility. A 1.5% discount rate will be considered for periods higher than one year and sensitivity analysis will be performed [68]. To estimate the confidence interval on the difference in costs, we will perform non-parametric analyses with 5,000 bootstrap replications. We will also perform cost-effectiveness acceptability

curves to compare the cost-effectiveness thresholds for different costs per unit gain [68,69].

Methodology and analyses of qualitative substudy

In addition to the simple satisfaction questionnaire, an in-depth, qualitative iterative exploration of patient's perceptions of the FFFP and medical care will be performed. Purposive sampling will be used to create the two sub-groups in each clinic, based on the technique of critical incidents using patients' characteristics (levels of satisfaction with their care based on questionnaires, fertility or pregnancy outcomes, loss or gain of weight during follow-up, ethnic group, etc.). A semi-structured interview guide will be used for the focus groups, tailored to each trial group, with open-ended questions adapted from results of previous studies on similar topics [70].The 90-minute focus group meetings will be led by a facilitator who will encourage participation and discussions [71,72]. An experienced observer from our research group will participate remotely from Sherbrooke: he will take notes and support the facilitator, by asking follow-up questions for example. Data will be analyzed as soon as possible by a member of the research team, using Miles, Huberman & Saldana's method. The analysis of the content of the focus groups as they are conducted will help enrich the subsequent focus groups (iterative approach) [73]. A preliminary analysis grid with various categories based on our previous work will be used, to which emerging categories will be added successively. Regular discussions with the research team will take place during the analysis process to promote a comprehensive understanding of the material collected.

After the trial completion, health professionals' perceptions, self-efficacy, inter-professional collaboration, and satisfaction toward obesity management will be evaluated through a taped-recorded semi-structured focus group interviews in each clinic, as we have previously done [46,60,74]. Discussions among physicians, nurses, dietitians, kinesiologists, clinic administrative personnel, and directors will be encouraged. These focus groups will be performed and analyzed using the same methods as described above for patients.

Discussion

In this paper, we present the research protocol for a multicentre pragmatic RCT assessing clinical and economic outcomes of an interdisciplinary lifestyle intervention targeting women with subfertility and obesity (the Fit-For-Fertility program) that takes place 6 months before initiating fertility treatments and, for the first time, continues in combination with usual fertility care as well as during pregnancy. This study will highlight the effectiveness, cost-effectiveness and transferability of such a program in a diverse population.

Obesity has been shown to negatively impact on women's reproductive capacity by reducing chances of pregnancy, with or without the help of fertility treatments [12,16,18,19]. Women with obesity are also at a higher risk of complications during pregnancy. Interventions supporting changes in lifestyle habits and a moderate weight loss of 5-10% of the initial weight are highly recommended for women who are trying to conceive [31-33]. Unfortunately, there is little evidence from large and of good quality RCTs in this population supporting this recommendation. To our knowledge, there is only one published RCT (the LIFESTYLE study) evaluating the impacts of a 6-month lifestyle intervention on fertility outcomes among a general population of women with obesity and subfertility, not specifically affected with PCOS [35]. Although the authors did not observe an improvement in their primary outcome (vaginal birth of a healthy singleton) with their lifestyle intervention as compared to usual care, they reported a higher proportion of women in the intervention group achieving a spontaneous pregnancy (26.1% vs 16.2%, RR [95% CI: 1.61 [1.16-2.24]) and a reduced total number of treatment cycles. Our trial

will therefore contribute significantly to the actual knowledge and levels of evidence in the literature.

