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# 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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**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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56 49 **Protocol date and version: October 14<sup>th</sup>, 2021 (version 1)**  
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3 **50 Abstract**  
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5 51  
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7 52 *Introduction:*  
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10 53 Women with obesity are at a higher risk of infertility as well as gestational and neonatal  
11  
12 54 complications. Lifestyle changes are universally recommended for women with obesity  
13  
14 55 seeking fertility treatments, but such intervention has only been assessed in very few  
15  
16 56 robust studies. This study's objectives are therefore to assess the clinical outcomes and  
17  
18 57 cost-effectiveness of an interdisciplinary lifestyle intervention (the Fit-For-Fertility  
19  
20 58 Program; FFFP) targeting women with obesity and subfertility in a diverse population.  
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26 60 *Methods and Analysis:*  
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28 61 This pragmatic multicentre randomized controlled trial (RCT) will include 616 women with  
29  
30 62 obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with polycystic ovary syndrome or at-risk  
31  
32 63 ethnicities) who are evaluated at a Canadian fertility clinic for subfertility. Women will be  
33  
34 64 randomized either to 1) the FFFP (experimental arm) alone for 6 months, and then in  
35  
36 65 combination with usual care for infertility if not pregnant; or 2) directly to usual fertility care  
37  
38 66 (control arm). Women in the intervention group benefit from the program up to 18 months  
39  
40 67 or, if pregnant, up to 24 months or the end of the pregnancy (whichever comes first).  
41  
42 68 Women from both groups are evaluated every 6 months for a maximum of 18 months.  
43  
44 69 The primary outcome is live birth rate at 24 months. Secondary outcomes include fertility,  
45  
46 70 pregnancy and neonatal outcomes; lifestyle and anthropometric measures; and cost-  
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48 71 effectiveness. Qualitative data collected from focus groups of participants and  
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50 72 professionals will also be analyzed.  
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#### 74 *Ethics and Dissemination:*

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

#### 82 Trial Registration:

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

84 Protocol version: 1.1, April 13, 2019

#### 86 **Strengths and limitations of this study**

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

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2  
3 97 will increase the feasibility of the trial and the potential impact and use of the  
4  
5 98 findings to influence policies and priorities of institutions and governments.

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8 99 • It is not possible to blind the intervention and data collection since the tested  
9  
10 100 intervention is a lifestyle program, but the study primary outcome of live birth is a  
11  
12 101 robust clinical outcome that is not susceptible to bias.

13  
14 102 • Self-reported questionnaires may introduce desirability or recall biases, but the  
15  
16 103 study uses tools validated in such setting and these biases should be similar in the  
17  
18 104 intervention and control groups.

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23  
24 106 **Keywords**

25  
26 107 Obesity, Fertility, Women, Lifestyle, Weight loss, Pregnancy, Randomized controlled trial,

27  
28 108 Live birth, Cost-Effectiveness, Polycystic ovary syndrome

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32  
33 110 **Word Count:** 7,703

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36 111

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38 112 Number of **tables:** 3; and **figures:** 1

39  
40 113

41  
42 114 **List of abbreviations**

43  
44 115 AEOsI, Adverse Events of Special Interest;

45  
46 116 ART, assisted reproduction technology;

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48 117 ALT, alanine amino transferase;

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50 118  $\beta$ -hCG, human chorionic gonadotropin;

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52 119 BMI, body mass index;

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54 120 CHUM, Centre hospitalier universitaire de Montréal;



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3 121 CHUQ, Centre hospitalier universitaire de Québec;  
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5 122 CHUS, Centre hospitalier universitaire de Sherbrooke;  
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8 123 CI, confidence intervalle;  
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10 124 CIUSSS, Centre intégré universitaire de santé et des services sociaux;  
11  
12 125 COVID-19, Coronavirus Disease 2019;  
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14 126 EOSS, Edmonton Obesity Staging System;  
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16  
17 127 FertiQoL, Fertility Quality of Life questionnaire;  
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19 128 FFQ, Food Frequency Questionnaire;  
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21 129 FSH, follicle stimulating hormone;  
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24 130 HADS, Hospital Anxiety and Depression Scale;  
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26 131 HbA1c, glycated hemoglobin;  
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28 132 HDL, high-density lipoprotein cholesterol;  
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31 133 ICER, incremental cost-effectiveness ratio;  
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33 134 IPAQ, International Physical Activity Questionnaire;  
34  
35 135 ITT, intent-to-treat;  
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37 136 IUSMM, Institut universitaire en santé mentale de Montréal;  
38  
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40 137 IVF, *in vitro* fertilization;  
41  
42 138 LDL, low-density lipoprotein cholesterol;  
43  
44 139 LH, luteinizing hormone;  
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46  
47 140 MAR, medically assisted reproduction;  
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49 141 OR, odd ratio;  
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51 142 PCOS, polycystic ovary syndrome;  
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54 143 PRECIS, PRagmatic-Explanatory Continuum Indicator Summary;  
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56 144 PRL, prolactin;  
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3 145 PSQI, Pittsburg Sleep Quality Index;  
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5 146 PV, Pregnancy visit;  
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7 147 QALY, Quality-Adjusted Life Years;  
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9 148 REDCap, Research Electronic Data Capture;  
10  
11 149 RCT, randomized controlled trial;  
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13 150 REB, Research Ethics Board;  
14  
15 151 SAE, Serious Adverse Events;  
16  
17 152 SF-6Dv2, Short Form-6 Dimensions – version 2;  
18  
19 153 SHBG, sex hormone-binding globulin;  
20  
21 154 SMART, Specific, Measurable, Attainable, Realistic and Timely;  
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23 155 TSH, thyroid-stimulating hormone;  
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25 156 V0, baseline research visit at time 0; and  
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27 157 WHO, World Health Organization.  
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5 160 **Introduction**

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10 162 *Women with obesity and infertility*

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14 164 Infertility affects approximately 10-15% of couples in Canada and the rest of North  
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17 165 America [1]. According to the International Glossary on Infertility and Fertility Care,  
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19 166 infertility is “a disease characterized by the failure to establish a clinical pregnancy after  
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21 167 12 months of regular, unprotected sexual intercourse or due to an impairment of a  
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23 168 person’s capacity to reproduce either as an individual or with his/her partner” [2]. For the  
24  
25 169 purpose of this study, subfertility is defined as an infertility with a reasonable probability of  
26  
27 170 spontaneous pregnancy without medical intervention, which excludes couples with sterility  
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29 171 or severe infertility (such as bilateral irreversible tubal factor or severe male factor).  
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31 172 Medically assisted reproduction (MAR), including ovulation induction, ovarian stimulation,  
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33 173 intra-uterine insemination and assisted reproductive technology (ART) [2] are part of the  
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35 174 current clinical management of infertility and have become more and more used and  
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37 175 effective in helping infertile couples to achieve a pregnancy [3]. Unfortunately, these  
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39 176 procedures are costly and carry risks for both women and infants. These risks can occur  
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41 177 at different stages of ART: ovarian stimulation (ovarian hyperstimulation syndrome,  
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43 178 thromboembolism, and ovarian torsion), oocyte retrieval (infection and bleeding) and early  
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45 179 pregnancy (ectopic or heterotopic pregnancy, and multiple gestations[4]). Although these  
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47 180 risks are rare, they can have significant consequences. Furthermore, some studies have  
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49 181 suggested that ART procedures may have negative neonatal consequences, such as  
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3 182 higher frequencies of alterations in DNA methylation patterns associated with DNA  
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5 183 imprinting disorders in children conceived through ART [5].  
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10 185 Obesity (defined operationally as a BMI  $\geq 30$  kg/m<sup>2</sup> [6]), is a known modifiable risk  
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12 186 factor associated with female infertility [7] and the population affected worldwide is high  
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14 187 enough for obesity to be recognized as a global epidemic by the World Health  
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16 188 Organization since 2000 [8]. The prevalence of obesity has been estimated to be as high  
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18 189 as 30% in Canadian and 38% in American populations, respectively [9]. More precisely,  
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20 190 21% of Canadian women of reproductive age had obesity in 2015 [10]. Women who plan  
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22 191 to get pregnant are currently more likely to be affected by obesity [11], which can  
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24 192 significantly affect their fertility. For instance, a very large cohort study including more than  
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26 193 40,000 couples estimated that women with obesity display a 78% higher risk of having  
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28 194 infertility compared to women with a normal BMI (18.50-24.99 kg/m<sup>2</sup>) (odd ratio [OR] with  
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30 195 95% confidence interval [CI]: 1.78 [1.63-1.95]) [12]. Women with obesity are also more  
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32 196 likely to develop polycystic ovary syndrome (PCOS), which is the leading cause of  
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34 197 anovulatory infertility, affecting 6-10% of women of childbearing age [13]. Furthermore, a  
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36 198 higher BMI has been associated with reduced pregnancy rates even in women with  
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38 199 ovulatory cycles, equating to a 4% decrease in pregnancy rate per kg/m<sup>2</sup> of BMI increase  
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40 200 in women with a BMI  $\geq 29$ kg/m [14].  
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48 201 Moreover, studies assessing MAR procedures have reported that women with  
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50 202 obesity: i) require higher doses and a longer duration of clomiphene [15] and  
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52 203 gonadotrophins [16-19] to achieve ovulation, ii) display a lower pregnancy rate per cycle  
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54 204 [18], and iii) are at a higher risk of cycle cancellation [16,18] and miscarriage [20,21].  
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3 205 Obesity also increases the risk of complications during pregnancy, such as gestational  
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5 206 diabetes, pre-eclampsia, caesarean section and intrauterine death [22,23]. In keeping with  
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7 207 the Developmental Origins of Health and Disease paradigm, maternal pre-pregnancy BMI  
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9 208 and excessive gestational weight gain are consistently associated with the early  
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11 209 development of obesity and diabetes in the offspring [24]. Obesity in childhood is closely  
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13 210 linked to adult obesity [25,26], perpetuating the intergenerational cycle of obesity [27-29].  
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15 211 Adopting a healthy lifestyle before conception and restoring of a healthy metabolic  
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17 212 environment early during pregnancy likely represents the best approach to break the  
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19 213 vicious circle of intergenerational propagation of obesity and diabetes.  
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25 214 Accordingly, targeting women with obesity prior to conception may be essential to  
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27 215 reduce the burden of infertility and MAR costs, as well as obesity and cardiometabolic  
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29 216 diseases in our societies.  
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### 35 218 *Infertility management in women with obesity seeking fertility treatments*

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40 220 To prevent the adverse effects of obesity on female fertility and on gestational and  
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42 221 neonatal health, many organizations have recommended that women with obesity should  
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44 222 be assisted, before conception, to lose weight (5 to 10 % of their initial weight) and adopt  
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46 223 a healthy lifestyle, and maintain that healthy lifestyle during pregnancy [30-33]. Results  
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48 224 from a recent systematic review support lifestyle modification prior to ART in women with  
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50 225 overweight or obesity [34]. The authors pointed out that despite the lack of RCTs in the  
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52 226 area, pre-conception weight loss in women with overweight or obesity can help improve  
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54 227 fertility and pregnancy outcomes. Out of the 7 RCTs assessing non-surgical methods of  
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3 228 weight loss, including some form of lifestyle intervention, the most methodologically  
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5 229 rigorous study was a RCT published in the *New England Journal of Medicine* in 2016 [35].  
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8 230 This study compared 287 women with obesity and subfertility who were randomized to a  
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10 231 6-month structured lifestyle intervention (including 6 outpatient visits and 4 telephone  
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12 232 consultations with a nurse or dietician) and 285 women assigned to prompt fertility  
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14 233 treatments. The lifestyle intervention lasted only 6 months and was not continued during  
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17 234 fertility treatments or pregnancy. After a follow-up of 24 months, the lifestyle program did  
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19 235 not improve the live birth rate, but resulted in a significant increase in the rate of  
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21 236 spontaneous pregnancies (rate ratio [95% confidence]: 1.61 [1.16-2.24]) and reduced the  
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24 237 need for fertility treatments (rate ratio [95% confidence]: 0.78 [0.70-0.86]) [36]. In a follow-  
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26 238 up article, the same group of authors observed, from a hospital perspective, an  
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28 239 incremental cost-effectiveness ratio (ICER) of €15,845 per additional point of percentage  
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31 240 in the healthy live birth rate resulting from the lifestyle program compared to usual care.  
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33 241 The authors concluded that their intervention may be deemed as cost-effective, especially  
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35 242 for longer follow-up timelines, in anovulatory women, women who completed the study or  
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38 243 women  $\geq 36$  years of age [37].  
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42 245 Interestingly, in a survey asking women with obesity or overweight and considering  
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44 246 pregnancy if they were interested in adopting a healthier lifestyle prior to conception, 91%  
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47 247 reported their willingness to participate in a lifestyle program [38]. However, despite the  
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49 248 patients' motivation and the international recommendations to encourage women to  
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51 249 optimize their lifestyle before starting fertility treatments, most women with obesity do not  
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54 250 have access to such targeted lifestyle programs integrated within their fertility care.  
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56 251 Therefore, our objective is to give these women access to the Fit-For-Fertility Program  
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3 252 (FFFP), an interdisciplinary lifestyle intervention, integrated into the fertility clinic care  
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5 253 pathway. This program supports participants in adopting sustainable healthy behaviours,  
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7 254 in pre-conception, throughout fertility treatments, and during pregnancy. In response to  
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9 255 the national priority to improve the quality and costs of reproductive and perinatal care  
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11 256 established by our *Canadian network on reproductive and maternal health of women with*  
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13 257 *obesity and infertility*, we will conduct a multicentre RCT assessing the FFFP in women  
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15 258 with subfertility and obesity.  
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21 260 *Research question and hypotheses*  
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26 262 For this RCT, our research question is: Compared to usual care, does the FFFP  
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28 263 cost-effectively improve i) the live birth rate and other fertility outcomes and ii) pregnancy  
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30 264 and neonatal outcomes, in women with obesity and subfertility who seek fertility  
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32 265 treatments. We hypothesize that in comparison to prompt initiation of usual fertility care,  
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34 266 participation in the FFFP, alone for 6 months and then in combination with usual care for  
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36 267 infertility, will: 1) improve the fertility of women with obesity, 2) reduce costs associated  
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38 268 with fertility treatments, and 3) decrease the occurrence of some complications related to  
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40 269 maternal weight during the pregnancy and for their offspring.  
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46 271 *Study objectives*  
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51 273 The primary objective of this study is to assess the effectiveness of the FFFP on  
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53 274 fertility outcomes in a diverse Canadian population of women with obesity and subfertility  
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55 275 who are seeking fertility treatments. Secondary objectives are to assess the FFFP's 1)  
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3 276 cost-effectiveness, primarily in terms of costs per live birth, as well as other measures of  
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5 277 the program's costs and effectiveness measures, and 2) impacts on maternal and  
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7 278 neonatal health.  
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## 11 280 **Methods and Analysis**

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### 13 282 ***Study design***

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15 284 This study is a multicentre, two-arm, parallel pragmatic RCT comparing the FFFP to  
16 285 usual fertility care, using quantitative and qualitative assessments (ClinicalTrials.gov:  
17 286 NCT03908099). More specifically, we developed a pragmatic RCT based on the PRECIS-  
18 287 2 principles [39].  
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### 22 289 ***Patient and Public Involvement***

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24 291 Our study relies on the early and regular involvement of knowledge users and  
25 292 decision-makers to ensure their appropriation of the results. Engaged patients have been  
26 293 implicated early in the development of this protocol to ensure that the results will be  
27 294 relevant for the target population and that the methods are appropriate for the participants.  
28 295 Following these principles increases the potential impact and use of the findings to  
29 296 influence policies and priorities of institutions and governments.  
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### 33 298 ***Setting and recruitment***

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3 300 The study will be conducted in seven Canadian fertility clinics from coast to coast  
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5 301 and in an ethnically diverse population of women: Olive Fertility Centre in Vancouver  
6  
7 302 (British-Columbia), with its Asian population; Mount Sinai Hospital in Toronto (Ontario)  
8  
9  
10 303 and *Centre hospitalier de l'Université de Montréal* (CHUM), with large multiethnic  
11  
12 304 communities; *Centre hospitalier universitaire de Sherbrooke* (CHUS) and *Centre*  
13  
14 305 *hospitalier universitaire de Québec de l'Université de Laval* (CHU de Quebec-UL)  
15  
16 306 (Quebec), which are smaller centres with mainly a Caucasian population; and Atlantic  
17  
18 307 Assisted Reproductive Therapies Clinic in Halifax (Nova Scotia) that has a Caucasian and  
19  
20 308 Afro-American populations. We are also in the process of recruiting a 7<sup>th</sup> centre, ideally in  
21  
22 309 the province of Manitoba.  
23  
24  
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26 310  
27  
28 311 Potentially eligible patients can be approached in one of two ways: 1) by a member  
29  
30 312 within their circle of care (nurse, physician, receptionist, etc.) who then provides contact  
31  
32 313 info to research staff, or 2) by responding to an advertisement indicating their interest to  
33  
34 314 learn more about the study. Written informed consent is obtained individually for each  
35  
36 315 patient during the baseline research visit (V0), after a full explanation of the study's  
37  
38 316 protocol and answers to the patient's questions by the research staff, and before any data  
39  
40 317 collection or study procedures. The following screening and baseline data are obtained  
41  
42 318 during this visit: eligibility assessment (inclusion/exclusion criteria), medical history,  
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44 319 concomitant medications, patient demographics and a baseline evaluation of study  
45  
46 320 outcomes. Eligibility is confirmed by the site investigator before randomization.  
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54 322 ***Participant eligibility***

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3 324 Patients who meet the following inclusion criteria can participate in the study:  
4

- 5 325 1) Being infertile, defined as (a) failure to achieve a clinical pregnancy after  $\geq 12$   
6  
7 326 months of regular unprotected sexual intercourse, (b) not conceiving after having  
8  
9  
10 327 attempted  $\geq 6$  months in women with irregular menstrual cycles or  $\geq 35$  years of age;  
11  
12 328 or (c) women with an established cause of infertility;  
13  
14 329 2) Aged between 18 and 40 years (since initiation of fertility treatments should not be  
15  
16 330 delayed in women above 40 y.o.); and  
17  
18 331 3) With obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or 27 kg/m<sup>2</sup> for Asian and Latin American, based on  
19  
20 332 WHO 2004 [40]), or with a BMI  $\geq 27$  kg/m<sup>2</sup> for women with PCOS. These women  
21  
22 333 display the metabolic consequences of non-PCOS women with obesity at a lower  
23  
24 334 BMI, and benefit more from lifestyle modifications.  
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31 336 Women presenting at least one the following exclusion criteria will not be eligible to  
32  
33 337 enroll in the study:  
34