Although this study uses a robust methodology, as all studies, it has a few limitations. First, it is not possible to blind the intervention and data collection, either to the participants nor the professionals (research or clinical), since the tested intervention is a lifestyle program. Although a blind research study adds robustness and limits potential bias, we do not think this represents an important stake, because the study's primary outcome is life birth, which is a robust clinical outcome that is not susceptible to bias. Secondly, data collection is done mainly using self-reported questionnaires that can result in a desirability bias. However, most of the questionnaires used have been validated and used in previous studies, and the bias should be similar in the intervention and control groups. Additionally, self-reported questionnaires may introduce a recall bias when patients have to report on previous events (e.g., costs, nutritional intake in the last month). In that perspective, clear and detailed instructions are given to patients at each research visit to assist them in completing the questionnaires to the best of their ability. Thirdly, there may be a degree of diversity in the FFFP delivery due to the multicentre nature of the study. In the context of a pragmatic RCT, this diversity would in fact, reflect the real-world reality of program implementation in different fertility clinics. While we consider this aspect to be a strength contributing to the generalizability of the results, it could also result in a variability in the efficacy of the intervention at each centre. To mitigate this concern, formal training is provided to all health professionals regarding motivational interviewing techniques, with coaching for the first meetings with participants until the professional masters these skills appropriately. Fidelity of the proper use of motivational

communication in real clinical settings will be monitored throughout the study and corrective measures will be initially suggested to professionals, if needed. Furthermore, some standardization in administering the core concepts of the FFFP is provided to health professionals beforehand to ensure that the interventions are as effective as possible.

Despite its limitations, this study is highly relevant and uses a robust study design. The multicentre setting allows our work to be more generalizable, because of the diversity in the sub-populations and healthcare systems enrolled. The slight differences in provincial healthcare systems in Canada will allow us to examine the potential of the FFFP to be implemented in various health care contexts. The proposed study relies on early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations, which will increase the potential impact and use of the findings to influence policies and priorities of institutions and governments. The results of our multicentre RCT will have major scientific impact since they will provide important data on the importance of a lifestyle program supporting women with obesity seeking fertility treatments. We believe our work will promote better fertility outcomes and response to ART as well as contribute in achieving a healthy pregnancy and giving birth to a healthy baby. This study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system. Therefore, the FIT-For-Fertility study has the potential to improve the care trajectory of women with subfertility and obesity seeking fertility treatments, and do so at an acceptable cost both for patients and government-funded providers.

Ethics approval and consent to participate

This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universtaire de santé et des services sociaux de l'Estrie – CHUS* (*CIUSSS de l'Estrie – CHUS*) (research coordinating centre) on December 10, 2018 (approval number: MP-31-2019-2802). The central REB of *CIUSSS de l'Estrie – CHUS* acts as the central REB for centres in the Province of Quebec and individual ethics approval has been obtained for all participating centres in the other provinces (IWM Research Ethics Board (IWK-REB); approval number: #1025047, Office of Research Ethics from the University of British Columbia; approval number: H18-03597, Research Ethics Board from Mount Sinai Hospital; approval number: 19-0317-A), and will be obtained for the 7th centre to be recruited. Ethics approval will be maintained annually. Informed consent is obtained from participants before beginning any research procedure and supported throughout their participation in the trial. The participant may withdraw at any time during the study without impact on their regular medical care. If the study participant decides to leave the study, the information that was collected will still be available in order to help answer study research questions unless the participant provides written documentation of their wish to have the data removed. All personal health information will be treated in a confidential manner with respect to its collection, use and disclosure. Participant names or potentially identifying personal health information will not leave the institution. A master list that links participant identifiers to their unique participant number will be maintained at all study sites, stored separately from all other study records according to local institutional policies, and locked by key or password.

Consent for publication

Not applicable.

Trial status

Due to the widespread public health rules and restrictions implemented in the province of Quebec from March 2020 due to the COVID-19 pandemic, the RCT has experienced considerable delays in the initiation of the study in each centre. Furthermore, one centre located in the province of Alberta had to withdraw from the trial for considerations related to the pandemic. Recruitment has begun in Sherbrooke, Quebec, with its first randomization in May 2019 (n=33 as of November 2021), Québec city, Quebec, in February 2020 (n=14), Toronto, Ontario, in May 2021 (n=1), and in Montreal, Quebec, in November 2021 (n=1). The centre in Halifax has not yet begun recruiting because of COVID-19 restrictions in its province. Other centres are ready and allowed to start recruiting at this time. We are also in the process of recruiting a 7th centre in the province of Manitoba.