- 35 338 1) Any uncontrolled medical or mental condition that contra-indicates fertility  
36  
37 339 treatments, based on clinical judgment of the fertility specialist;  
38  
39 340 2) Natural conception is impossible or highly unlikely (e.g., bilateral tubal factor,  
40  
41 341 severe male factor defined as a total motile sperm count  $< 5$  million on the most  
42  
43 342 recent partner's seminal analysis), where the only indicated MAR procedures are  
44  
45 343 IVF or donor sperm insemination (this exclusion criteria defines subfertility, such  
46  
47 344 that only subfertile couples are enrolled);  
48  
49  
50 345 3) History of recurrent spontaneous abortions ( $> 2$  miscarriages at less than 22 weeks  
51  
52 346 of gestation), with evidence of conception (such as positive  $\beta$ -hCG), within the last  
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3 347 12 months (since these women are more likely to have a defect that cannot be  
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5 348 improved by lifestyle);  
6  
7 349 4) Previously diagnosed uncontrolled eating disorder or major depression that would  
8  
9  
10 350 contra-indicate the initiation of a lifestyle intervention;  
11  
12 351 5) A high level of depressive state, as determined by a score for depression on the  
13  
14 352 Hospital Anxiety and Depression Scale (HADS)  $\geq 15$  [41,42], which is not a  
15  
16 353 diagnostic of depression but would also contra-indicate the initiation of a lifestyle  
17  
18 354 intervention;  
19  
20 355 6) Planning for or past history of bariatric surgery, which would confound the impact  
21  
22 356 of the lifestyle intervention tested;  
23  
24 357 7) Planning for or engaging in another lifestyle intervention that would be similar to  
25  
26 358 the intervention tested, e.g., including individual visits every 8 weeks or less, which  
27  
28 359 would also confound the impact of the FFFP;  
29  
30 360 8) Inability to understand the language in which group sessions is provided in the  
31  
32 361 participating centre, i.e., French in the province of Quebec and English in other  
33  
34 362 provinces; and  
35  
36 363 9) Unable to attend research visits at the participating centre for the next 18 months.  
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### 365 **Randomization**

49 367 Randomization to the FFFP or control group occurs after completion of the V0 and  
50  
51 368 the eligibility assessment. Group allocation is concealed using online computerized  
52  
53 369 randomization using REDCap (Research Electronic Data Capture tool hosted at the  
54  
55 370 Université de Sherbrooke) [43] with permuted blocks of variable block sizes (2 to 6),  
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3 371 stratified by centre and PCOS status (yes/no). PCOS is an important potential confounder  
4  
5 372 or modifier since it decreases fertility and may affect the response to the lifestyle  
6  
7 373 intervention [13]. The randomization list has been generated by an independent  
8  
9  
10 374 statistician and participants are randomized in one of two arms using a 1:1 ratio. The  
11  
12 375 randomization process is initiated by the site investigator or delegate who accesses the  
13  
14 376 web-based system and confirms patient's eligibility and informed consent. The patient's  
15  
16 377 unique study identifier and open-label study treatment allocation is then automatically and  
17  
18 378 electronically delivered to the local site investigator or delegate.  
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23  
24 380 Following randomization, the research staff informs the fertility care team of the  
25  
26 381 patient's allocation group. On the one hand, if the participant is randomized to the control  
27  
28 382 group, the fertility care team is informed that their patient can undergo fertility treatments  
29  
30 383 immediately, according to their usual care. On the other hand, if the participant is  
31  
32 384 randomized to the intervention group, the fertility clinic will be notified that the patient has  
33  
34 385 to postpone any MAR procedures for the following 6 months, during which the patient is  
35  
36 386 enrolled in the FFFP. At the end of this first 6-month period, if the participant failed to  
37  
38 387 conceive, the research staff contacts the fertility clinic team to inform them that the  
39  
40 388 participant can now undergo usual fertility care, in combination with the FFFP.  
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## 46 390 ***Interventions***

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49 391

### 51 392 Control Arm

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3 394 Participants randomized to the control group are provided immediate access to the  
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5 395 usual fertility care, as recommended by their fertility specialist, for a maximum of  
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7 396 24 months. This may include lifestyle counselling by their fertility specialist and usual  
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9  
10 397 fertility treatments. Since this is a pragmatic trial, they may undergo any lifestyle  
11  
12 398 approaches or consult any professionals they want on their own, but are discouraged to  
13  
14 399 engage in a lifestyle program similar to the FFFP, as they agreed when recruited for the  
15  
16  
17 400 study, in order to avoid such an important contamination between intervention arms.  
18

19 401

20  
21 402 Experimental Arm  
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26 404 Participants randomized to the intervention group follow the FFFP alone for the first  
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28 405 6 months, then in combination with usual fertility care for an additional 12 months if not  
29  
30  
31 406 pregnant. After these 18 months, usual fertility care can continue to be provided alone for  
32  
33 407 a maximum follow-up of 24 months. The FFFP is also provided throughout gestation for  
34  
35 408 participants who achieve a successful pregnancy. Accordingly, the lifestyle program is  
36  
37 409 provided for a maximum of 18 months if there is no pregnancy, or otherwise, up to the end  
38  
39  
40 410 of pregnancy or to a total study follow-up of 24 months (whichever comes first).  
41

42 411

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44 412 The FFFP was initially developed based on 2007 Canadian clinical practice  
45  
46 413 guidelines [44] and the approach implemented by our group at the CHUS obesity clinic  
47  
48 414 [45], and was then improved and adapted based on the experience gained from our  
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51 415 completed pilot study [46] and focus groups with study participants. This intervention is  
52  
53 416 aimed at supporting participants to implement progressive and sustainable lifestyle  
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56 417 changes. Participants attend 30-minute individual sessions with a dietitian and a  
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3 418 kinesiologist, respectively, every 6 weeks for the first 6 months, then every 8 weeks for  
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5 419 the following 6 months, and then every 12 weeks until the end of the treatment period.  
6  
7 420 These individual meetings take place in person with the participant, or virtually using an  
8  
9 421 authorized system of telemedicine in the event that face-to-face meetings are not possible  
10  
11 422 (e.g., due to public health rules such as during the COVID-19 pandemic). Personal remote  
12  
13 423 contact (e.g., by phone, e-mail) is offered between in-person meetings. Patients are  
14  
15 424 guided by the dietitian and kinesiologist to formulate SMART goals (Specific, Measurable,  
16  
17 425 Attainable, Realistic and Timely) [47]. These professionals are trained in evidence-based  
18  
19 426 motivational communication skills [48], with emphasis placed on how to arm women with  
20  
21 427 the knowledge, motivation, and skills to achieve sustainable lifestyle changes. To ensure  
22  
23 428 equitable delivery of the intervention, we will implement an internal quality control and  
24  
25 429 training process. Therefore, after receiving training in motivational communication by our  
26  
27 430 leading expert (KLL), each professional will audio-record their first three individual  
28  
29 431 meetings. These recordings will be evaluated by an expert in motivational communication  
30  
31 432 using a coding scheme to verify fidelity. Feedback regarding the professional's application  
32  
33 433 of motivational communication techniques will be provided as needed, and additional  
34  
35 434 recordings may be necessary based on the trainer's assessment. After 6 and 12 months,  
36  
37 435 three more individual sessions are recorded and used to analyze the quality and fidelity  
38  
39 436 of the intervention from a research perspective. Consent for recording individual meetings  
40  
41 437 is a specific question in the informed consent form and participants have the opportunity  
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43 438 to revoke their agreement at any time during the course of their participation in the study.  
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53 440 Participants also benefit from weekly group sessions divided into 2 parts of 45  
54  
55 441 minutes each [46] (see Table 1 for group sessions' topics): 1) Workshops that cover 8  
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3 442 different topics addressing nutritional aspects and relevant healthy lifestyle habits  
4  
5 443 (alcohol, tobacco and motivational issues) and 2) Supervised classes of physical activity  
6  
7 444 where one of 8 different types of exercise are practiced. Women are invited to participate  
8  
9 445 in group sessions every week throughout the study, but are required to attend all 8  
10  
11 446 different sessions within the first 6 months. The spouses of participants are highly  
12  
13 447 encouraged to participate in all activities, as lifestyle modification is also important for the  
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15 448 partner to improve a couple's fertility [49,50].  
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**Table 1. Topics of the Fit-For-Fertility's Interactive workshops and physical activity sessions.**

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

450

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

456

### 457 **Data collection**

458

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

466

|  | V0 | V6 | V12 | V18 | PV1 | PV2 |
|--|----|----|-----|-----|-----|-----|
| 41 <b>Informed consent</b>   | ●  |    |     |     |     |     |
| 42 <b>Physical exam</b><br>43 <b>(anthropometry, blood</b><br>44 <b>pressure and heart rate)</b> | ●  | ●  | ●   | ●   | ●   | ●   |
| 45 <b>Concomitant medications</b>  | ●  | ●  | ●   | ●   | ●   | ●   |
| 46 <b>Blood sample</b>   |    |    |     |     |     |     |
| 47 <b>Fasting levels of sex</b><br>48 <b>steroids</b>  | ●  | ●  | ●   | ●   |     |     |
| 49 <b>FSH, LH</b>  | ●  | ●  | ●   | ●   |     |     |
| 50 <b>TSH</b>  | ●  | ●  | ●   | ●   | ●   | ●   |



|    |   |   |   |   |   |   |   |  |
|----|---|---|---|---|---|---|---|--|
| 1  |   |   |   |   |   |   |   |  |
| 2  |   |   |   |   |   |   |   |  |
| 3  | <b>Prolactin</b>  | ● | ● | ● | ● |   |   |  |
| 4  | <b>β-hCG</b>  | ● | ● | ● | ● | ● |   |  |
| 5  | <b>ALT</b>  | ● | ● | ● | ● | ● | ● |  |
| 6  | <b>HbA1c</b>  | ● | ● | ● | ● | ● | ● |  |
| 7  | <b>Glucose</b>  | ● | ● | ● | ● | ● | ● |  |
| 8  | <b>Lipids</b>   | ● | ● | ● | ● |   |   |  |
| 9  | <b>Creatinine</b>   | ● |   |   |   |   |   |  |
| 10 | <b>Extra samples shipped to the coordinating site (Sherb., QC)</b>  | ● | ● | ● | ● | ● | ● |  |
| 11 | <b>Initial Medical Questionnaire</b>  | ● |   |   |   |   |   |  |
| 12 | <b>Actual Health Status Questionnaire</b>   |   | ● | ● | ● | ● | ● |  |
| 13 | <b>FertiQoL</b>   | ● | ● | ● | ● |   |   |  |
| 14 | <b>HADS</b>   | ● | ● | ● | ● | ● | ● |  |
| 15 | <b>IPAQ</b>   | ● | ● | ● | ● | ● | ● |  |
| 16 | <b>Readiness to Change Questionnaire</b>  | ● | ● | ● | ● | ● | ● |  |
| 17 | <b>PSQI</b>   | ● | ● | ● | ● | ● | ● |  |
| 18 | <b>Socio-demographic Questionnaire</b>  | ● |   |   |   |   |   |  |
| 19 | <b>Patient's Costs Questionnaire</b>  |   | ● | ● | ● | ● | ● |  |
| 20 | <b>SF-6D.v2</b>   | ● | ● | ● | ● | ● | ● |  |
| 21 | <b>FFQ web</b>  | ● | ● | ● | ● | ● | ● |  |
| 22 | <b>Fitbit &amp; Fitbit Journal</b>  | ● | ● | ● | ● | ● | ● |  |
| 23 | <b>6 minutes walking test</b>   | ● | ● | ● | ● | ● |   |  |
| 24 | <b>Participant's Satisfaction Questionnaire</b>   |   |   |   | ● |   | ● |  |
| 25 | <b>AEoSI and SAE review</b>   | ● | ● | ● | ● | ● | ● |  |
| 26 | 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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3 469 Participants are instructed to contact the study team between visits or phone calls  
4  
5 470 if they become pregnant or if any relevant situations occur (e.g., miscarriage, accident,  
6  
7 471 moving, changing phone number). Importantly, all clinical outcomes are ascertained with  
8  
9 472 participants and their medical records 24 months after participants' randomization,  
10  
11 473 regardless of the timing of their last research visit and the occurrence of a pregnancy.  
12  
13 474 Pregnancy and neonatal outcomes occurring 24 months after randomization will not be  
14  
15 475 included in the primary analysis of the primary outcome, but are recorded for secondary  
16  
17 476 analyses.  
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### 478 ***Outcome measures and their assessment***

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28 480 *Fertility outcomes:* The primary outcome is the cumulative incidence of live birth at  
29  
30 481 24 months. Secondary fertility outcomes are also collected from medical records at  
31  
32 482 24 months and include: the rate of biochemical pregnancy (confirmed by a positive serum  
33  
34 483  $\beta$ -hCG), ongoing confirmed pregnancy (viable pregnancy at  $\geq 10$  weeks of gestation),  
35  
36 484 spontaneous miscarriage of a confirmed pregnancy ( $< 22$  gestational weeks), multiple  
37  
38 485 gestation, spontaneous pregnancy, pregnancy following MAR procedures, doses of  
39  
40 486 fertility medications, number of MAR and/or ART cycles, number of embryo transfers, and  
41  
42 487 complications due to MAR procedures.  
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478

49 489 *Pregnancy outcomes (all secondary outcomes):* Total gestational weight gain,  
50  
51 490 calculated by subtracting weight at the research visit closest to the onset of pregnancy  
52  
53 491 from the last weight available in the antenatal record. Weekly gestational weight gain,  
54  
55 492 calculated by dividing total weight gestational gain by the number of weeks between the  
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2  
3 493 first and last measure of weight. Pregnancy complications, which are retrieved from  
4  
5 494 medical records, include gestational diabetes, gestational hypertensive disorders,  
6  
7 495 thromboembolism, preterm birth, late fetal loss, stillbirth and post-partum hospital stay  
8  
9  
10 496 >7 days.

11  
12 497  
13  
14 498 *Neonatal outcomes (all secondary outcomes):* Birth weight, Apgar scores,  
15  
16 499 hypoglycemic episodes, hyperbilirubinemia, birth trauma, admission to neonatal intensive  
17  
18 500 care unit and neonatal death (up to 28 days of life), which are retrieved from medical  
19  
20 501 records.

21  
22 502  
23  
24 503 *Anthropometric measures and vital signs (all secondary outcomes):*  
25  
26 504 Anthropometric measures are collected at each research visit. Weight is measured with a  
27  
28 505 standard calibrated scale and height is measured with a stadiometer, based on the models  
29  
30 506 available at each centre. Foot-to-foot bioelectrical impedance analysis technology is used  
31  
32 507 to estimate the percentage of fat mass and fat free mass [52] in most, but not all centres  
33  
34 508 (models depend on each centre). Waist circumference measurement is done with a  
35  
36 509 measuring tape according to the National Institutes of Health [53]. Heart rate and blood  
37  
38 510 pressure are measured after a five-minute rest period in a sitting position. Two  
39  
40 511 measurements are taken for waist circumference and vital signs, with the average being  
41  
42 512 used for analyses.

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44 513  
45  
46 514 *Endocrine and metabolic blood markers (all secondary outcomes):* A blood sample  
47  
48 515 is taken at each research visit to measure different hormonal and metabolic biological  
49  
50 516 markers: luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid-stimulating

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2  
3 517 hormone (TSH), prolactin (PRL), human chorionic gonadotropin ( $\beta$ -hCG), serum  
4  
5 518 progesterone, androstenedione, estradiol, total and calculated free testosterone, sex  
6  
7 519 hormone-binding globulin (SHBG), glycated hemoglobin (HbA1c), total cholesterol,  
8  
9  
10 520 triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein  
11  
12 521 cholesterol (LDL), cholesterol ratio, glucose, alanine amino transferase (ALT) and  
13  
14 522 creatinine (at initial research visit only). All markers are assessed at local laboratories,  
15  
16 523 since they are clinically indicated. Additional plasma samples are shipped to CHUS and  
17  
18 524 stored for future analyses relevant to this study's objectives, when further funding  
19  
20 525 becomes available.  
21  
22  
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24 526

25  
26 527 *Lifestyle outcomes (all secondary outcomes):* Lifestyle outcomes are assessed at  
27  
28 528 each research visit. Nutritional intake is evaluated using the validated web version of the  
29  
30 529 Food Frequency Questionnaire (FFQ web), referring to the patient's nutritional  
31  
32 530 consumption of the last month. This questionnaire enables to extract data on specific food  
33  
34 531 groups and micro- or macronutrients. This questionnaire has been shown to have a  
35  
36 532 moderate validity and a good reproducibility for assessing nutrient intakes in healthy adults  
37  
38 533 [54]. Participants complete the questionnaire at the research centre at their first research  
39  
40 534 visit to ensure good understanding of the questions. For subsequent research visits,  
41  
42 535 participants have the possibility to receive a link to complete the FFQ web electronically  
43  
44 536 from home. Sleep duration and quality are evaluated by the Pittsburg Sleep Quality Index  
45  
46 537 (PSQI) questionnaire, which has been shown to have a strong reliability and validity, as  
47  
48 538 well as a moderate structural validity in the context of screening for sleep dysfunction [55].  
49  
50 539 The International Physical Activity Questionnaire (IPAQ) – short version – is used to  
51  
52 540 assess physical activity practice over the past 7 days: it was shown to have a good  
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3 541 repeatability of data and is as reliable as other self-administered physical activity  
4  
5 542 questionnaires [56]. Furthermore, participants are asked to wear after the research visit a  
6  
7 543 Fitbit© Flex 2 monitor during 7 consecutive days, 24 hours/day, in order to objectively  
8  
9 544 assess physical activity levels (energy expenditure, number of steps, distance walked,  
10  
11 545 time spent being inactive, lightly active, active and very active), as well as sleep data  
12  
13 546 (minutes spent asleep, awake and restless (when moving while sleeping)). Fitbit© devices  
14  
15 547 have been shown to accurately estimate the daily number of steps and the time spent in  
16  
17 548 bed and sleeping, while overestimating the time spent doing highly intense activities [57].  
18  
19 549 However, data extracted will be mainly used to assess the change of physical activity  
20  
21 550 levels and sleep over time and not whether physical activity recommendations are met.  
22  
23 551 This estimation bias should be consistent at each measurement time point and will be  
24  
25 552 adjusted for baseline measures. The participant's physical fitness level is assessed using  
26  
27 553 the 6-minute walk test (6mWT), which has shown to be a simple, safe and low-cost test  
28  
29 554 to assess the effect of an intervention on the physical performance and walk capacity  
30  
31 555 beyond weight loss [58]. Other lifestyle habits, such as alcohol, tobacco and drugs  
32  
33 556 consumption, are measured by a study-specific self-reported questionnaire.  
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42 558 *Quality of life (secondary outcome):* Participants' quality of life specifically related  
43  
44 559 to infertility and its treatments are assessed using the Fertility Quality of Life questionnaire  
45  
46 560 (FertiQoL) [59]. Moreover, the Short Form-6 Dimensions – version 2 (SF-6Dv2) is used to  
47  
48 561 determine Quality-Adjusted Life Years (QALY), which is an important variable for the  
49  
50 562 economic evaluation of the intervention, and to assess the general quality of life of our  
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52 563 participants, as well as the impact of our intervention on dimensions of quality of life.  
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3 565 *Patients' perceptions and satisfaction (all secondary outcomes):* Based on  
4  
5 566 experience from previous studies [46,60,61], we will evaluate the expectations,  
6  
7 567 perceptions and satisfaction towards care provided for fertility and weight management in  
8  
9 568 all participants with a questionnaire, and will further assess these aspects in a small  
10  
11 569 sample (from both groups) using focus groups. The satisfaction questionnaire is given at  
12  
13 570 the 18-month research visit (V18) or at the second pregnancy research visit (PV2) if  
14  
15 571 pregnant. Focus groups will take place at 2 time points: 1) after completion of the study  
16  
17 572 by half of the participants and 2) close to the end of the trial. A total of 168 patients (27%  
18  
19 573 of all participants) will participate in the focus groups across all 7 centres, each centre  
20  
21 574 evaluating two separate sub-groups of 6 patients from the intervention and control groups.  
22  
23 575 The number of participants for the second series of focus groups may be adjusted to reach  
24  
25 576 data saturation. See below under "Methodology and analyses of qualitative substudy" for  
26  
27 577 more details.  
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33 578  
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35 579 *Health-related costs (secondary outcomes):* Data is collected from both the patient  
36  
37 580 and the health care system perspectives for each mother/child dyad. Costs of interest  
38  
39 581 include costs related to the FFFP, fertility treatments, adverse events or complications,  
40  
41 582 pregnancy-related visits and hospital admissions, and patient out-of-pocket expenses.  
42  
43 583 Data collection for this component will be done through patient questionnaires, charts  
44  
45 584 reviews, administrative data, and interviews with healthcare providers and fertility clinic  
46  
47 585 staff for the description of care procedures.  
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53 587 *Medical history and physical health (all secondary outcomes):* A study-specific self-  
54  
55 588 administered questionnaire will be used to evaluate participant's relevant medical history,  
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3 589 use of medications or natural products, and physical health during daily activities. It will  
4  
5 590 be possible with the data of this questionnaire to use the Edmonton Obesity Staging  
6  
7 591 System (EOSS), which has been shown to be an effective classification tool for obesity  
8  
9  
10 592 risk assessment, including in the context of obesity and infertility [62].  
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12 593