Availability of data and material for site investigator and their teams

Only the coordinating centre (Sherbrooke, Québec, Canada) will have access to the data from all centres for data management purposes. Contract agreements have been signed specifying that participating centres will only have access at their site's dataset, except for access to coded multicenter data granted by the Steering Committee to perform approved specific sub-studies, in agreement with REB approvals.

Availability of data and material for other research teams

Access to anonymized multicenter data can be granted to other research teams by the Steering Committee to perform approved specific sub-studies, in agreement with REB approvals.

Competing interests

Ferring Inc. has provided an unrestricted grant for the trial, without influencing the design or conduct of the trial, or the analysis or dissemination of the study's results.

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Authors' contributions

JPB is the senior author of the manuscript, he designed the study and obtained funding as principal investigator of the trial; and MB wrote the first draft of the manuscript in

collaboration with MG, FJD and JPB. Authors have made substantial contributions to the conception or design of the trial (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP, FJD, RB, MS , BT, NC), contribute or will likely contribute to the acquisition of data for the study (JPB, MG, BCM, ASM, FG, MHP, FJD, RB, AG, EG, CKN, WK, SL, BT), and/or will likely contribute to analysis or interpretation of future data (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP, RB, WF, EG, CKN, MS, BT). All authors revised critically this manuscript for intellectual content, approved the version to be published and agreed to be accountable for all aspects of the work.

Authorship guidelines

Under the direction of the Principal Investigator, the named co-authors will be responsible for the preparation of the manuscripts. With the agreement of the Steering Committee, the Principal Investigator will determine co-authors based on the ICMJE authorship requirements (available at http://icmje.org/).

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of Quebec Ministry of Health, Mother-Child Services of Quebec Ministry of Health, *Association des obstétriciens gynécologues du Québec*, Conceivable Dreams, and Reproductive Care Program of Nova Scotia.

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Figure legend:

Figure 1 – Fit-For-Fertility's Study Flowchart.

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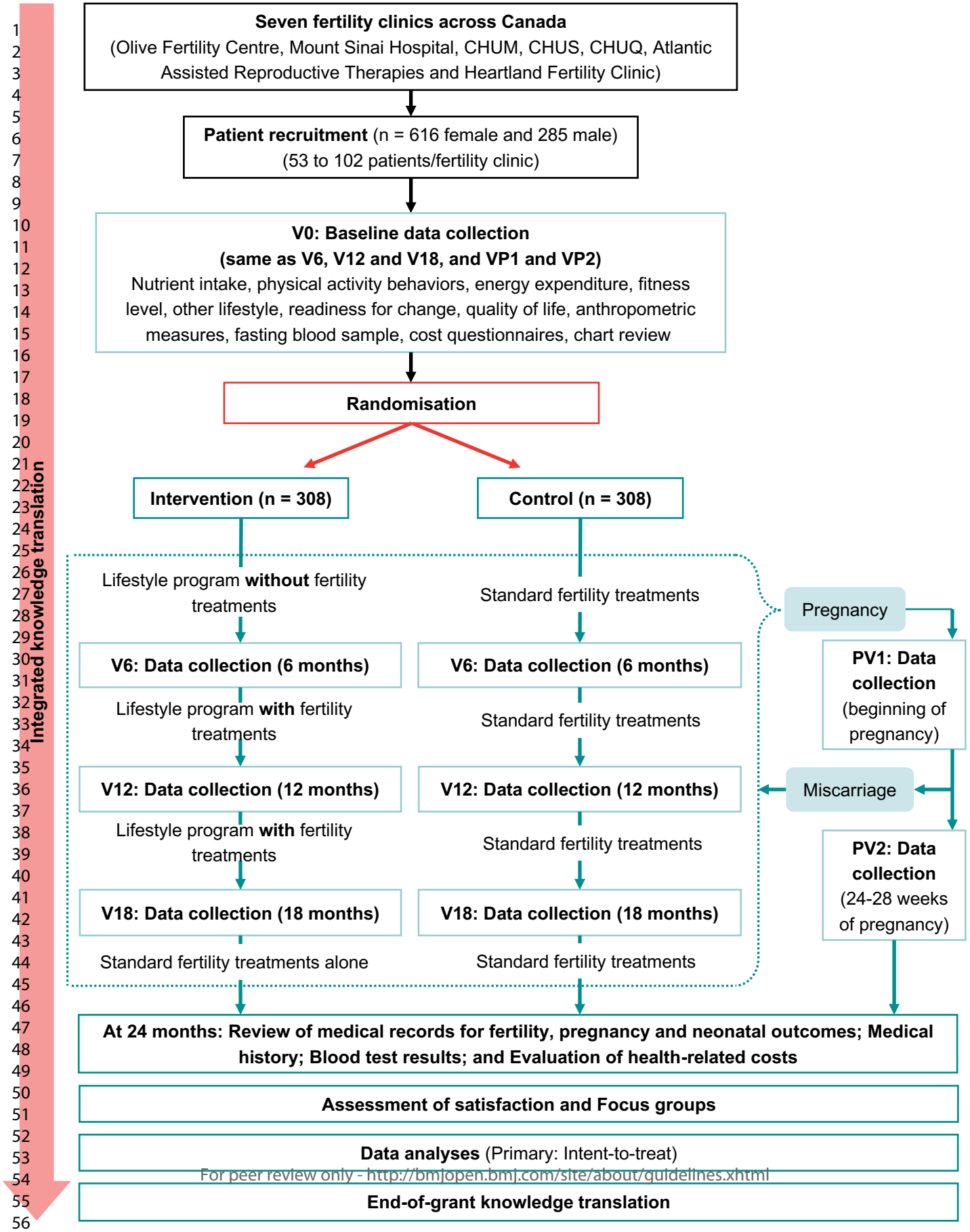