### 14 594 ***Data management, monitoring and quality assessment***

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18  
19 596 Research measures and outcomes are recorded through printed or online versions  
20  
21 597 of the questionnaires and paper Case Report Forms at each relevant timepoint. These  
22  
23 598 are checked for integrity by each site's research assistant before being entered into the  
24  
25  
26 599 centralized web-based database REDCap.  
27

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30  
31 601 The central coordinator at the CHUS is responsible for training of the research staff  
32  
33 602 and health professionals (dietitians and kinesiologists), and the monitoring at all centres.  
34  
35 603 The central coordinator is also responsible for ensuring that patient safety, study  
36  
37 604 procedures and data collection are performed at each centre according to the research  
38  
39 605 protocol and Good Clinical Practice guidelines [63]. The central coordinator sends regular  
40  
41 606 queries to site coordinators to resolve discrepancies identified in the database and  
42  
43 607 performs regular onsite visits. These visits will begin after the site research teams have  
44  
45 608 recruited their first 35 participants (corresponding to one-third of participants to be  
46  
47 609 recruited per sites). Then they will be held at every 6-month intervals to assess protocol  
48  
49 610 adherence, intervention standardization, as well as data completeness and quality. During  
50  
51 611 onsite monitoring visits, approximately 10% of participants' records will be reviewed.  
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54 612 Concordance with the original data entered by the site will be assessed using the Cohen's  
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3 613 kappa statistics. A kappa coefficient below 0.60 for one site at the time of a visit, which is  
4  
5 614 considered as less than a moderate concordance [64], will require repeating the training  
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7 615 of research staff at this site and, if necessary, revising of all records of participants who  
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9 616 completed the study at this site, if possible.  
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12 617  
13  
14 618 The trial steering committee of this projects includes JPB, RB, AG, EG, WK, BCM,  
15  
16 619 ASM, CKN, MHP, BT, and their key research team members. An advisory committee is  
17  
18 620 also in place and includes JPB, WF, FG, MFL, KL, TP, ASM, SNR, KA, NC, PS, SL, Becky  
19  
20 621 Attenborough, now retired from the Reproductive Care Program of Nova Scotia, Celine  
21  
22 622 Braun, president of the *Association des couples infertiles du Québec*, Rahda Chari, now  
23  
24 623 retired from the Maternal Newborn Child & Youth Strategic Clinical Network, Alberta, Anne  
25  
26 624 Hayes from the Ministry of Health and Long-Term Care of Ontario, Tamil Kendall, past  
27  
28 625 provincial executive director of perinatal services BC, Martine Pageau, *Directrice du sport,*  
29  
30 626 *du loisir et de l'activité physique* at *Ministère de l'Éducation et de l'Enseignement supérieur*  
31  
32 627 *du Québec*, Daniel Riverin, past director of Mother-Child Services of Quebec Ministry of  
33  
34 628 Health and Danielle Xavier, past president of Conceiveable Dream. The steering and  
35  
36 629 advisory committees meet periodically to support the coordination of the FFF study, and  
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38 630 their implication had already started at the protocol design stage.  
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### 47 632 **Safety measurement**

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49 634 Due to the relatively short duration of recruitment and follow-up of participants, it  
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51 635 will not be relevant to perform formal interim efficacy analyses for futility or superiority and  
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53 636 interim safety analyses. Furthermore, it is very unlikely that the proposed lifestyle  
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3 637 intervention, which is already recommended during preconception and pregnancy in  
4  
5 638 women with obesity, would cause any safety issues. For these reasons, a Data and Safety  
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7 639 Monitoring Board (DSMB) will not be required for this trial, and no interim analyses will be  
8  
9 640 performed. However, Adverse Events of Special Interest (AEoSI) and Serious Adverse  
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11 641 Events (SAE) will be closely monitored throughout the study (see Table 3). These potential  
12  
13 642 events will be evaluated according to their causality and severity. Furthermore, after  
14  
15 643 randomization of the first 50 patients, the trial's steering committee will produce a quarterly  
16  
17 644 blinded report of AEoSI and SAE for each treatment group, including the grades of  
18  
19 645 causality with the intervention. If SAE occur, these events will be reported to the  
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21 646 coordination centre and local Research Ethics Board (REB), as well as the central REB  
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23 647 of the Province of Quebec.  
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**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 <10<sup>th</sup> percentile of the sex-specific birth weight for gestational age reference)

|  |
|--|
| Newborn large for gestational (birth weight >90 <sup>th</sup> percentile of the sex-specific birth weight for gestational age reference) |
| <b>SAE</b>   |
| 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  |

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## 651 **Statistical analyses and sample size**

652

### 653 *Sample size calculation*

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

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3 666 102 participants (i.e., 68 per year). These recruitment rates are feasible given the data  
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5 667 from our pre-trial survey of participating fertility clinics that showed that smaller practices  
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7 668 (CHUS, CHUQ) evaluate 80 to 315 new women with obesity per year, and larger  
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9 669 practices, between 265 and 810.  
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14 671 *Statistical analyses of quantitative data*

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17 672 The primary outcome is 24-month live birth cumulative incidence and the primary  
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19 673 analyses of interest will be ITT, including all randomized participants with available data  
20  
21 674 and no violation of eligibility criteria. The ITT analyses will be supplemented by  
22  
23 675 per-protocol analyses that will exclude women who dropped out of the study during their  
24  
25 676 first 6 months in both groups, i.e. who signified their desire to stop participating in the  
26  
27 677 study and/or intervention visits, or were unreachable from that period up to the end of the  
28  
29 678 trial. The per-protocol analyses will keep all women who persevered in the study for at  
30  
31 679 least 6 months and were therefore appropriately exposed to the intervention (intervention  
32  
33 680 group) and adherent to the 6-month study visit (both group). The 24-month cumulative  
34  
35 681 incidence of live birth will be compared between the two arms using the Mantel-Haenszel  
36  
37 682 test with stratification by centre and PCOS status. This analysis will be supplemented by  
38  
39 683 a survival analysis (log rank test) where the time to live birth will be used. Randomized  
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41 684 groups will be examined at baseline to ensure demographic and clinical data are  
42  
43 685 comparable. If substantial imbalance is found, which is very unlikely, additional analyses  
44  
45 686 will be carried out to assess the potential confounding effects of this imbalance, using  
46  
47 687 multiple logistic regression and Cox proportional hazards model. Similar analyses will be  
48  
49 688 used for the other clinical outcome variables that are categorical. Continuous outcome  
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3 689 variables will also be compared between groups based on either ITT or per-protocol  
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5 690 analyses, using linear mixed models with repeated measures.  
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7  
8 691 We will also analyze the impact of the FFFP on lifestyle and anthropometric  
9  
10 692 outcomes, as well as other outcomes measured during a research visit, at 6 months  
11  
12 693 (including research visits occurring  $6 \pm 1$  months after randomization), as frequently  
13  
14 694 reported in previous and similar trials. For these analyses, continuous variables will be  
15  
16 695 compared between groups using unpaired *t* tests and categorical variables will be  
17  
18 696 examined using chi-square tests. Missing data due to missed research visits or incomplete  
19  
20 697 data collection will not be imputed, due to the relatively small sample size, such that these  
21  
22 698 analyses might be subjected to non-random missing data differing between groups.  
23  
24 699 Therefore, these tests will be corrected for potential baseline imbalances and confounding  
25  
26 700 effects as mentioned above. Variables that are not normally distributed will be  
27  
28 701 mathematically transformed to fit a normal distribution allowing their use in these models.  
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30  
31 702 Subgroup analyses will be performed for all outcomes based on baseline age, level of  
32  
33 703 obesity (BMI  $\geq 35$  vs  $< 35$  kg/m<sup>2</sup>), ethnic origins, socio-economic status, the cause of  
34  
35 704 subfertility and polycystic ovary syndrome status. A 5% level of significance will be used  
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37 705 for all analyses.  
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#### 44 707 *Economic evaluation*