RESEARCH INFORMATION AND CONSENT FORM

Study title:	***Fit-for-Fertility Multicenter Randomized Controlled Trial***: Improving Reproductive, Maternal and Neonatal Outcomes in Obese and Infertile
Study number:	MP-31-2019-2802
Study funding	Canadian Institutes of health research Ferring Inc.
Principal investigator:	Jean-Patrice Baillargeon, Department of Medicine, Division of Endocrinology
Co-investigator(s):	Belina Carranza-Mamane, Department of Obstetrics and Gynecology Marie-Hélène Pesant, Department of Medicine, Division of Endocrinology

For information
From Monday through Friday, from 8 a.m. to 4 p. m.:

Dr. Jean-Patrice Baillargeon Endocrinologist	Tel.: 819-346-1110, ext. 14853 or dial "0" and ask the operator to call him on pager # 9401.
Ms. Farrah Jean-Denis, Research Coordinator	Tel.: 819-346-1110, ext. 12814 or dial "0" and ask the operator to call her on pager # 8869.

We are asking for your participation in a research study because you are currently consulting for a fertility problem. However, before agreeing to participate in this study, please take the time to carefully read, understand and consider the following information. If you accept to take part in this research study, you will be required to sign the consent form at the end of this document, and we will give you a signed copy for your records.

This information and consent form explains the purpose of this research project, its procedures, risks and inconveniences as well as the benefits, and who to contact if necessary. This document may contain words you do not understand. We invite you to ask any questions you may have to the study investigator or other people involved in

the research project and ask them to explain any words or information you do not understand.

NATURE AND OBJECTIVES OF THE RESEARCH STUDY

Obesity increases the risk of developing the polycystic ovary syndrome (PCOS), which is characterized by the absence of ovulation, but it is also associated with fertility problems even in women who ovulate. In addition, obesity reduces the effectiveness of assisted reproduction procedures, including fertility drug treatments. It has also been observed that women who become pregnant and who are obese have a higher risk of complications during pregnancy, delivery and for the newborn. However, it has been shown that a slight weight loss of about 5% of total weight can restore ovulation and improve pregnancy rates.

The purpose of this study is to evaluate the effects of a lifestyle management program on fertility, the course of pregnancy and childbirth, and the health of the newborn. We anticipate that a total of approximately 616 patients from 7 fertility clinics across Canada will participate. Of this total, approximately 53 patients will be from the *CIUSSS de l'Estrie – CHUS*.