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46 708 The economic evaluation of the FFFP represents the second objective of this study.  
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48 709 The primary economic analysis will be based on the incremental cost-effectiveness ratio  
49  
50 710 (ICER), using live birth as the primary effectiveness outcome. As a secondary measure of  
51  
52 711 cost-effectiveness, QALYs will be calculated from the SF-6Dv2 [65,66], using the  
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54 712 algorithm developed by Mulhern et al [67]. QALYs will help in considering the aspect of  
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3 713 health related quality of life affected by weight reduction, healthy lifestyle and  
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5 714 psychological impacts of subfertility. A 1.5% discount rate will be considered for periods  
6  
7 715 higher than one year and sensitivity analysis will be performed [68]. To estimate the  
8  
9 716 confidence interval on the difference in costs, we will perform non-parametric analyses  
10  
11 717 with 5,000 bootstrap replications. We will also perform cost-effectiveness acceptability  
12  
13 718 curves to compare the cost-effectiveness thresholds for different costs per unit gain  
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15 719 [68,69].  
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21  
22 721 *Methodology and analyses of qualitative substudy*  
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24 722 In addition to the simple satisfaction questionnaire, an in-depth, qualitative iterative  
25  
26 723 exploration of patient's perceptions of the FFFP and medical care will be performed.  
27  
28 724 Purposive sampling will be used to create the two sub-groups in each clinic, based on the  
29  
30 725 technique of critical incidents using patients' characteristics (levels of satisfaction with  
31  
32 726 their care based on questionnaires, fertility or pregnancy outcomes, loss or gain of weight  
33  
34 727 during follow-up, ethnic group, etc.). A semi-structured interview guide will be used for the  
35  
36 728 focus groups, tailored to each trial group, with open-ended questions adapted from results  
37  
38 729 of previous studies on similar topics [70]. The 90-minute focus group meetings will be led  
39  
40 730 by a facilitator who will encourage participation and discussions [71,72]. An experienced  
41  
42 731 observer from our research group will participate remotely from Sherbrooke: he will take  
43  
44 732 notes and support the facilitator, by asking follow-up questions for example. Data will be  
45  
46 733 analyzed as soon as possible by a member of the research team, using Miles, Huberman  
47  
48 734 & Saldana's method. The analysis of the content of the focus groups as they are  
49  
50 735 conducted will help enrich the subsequent focus groups (iterative approach) [73]. A  
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3 736 preliminary analysis grid with various categories based on our previous work will be used,  
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5 737 to which emerging categories will be added successively. Regular discussions with the  
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7 738 research team will take place during the analysis process to promote a comprehensive  
8  
9  
10 739 understanding of the material collected.  
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12 740  
13  
14 741 After the trial completion, health professionals' perceptions, self-efficacy,  
15  
16 742 inter-professional collaboration, and satisfaction toward obesity management will be  
17  
18 743 evaluated through a taped-recorded semi-structured focus group interviews in each clinic,  
19  
20 744 as we have previously done [46,60,74]. Discussions among physicians, nurses, dietitians,  
21  
22 745 kinesiologists, clinic administrative personnel, and directors will be encouraged. These  
23  
24 746 focus groups will be performed and analyzed using the same methods as described above  
25  
26 747 for patients.  
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3 750 **Discussion**  
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7 752 In this paper, we present the research protocol for a multicentre pragmatic RCT  
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10 753 assessing clinical and economic outcomes of an interdisciplinary lifestyle intervention  
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12 754 targeting women with subfertility and obesity (the Fit-For-Fertility program) that takes  
13  
14 755 place 6 months before initiating fertility treatments and, for the first time, continues in  
15  
16 756 combination with usual fertility care as well as during pregnancy. This study will highlight  
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18  
19 757 on important aspects related to the effectiveness, cost-effectiveness and transferability of  
20  
21 758 such a program in a diverse population.  
22

23 759  
24  
25 760 Obesity has been shown to negatively impact on women's reproductive capacity  
26  
27 761 by reducing chances of pregnancy, with or without the help of fertility treatments  
28  
29 762 [12,16,18,19]. Women with obesity are also at a higher risk of complications during  
30  
31 763 pregnancy. Interventions supporting changes in lifestyle habits and a moderate weight  
32  
33 764 loss of 5-10% of the initial weight are highly recommended for women who are trying to  
34  
35 765 conceive [31-33]. Unfortunately, there is little evidence from large and of good quality  
36  
37 766 RCTs in this population supporting this recommendation. To our knowledge, there is only  
38  
39 767 one published RCT (the LIFESTYLE study) evaluating the impacts of a 6-month lifestyle  
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41 768 intervention on fertility outcomes among a general population of women with obesity and  
42  
43 769 subfertility, not specifically affected with PCOS [35]. Although the authors did not observe  
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45 770 an improvement in their primary outcome (vaginal birth of a healthy singleton) with their  
46  
47 771 lifestyle intervention as compared to usual care, they reported a higher proportion of  
48  
49 772 women in the intervention group achieving a spontaneous pregnancy (26.1% vs 16.2%,  
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51 773 RR [95% CI: 1.61 [1.16-2.24]) and a reduced total number of treatment cycles. Our trial  
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3 774 will therefore contribute significantly to the actual knowledge and levels of evidence in the  
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5 775 literature.

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10 777 Although this study uses a robust methodology, as all studies, it has a few  
11  
12 778 limitations. First, data collection is done mainly using self-reported questionnaires that can  
13  
14 779 result in a desirability bias. However, most of the questionnaires used have been validated  
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16  
17 780 and used in previous studies, and the bias should be similar in the intervention and control  
18  
19 781 groups. Additionally, self-reported questionnaires may introduce a recall bias when  
20  
21 782 patients have to report on previous events (e.g., costs, nutritional intake in the last month).  
22  
23 783 In that perspective, clear and detailed instructions are given to patients at each research  
24  
25 784 visit to assist them in completing the questionnaires to the best of their ability. Fourth,  
26  
27 785 there may be a degree of diversity in the FFFP delivery due to the multicentre nature of  
28  
29 786 the study. In the context of a pragmatic RCT, this diversity would in fact, reflect the real-  
30  
31 787 world reality of program implementation in different fertility clinics. While we consider this  
32  
33 788 aspect to be a strength contributing to the generalizability of the results, it could also result  
34  
35 789 in a variability in the efficacy of the intervention at each centre. To mitigate this concern,  
36  
37 790 formal training is provided to all health professionals regarding motivational interviewing  
38  
39 791 techniques, with coaching for the first meetings with participants until the professional  
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41 792 masters these skills appropriately. Fidelity of the proper use of motivational  
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43 793 communication in real clinical settings will be monitored throughout the study and  
44  
45 794 corrective measures will be initially suggested to professionals, if needed. Furthermore,  
46  
47 795 some standardization in administering the core concepts of the FFFP is provided to health  
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49 796 professionals beforehand to ensure that the interventions are as effective as possible.  
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3 798           Despite its limitations, this study is highly relevant and uses a robust study design.  
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5 799   The multicentre setting allows our work to be more generalizable, because of the diversity  
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7 800   in the sub-populations and healthcare systems enrolled. The slight differences in  
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9 801   provincial healthcare systems in Canada will allow us to examine the potential of the FFFP  
10  
11 802   to be implemented in various health care contexts. The proposed study relies on early  
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13 803   involvement of engaged patients, key decision-makers from each province, directors of  
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15 804   fertility clinics, as well as professional and public health associations, which will increase  
16  
17 805   the potential impact and use of the findings to influence policies and priorities of institutions  
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19 806   and governments. The results of our multicentre RCT will have major scientific impact  
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21 807   since they will provide important data on the importance of a lifestyle program supporting  
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23 808   women with obesity seeking fertility treatments. We believe our work will promote better  
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25 809   fertility outcomes and response to ART as well as contribute in achieving a healthy  
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27 810   pregnancy and giving birth to a healthy baby. This study will also provide valuable  
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29 811   information on potential cost-effectiveness for individuals and the healthcare system.  
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31 812   Therefore, the FIT-For-Fertility study has the potential to improve the care trajectory of  
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33 813   women with subfertility and obesity seeking fertility treatments, and do so at an acceptable  
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35 814   cost both for patients and government-funded providers.  
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3 815 ***Ethics approval and consent to participate***  
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5 816 This research study has been approved by the Research Ethics Board (REB) of *Centre*  
6  
7 817 *intégré universitaire de santé et des services sociaux de l'Estrie – CHUS (CIUSSS de*  
8  
9 818 *l'Estrie – CHUS)* (research coordinating centre) on December 10, 2018 (reference  
10  
11 819 number: MP-31-2019-2802). The central REB of *CIUSSS de l'Estrie – CHUS* acts as the  
12  
13 820 central REB for centres in the Province of Quebec and individual ethics approval has been  
14  
15 821 obtained for all participating centres in the other provinces, and will be obtained for the 7<sup>th</sup>  
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17 822 centre to be recruited. Ethics approval will be maintained annually. Informed consent is  
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19 823 obtained from participants before beginning any research procedure and supported  
20  
21 824 throughout their participation in the trial. The participant may withdraw at any time during  
22  
23 825 the study without impact on their regular medical care. If the study participant decides to  
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25 826 leave the study, the information that was collected will still be available in order to help  
26  
27 827 answer study research questions unless the participant provides written documentation of  
28  
29 828 their wish to have the data removed. All personal health information will be treated in a  
30  
31 829 confidential manner with respect to its collection, use and disclosure. Participant names  
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33 830 or potentially identifying personal health information will not leave the institution. A master  
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35 831 list that links participant identifiers to their unique participant number will be maintained at  
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37 832 all study sites, stored separately from all other study records according to local institutional  
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39 833 policies, and locked by key or password.  
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49 835 ***Consent for publication***  
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51 836 Not applicable.  
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56 838 ***Trial status***  
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3 839 Due to the widespread public health rules and restrictions implemented in the province of  
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5 840 Quebec from March 2020 due to the COVID-19 pandemic, the RCT has experienced  
6  
7 841 considerable delays in the initiation of the study in each centre. Furthermore, one centre  
8  
9 842 located in the province of Alberta had to withdraw from the trial for considerations related  
10  
11 843 to the pandemic. Recruitment has begun in Sherbrooke, Quebec, with its first  
12  
13 844 randomization in May 2019 (n=33 as of November 2021), Québec city, Quebec, in  
14  
15 845 February 2020 (n=14), Toronto, Ontario, in May 2021 (n=1), and in Montreal, Quebec, in  
16  
17 846 November 2021 (n=1). The centre in Halifax has not yet begun recruiting because of  
18  
19 847 COVID-19 restrictions in its province. Other centres are ready and allowed to start  
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21 848 recruiting at this time. We are also in the process of recruiting a 7<sup>th</sup> centre in the province  
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23 849 of Manitoba.  
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### 851 ***Availability of data and material***

852 Not applicable.

853

### 854 ***Competing interests***

855 Ferring Inc. has provided an unrestricted grant for the trial, without influencing the design  
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857

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### 21 871 ***Authors' contributions***

22  
23  
24 872 JPB is the senior author of the manuscript, he designed the study and obtained funding  
25  
26 873 as principal investigator of the trial; and MB wrote the first draft of the manuscript in  
27  
28 874 collaboration with MG, FJD and JPB. Authors have made substantial contributions to the  
29  
30 875 conception or design of the trial (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP,  
31  
32 876 FJD, RB, MS , BT, NC), contribute or will likely contribute to the acquisition of data for the  
33  
34 877 study (JPB, MG, BCM, ASM, FG, MHP, FJD, RB, AG, EG, CKN, WK, SL, BT), and/or will  
35  
36 878 likely contribute to analysis or interpretation of future data (JPB, BCM, MFL, ASM, SMR,  
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39  
40 880 manuscript for intellectual content, approved the version to be published and agreed to  
41  
42 881 be accountable for all aspects of the work.  
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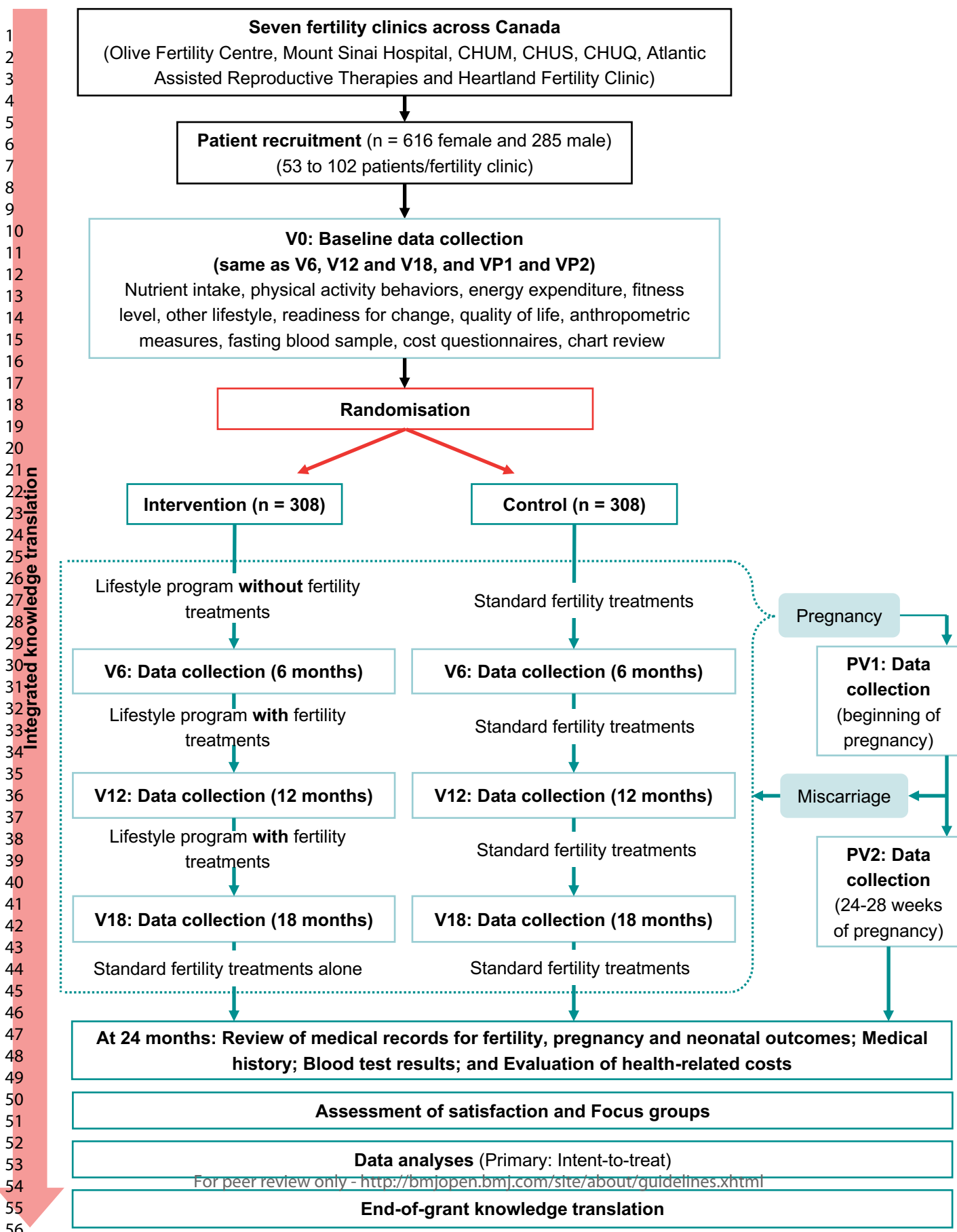
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13 1118 Figure legend:

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15 1119 Figure 1 – Fit-For-Fertility's Study Flowchart.  
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Integrated knowledge translation



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

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

|    |   |     |   |                 |
|----|---|-----|---|-----------------|
| 1  | <b>Introduction</b>                                       |     |   |                 |
| 2  |   |     |   |                 |
| 3  | Background and  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant   | <u>8-12</u>     |
| 4  | rationale   |     | studies (published and unpublished) examining benefits and harms for each intervention                        |                 |
| 5  |   |     |   |                 |
| 6  |   | 6b  | Explanation for choice of comparators   | <u>16-18</u>    |
| 7  |   |     |   |                 |
| 8  | Objectives  | 7   | Specific objectives or hypotheses   | <u>12-13</u>    |
| 9  |   |     |   |                 |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), | <u>13-21</u>    |
| 11 |   |     | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |                 |
| 12 |   |     |   |                 |
| 13 |   |     |   |                 |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |   |                 |
| 15 |   |     |   |                 |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will | <u>14</u>       |
| 17 |   |     | be collected. Reference to where list of study sites can be obtained  |                 |
| 18 |   |     |   |                 |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  | <u>15-16</u>    |
| 20 |   |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |                 |
| 21 |   |     |   |                 |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be | <u>17-21</u>    |
| 23 |   |     | administered  |                 |
| 24 |   |     |   |                 |
| 25 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  | <u>31-32</u>    |
| 26 |   |     | change in response to harms, participant request, or improving/worsening disease)                             |                 |
| 27 |   |     |   |                 |
| 28 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        | <u>30</u>       |
| 29 |   |     | (eg, drug tablet return, laboratory tests)  |                 |
| 30 |   |     |   |                 |
| 31 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 | <u>18</u>       |
| 32 |   |     |   |                 |
| 33 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       | <u>21-32</u>    |
| 34 |   |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |                 |
| 35 |   |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |                 |
| 36 |   |     | efficacy and harm outcomes is strongly recommended  |                 |
| 37 |   |     |   |                 |
| 38 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   | <u>18-22 +</u>  |
| 39 |   |     | participants. A schematic diagram is highly recommended (see Figure)  | <u>Figure 1</u> |
| 40 |   |     |   |                 |
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|---|-------------|----|---|--------------|
| 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 | <u>32-33</u> |
| 2 |             |    |   |              |
| 3 |             |    |   |              |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | <u>32-33</u> |
| 5 |             |    |   |              |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                    |     |  |              |
|----|--------------------|-----|--|--------------|
| 8  |                    |     |  |              |
| 9  |                    |     |  |              |
| 10 | Sequence           | 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 | <u>16-17</u> |
| 11 | generation         |     |  |              |
| 12 |                    |     |  |              |
| 13 |                    |     |  |              |
| 14 |                    |     |  |              |
| 15 |                    |     |  |              |
| 16 | Allocation         | 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  | <u>16-17</u> |
| 17 | concealment        |     |  |              |
| 18 | mechanism          |     |  |              |
| 19 |                    |     |  |              |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | <u>16-17</u> |
| 21 |                    |     |  |              |
| 22 |                    |     |  |              |
| 23 |                    |     |  |              |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | <u>N/A</u>   |
| 25 |                    |     |  |              |
| 26 |                    |     |  |              |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | <u>N/A</u>   |
| 28 |                    |     |  |              |
| 29 |                    |     |  |              |
| 30 |                    |     |  |              |