STUDY PROCEDURES

If you accept to participate in the study, you will have 2 to 5 evaluation visits at the Research Centre of the CHUS (RC-CHUS) (Fleurimont) over a period of about 18 months.

Initial visit:

- Measurement of your height, weight, body fat percentage (with electrical bioimpedance analysis) and waistline. The use of an electrical bioimpedance analysis in standing position involves the transmission of a very light electrical current through the body tissues from the soles of the feet for a few seconds. This electrical current causes no pain and is safe for the human health.
- Measurement of your blood pressure and your resting heart rate.
- Blood sample (approximately one tablespoon, or 15 mL).
- Questionnaires to fill (approximately 1 ½ hour).
- Walking test (walking as fast as possible for 6 minutes, going back and forth for a distance of 20 meters).
- You will be given a Fitbit monitor. You will have to wear it continuously for a period of 7 consecutive days. Wearing the monitor will allow us to assess your level of physical activity and the quality of your sleep over a week.

The duration of this initial visit is approximately 2 ½ hours.

After this visit, you will be assigned randomly (like at the flip of a coin) in one of the 2 groups: the intervention group or the control group.

Intervention group:
In the days following the initial visit, a second appointment will be scheduled for a one-hour meeting with the nutritionist and kinesiologist (30 minutes with each) to begin the lifestyle modification program. You will have an individualized follow-up with these professionals every 6 weeks (30 minutes with each) at the RC-CHUS or the first 6 months, then every 8 weeks for the next 6 months and every 12 weeks for the last 6 months or until delivery. During these visits, you will also be asked to fill out a short questionnaire concerning the costs that these meetings imply for you. In order to offer you more support, the nutritionist or kinesiologist will also follow up with you by phone or email between your appointments at the RC-CHUS. With your agreement and solely for the purpose of evaluating the intervention proposed in this research project, the individual meetings of the intervention program will be recorded.

Participants in the intervention group will also have a group session once a week where different nutrition topics are discussed (8 topics, 45-minutes each), in addition to sessions where physical activities are practiced (8 different physical activities). You will be required to attend all 8 different sessions at the CHUS at Hotel-Dieu, within the first 6 months of your participation. For the remaining duration of the project, up to 18 months or as long as there are no contraindications during pregnancy, you are encouraged to continue your participation in the physical activity sessions, which last 45 minutes.

During the first 6 months of the program, you must agree to receive no fertility treatments, including fertility medications. After this period, if you are not pregnant, you will be seen by your fertility specialist and received required interventions according to standard fertility care.

Control group:
From the beginning of the project, you will consult your fertility specialist and receive standard fertility care.

For both groups:
Evaluation visits at 6 months, 12 months and the final visit at 18 months if no pregnancy:
You must be fasting for the 12 hours preceding those visits. During those visits you will go through the same tests as the initial visit. The visits should last about 2 hours.

If you become pregnant, 2 visits are planned:
1st pregnancy visit (if no evaluation visit during the last month) and final pregnancy visit between 24 and 28 weeks of pregnancy:
You must be fasting for the 12 hours preceding those visits. During those visits you will go through the same tests as the initial visit, except for the walk test that will not be done at the final pregnancy visit. The visits should last about 2 hours.

Please refer to the calendar at the end of the present document for a global view of the tests and procedures realized during the research project.

In addition to these visits, we will consult your personal health records to gather information regarding the fertility treatments used, the progress of your pregnancy, your delivery and your baby. In order to obtain general health information on your baby, we will access his or her personal health records. We will also be able to assess some of the components of your health-related costs based on your hospital visits as described in your record. In case we need information from your personal health records in a hospital other than the CHUS, we will have you sign an access request.

At the end of the project, some patients from the control and the intervention groups will be invited to participate in a focus group. These patients will be selected according to a list of criteria. The following topics will be discussed: satisfaction and perceptions of the care received and the impact of the program on quality of live. To ensure accurate data collection, the discussion will be recorded. All records will be destroyed after transcription.

PARTICIPANT'S COOPERATION

We ask your collaboration to inform us as soon as possible in case of a pregnancy. For the participants in the intervention group, we ask that you attend all individual appointments in the lifestyle program and the 8 group sessions, and to notify us as soon as possible if you are unable to attend one of your appointments.

RISKS AND INCONVENIENCES THAT MAY ARISE FROM THE SUBJECT'S PARTICIPATION IN THE RESEARCH STUDY

Your participation in this study involves minimal risk. The risks associated with having blood samples taken are: mild pain, dizziness, fainting, bruising, bleeding, and in rare cases, blood clots and infection.

For the participants in the intervention group, exercise demonstrations will be done under the supervision of a kinesiologist. The risk of injury is very low since the exercise will be done in a way to provide a gradual effort and respect your abilities. However, you may feel muscle aches the day after the activity, but these will be only be short-lived.

Travel is required for participation in the lifestyle program: approximately 10 meetings for the individual follow-ups and at least 8 group sessions.

RISKS OF INFORMATION DISCLOSURE

For the participants in the intervention group, you may feel some discomfort with the recording of the individual meetings with the kinesiologist and the nutritionist. In such a case, you will be free to ask that the recording be stopped.

For the participants in the control and intervention groups who will take part in the focus group, the facilitation will be designed and carried out in such a way as to make you as

comfortable as possible, in particular by reminding everyone their right to be different. Furthermore, you are in no obligation to answer any questions. If you feel uncomfortable, you may share it with the facilitator in private or in front of the group. The facilitator will take the time to listen to you and see what can reassure you.

BENEFITS RESULTING FROM YOUR PARTICIPATION IN THE RESEARCH STUDY

There may be a personal benefit to you from your participation in this research project, but we cannot guarantee it. Furthermore, the ensuing information from this research project could contribute to the advancement of knowledge in the field of infertility.

VOLUNTARY PARTICIPATION AND RIGHT TO WITHDRAW

Your participation in this research project is voluntary. You are therefore free to refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the research team.

Your decision not to participate in the study, or to withdraw this research project, will bear no consequences on your relationship with the research team.

Unless you inform us otherwise, if you withdraw or are withdrawn from the study, the information and material already collected during the study will still be stored, analysed or used to ensure scientific integrity of the study.

Any new knowledge acquired during the course of the project that could have an impact on your decision to continue participating in this research project will be communicated to you as soon as possible.

CONFIDENTIALITY

Collection - Reason for which personal information is requested.
During your participation in this research project, the study investigator and his/her study staff will collect and record information about you in a study file. They will only collect information required to meet the scientific goals of this study.

Collection – What personal information will be collected
The study file may include information from your medical chart regarding your past and present state of health, your lifestyle, as well as the results of tests, exams, and procedures that you will undergo during this research project. Your research file could also contain other information, such as your name, sex, date of birth and ethnic origin.

Data/information storage - Protection
All the information collected will remain confidential to the extent provided by law. You will only be identified by a code number. The key to the code linking your name to your study file will be kept by the doctor in charge of this research study.
To ensure your safety, your participation in this research study will be mentioned in your medical chart. Consequently, any person or company to whom you give access to your medical file will have access to that information.

Duration of data storage

The research data will be kept during 25 years by the investigator in charge of the research study.

Dissemination of results

Results of the research could be published or discussed during scientific meetings, but it will be impossible to identify you.

Right of access for monitoring and safety

For monitoring, control, protection and safety, your study file could be examined by persons mandated by the institution or the Research Ethics Board. These individuals observe confidentiality policies.

You have the right to access your study file in order to verify the information gathered, and to have it corrected if necessary.

COMPENSATION

As compensation for the costs incurred as a result of your participation in the research project, you will receive an amount of 20$ per evaluation visit. If you withdraw or are withdrawn from the study before its completion (or if your participation is ended), the compensation will be proportional to the duration of your participation.

Your parking fees related to your evaluation visits will be covered using a prepaid code that we will be given for each of your research evaluation visits. This does not include the visits associated to the intervention program for the participants in this group.

FUNDING

This project is funded mainly by the Canadian Institutes of Health Research, an agency of the Government of Canada responsible for investing in health research. This project also benefits of the support of private companies, but no amount is intended to cover salaries or advantages for the research team. All the financial support is dedicated to the realization of the study.

IN CASE OF PREJUDICE

Should you suffer any harm as a result of your participation in the research project, you will receive all the care and services required by your health condition.

By agreeing to participate in this research project, you do not waive any of your legal rights nor do you release the researcher responsible for this research project and the establishment of their civil and professional responsibilities

CONTACT PERSONS

If you have any questions or problems related to the research study or if you wish to withdraw from the research project, you can contact the physician in charge or a person from the research team. Please refer to the box on page 1.

If you have any questions about your rights as a participant in this research study or if you have any complaints, you can contact the *CIUSSS de l'Estrie – CHUS'* Office of Complaints and Quality of Services at plaintes.ciussse-chus@ssss.gouv.qc.ca or at the following number: 1-866-917-7903.

MONITORING OF ETHICAL ASPECTS OF THE STUDY

The Research Ethics Board of the *CIUSSS de l'Estrie – CHUS* approved this study and is in charge of its monitoring for the participating institutions of the Québec Health and Social Services Network.

If you wish to contact a member of that board, you can reach the Research Ethics Support Services of the *CIUSSS de l'Estrie - CHUS* at ethique.chus@ssss.gouv.qc.ca or at the following number: 819-346-1110, ext. 12856.

FOLLOW-UP STUDIES

In the event that future research projects following or similar to the current project are conducted, would you agree to be contacted by a member of the research team to offer you a new participation? Of course, during this call, you would be entirely free to accept or refuse to participate.

☐ YES ☐ NO

CONSENT

I have reviewed the *Information and Consent Form*. The research project and this information and consent form have been explained to me. My questions were answered and I was given the time to decide. Upon reflection, I consent to participate in this research study project under the conditions stated above.

I authorize the research team to access my medical records.

I accept that the individual meetings for the purpose of the intervention program will be recorded.

☐ YES ☐ NO

Participant's name (block letters)	*Participant's signature*	*Date*

I explained the research project and this Information and Consent Form to the participant and answered her questions.

Name of the person who obtained consent (block letters)	*Signature of the person who obtained consent*	*Date*

CALENDAR FOR RESEARCH AND INTERVENTION VISITS

Boxes marked with an X indicated tests and data collected at each visit:

	Initial visit	6-month visit	12-month visit	18-month visit (final visit)	Intervention sessions[2]	Weekly Group Workshops (8 weeks)[2]
Physical examination (weight, height, blood pressure and pulse)	x	x	x	x	x	
Blood test	x	x	x	x		
Questionnaires	x	x	x	x	x	x
Fitbit journal	x	x	x	x		
6-minutes walk test	x	x	x	x		
Nutritionist and kinesiologist					x	x

For women who become pregnant during the study:

	First pregnancy visit[1]	24-28 weeks (final visit)	Intervention sessions[2]
Physical examination (weight, height, blood pressure and heartrate)	x	x	x
Blood test	x	x	
Questionnaires	x	x	x
Fitbit journal	x	x	
6-minutes walk test	x		
Nutritionist and kinesiologist			x

[1] Only if the last research visit > 1 month.
[2] For participants in the intervention group only.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	3-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	44
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2 and 44
	5b	Name and contact information for the trial sponsor	2
	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	43-44
	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)	31-33

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10-15
	6b	Explanation for choice of comparators	19-21
Objectives	7	Specific objectives or hypotheses	14-15
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15-24
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	16-17
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)	17-19
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	20-23
	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)	32-34
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	31-32
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	20-21
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	24-34
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)	20-26 + Figure 1

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	34-36
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	34-36
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19-20
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	19-20
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16-17, 19-20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	40
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	40
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	24-38
	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	35-36

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	31-33
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	35-38
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	35-38
	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)	35-36
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	29-31
	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	31
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	31-32
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	31
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	42
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)	32-33

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	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	42
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	43-44
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	43
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	32-33
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	45
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files
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	26

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