### 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |              |
|----|-----------------|-----|--|--------------|
| 32 |                 |     |  |              |
| 33 | Data collection | 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 | <u>21-31</u> |
| 34 | methods         |     |  |              |
| 35 |                 |     |  |              |
| 36 |                 |     |  |              |
| 37 |                 |     |  |              |
| 38 |                 |     |  |              |
| 39 |                 | 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  | <u>33-34</u> |
| 40 |                 |     |  |              |
| 41 |                 |     |  |              |
| 42 |                 |     |  |              |



|    |                                 |     |   |              |
|----|---------------------------------|-----|---|--------------|
| 1  | 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   | <u>29-31</u> |
| 2  |                                 |     |   |              |
| 3  |                                 |     |   |              |
| 4  |                                 |     |   |              |
| 5  | 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  | <u>33-36</u> |
| 6  |                                 |     |   |              |
| 7  |                                 |     |   |              |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>33-36</u> |
| 9  |                                 |     |   |              |
| 10 |                                 | 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)   | <u>34</u>    |
| 11 |                                 |     |   |              |
| 12 |                                 |     |   |              |
| 13 |                                 |     |   |              |
| 14 | <b>Methods: Monitoring</b>      |     |   |              |
| 15 |                                 |     |   |              |
| 16 | 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 | <u>29-31</u> |
| 17 |                                 |     |   |              |
| 18 |                                 |     |   |              |
| 19 |                                 |     |   |              |
| 20 |                                 |     |   |              |
| 21 |                                 |     |   |              |
| 22 |                                 | 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   | <u>31</u>    |
| 23 |                                 |     |   |              |
| 24 |                                 |     |   |              |
| 25 | 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   | <u>31-32</u> |
| 26 |                                 |     |   |              |
| 27 |                                 |     |   |              |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>31</u>    |
| 29 |                                 |     |   |              |
| 30 |                                 |     |   |              |
| 31 |                                 |     |   |              |
| 32 | <b>Ethics and dissemination</b> |     |   |              |
| 33 |                                 |     |   |              |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>39</u>    |
| 35 |                                 |     |   |              |
| 36 |                                 |     |   |              |
| 37 | 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)  | <u>30-31</u> |
| 38 |                                 |     |   |              |
| 39 |                                 |     |   |              |
| 40 |                                 |     |   |              |
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|----|-------------------------------|-----|---|--------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | <u>14</u>    |
| 2  |                               |     |   |              |
| 3  |                               |     |   |              |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | <u>N/A</u>   |
| 5  |                               |     |   |              |
| 6  |                               |     |   |              |
| 7  | 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  | <u>39</u>    |
| 8  |                               |     |   |              |
| 9  |                               |     |   |              |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | <u>40-41</u> |
| 11 |                               |     |   |              |
| 12 |                               |     |   |              |
| 13 | 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   | <u>17</u>    |
| 14 |                               |     |   |              |
| 15 |                               |     |   |              |
| 16 | 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   | <u>31</u>    |
| 17 |                               |     |   |              |
| 18 |                               |     |   |              |
| 19 |                               |     |   |              |
| 20 | 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 | <u>N/A</u>   |
| 21 |                               |     |   |              |
| 22 |                               |     |   |              |
| 23 |                               |     |   |              |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | <u>N/A</u>   |
| 25 |                               |     |   |              |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | <u>N/A</u>   |
| 27 |                               |     |   |              |
| 28 |                               |     |   |              |
| 29 | <b>Appendices</b>             |     |   |              |
| 30 |                               |     |   |              |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | <u>N/A</u>   |
| 32 |                               |     |   |              |
| 33 |                               |     |   |              |
| 34 | 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  | <u>26</u>    |
| 35 |                               |     |   |              |
| 36 |                               |     |   |              |

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2022-061554.R1   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 28-Mar-2022  |
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| <b>Primary Subject Heading</b>: | Reproductive medicine  |
| Secondary Subject Heading:      | Diabetes and endocrinology, Health economics, Nutrition and metabolism   |
| Keywords:                       | Subfertility < GYNAECOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Reproductive medicine < GYNAECOLOGY, Health economics  |

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Manuscripts

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

**Authors:** Belan M<sup>1,2</sup>, Gélinas M<sup>1</sup>, Carranza-Mamane B<sup>1,3</sup>, Langlois MF<sup>1,2</sup>, Morisset AS<sup>4</sup>, Ruchat SM<sup>5</sup>, Lavoie KL<sup>6,7</sup>, Adamo K<sup>8</sup>, Poder TG<sup>9,10</sup>, Gallagher F<sup>11</sup>, Pesant MH<sup>1,2</sup>, Jean-Denis F<sup>2</sup> and Baillargeon JP\*<sup>1,2</sup>, on behalf of the Fit-For-Fertility Study Group<sup>†</sup>

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56 49 **Protocol date and version: October 14<sup>th</sup>, 2021 (version 1)**  
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| Data category                                 | Information   |
|---|---|
| Primary registry and trial identifying number | ClinicalTrials.gov<br>NCT03908099   |
| Date of registration in primary registry      | April 9, 2019   |
| Secondary identifying numbers                 | MP-31-2019-2802, #1025047, H18-03597, 19-0317-A   |
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| Primary sponsor                               | Canadian Institutes of Health Research  |
| Secondary sponsor(s)                          | <i>Université de Sherbrooke</i><br><i>Centre hospitalier universitaire de Québec</i><br>Ferring Inc.  |
| Contact for public queries                    | Jean-Patrice Baillargeon [ <a href="mailto:Jean-Patrice.Baillargeon@USherbrooke.ca">Jean-Patrice.Baillargeon@USherbrooke.ca</a> ]   |
| Contact for scientific queries                | Jean-Patrice Baillargeon [ <a href="mailto:Jean-Patrice.Baillargeon@USherbrooke.ca">Jean-Patrice.Baillargeon@USherbrooke.ca</a> ]   |
| 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: $\geq 18$ years and $< 40$ years<br>Sexes eligible for study: women  |
|   | Inclusion criteria: infertile women with obesity (BMI $\geq 30$ kg/m <sup>2</sup> or 27 kg/m <sup>2</sup> for Asian and Latin American, based on WHO 2004), or with a BMI $\geq 27$ kg/m <sup>2</sup> 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 $\geq 15$ ), 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.  |

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3 51 **Abstract**  
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7 53 *Introduction:*  
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10 54 Women with obesity are at a higher risk of infertility as well as gestational and neonatal  
11  
12 55 complications. Lifestyle changes are universally recommended for women with obesity  
13  
14 56 seeking fertility treatments, but such intervention has only been assessed in very few  
15  
16 57 robust studies. This study's objectives are therefore to assess the clinical outcomes and  
17  
18 58 cost-effectiveness of an interdisciplinary lifestyle intervention (the Fit-For-Fertility  
19  
20 59 Program; FFFP) targeting women with obesity and subfertility in a diverse population.  
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26 61 *Methods and Analysis:*  
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28 62 This pragmatic multicentre randomized controlled trial (RCT) will include 616 women with  
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30 63 obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with polycystic ovary syndrome or at-risk  
31  
32 64 ethnicities) who are evaluated at a Canadian fertility clinic for subfertility. Women will be  
33  
34 65 randomized either to 1) the FFFP (experimental arm) alone for 6 months, and then in  
35  
36 66 combination with usual care for infertility if not pregnant; or 2) directly to usual fertility care  
37  
38 67 (control arm). Women in the intervention group benefit from the program up to 18 months  
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40 68 or, if pregnant, up to 24 months or the end of the pregnancy (whichever comes first).  
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42 69 Women from both groups are evaluated every 6 months for a maximum of 18 months.  
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44 70 The primary outcome is live birth rate at 24 months. Secondary outcomes include fertility,  
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46 71 pregnancy and neonatal outcomes; lifestyle and anthropometric measures; and cost-  
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48 72 effectiveness. Qualitative data collected from focus groups of participants and  
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50 73 professionals will also be analyzed.  
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### 75 *Ethics and Dissemination:*

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

### 83 **Trial Registration:**

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

85 Protocol version: 1.1, April 13, 2019

### 87 **Strengths and limitations of this study**

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

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3 98 will increase the feasibility of the trial and the potential impact and use of the  
4  
5 99 findings to influence policies and priorities of institutions and governments.  
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8 100 • It is not possible to blind the intervention and data collection since the tested  
9  
10 101 intervention is a lifestyle program, but the study primary outcome of live birth is a  
11  
12 102 robust clinical outcome that is not susceptible to bias.  
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14  
15 103 • Self-reported questionnaires may introduce desirability or recall biases, but the  
16  
17 104 study uses tools validated in such setting and these biases should be similar in the  
18  
19 105 intervention and control groups.  
20

21  
22 106

23  
24 107 **Keywords**

25  
26 108 Obesity, Fertility, Women, Lifestyle, Weight loss, Pregnancy, Randomized controlled trial,

27  
28 109 Live birth, Cost-Effectiveness, Polycystic ovary syndrome  
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33 111 **Word Count:** 8,029  
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38 113 Number of **tables:** 3; and **figures:** 1  
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41 114

42 115 **List of abbreviations**

43  
44 116 AEOsI, Adverse Events of Special Interest;  
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47 117 ART, assisted reproduction technology;  
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49 118 ALT, alanine amino transferase;  
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51 119  $\beta$ -hCG, human chorionic gonadotropin;  
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54 120 BMI, body mass index;  
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56 121 CHUM, Centre hospitalier universitaire de Montréal;  
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3 122 CHUQ, Centre hospitalier universitaire de Québec;  
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5 123 CHUS, Centre hospitalier universitaire de Sherbrooke;  
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8 124 CI, confidence intervalle;  
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10 125 CIUSSS, Centre intégré universitaire de santé et des services sociaux;  
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12 126 COVID-19, Coronavirus Disease 2019;  
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14 127 EOSS, Edmonton Obesity Staging System;  
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16  
17 128 FertiQoL, Fertility Quality of Life questionnaire;  
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19 129 FFQ, Food Frequency Questionnaire;  
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22 130 FSH, follicle stimulating hormone;  
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24 131 HADS, Hospital Anxiety and Depression Scale;  
25  
26 132 HbA1c, glycated hemoglobin;  
27  
28 133 HDL, high-density lipoprotein cholesterol;  
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31 134 ICER, incremental cost-effectiveness ratio;  
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33 135 IPAQ, International Physical Activity Questionnaire;  
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36 136 ITT, intent-to-treat;  
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38 137 IUSMM, Institut universitaire en santé mentale de Montréal;  
39  
40 138 IVF, *in vitro* fertilization;  
41  
42 139 LDL, low-density lipoprotein cholesterol;  
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45 140 LH, luteinizing hormone;  
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47 141 MAR, medically assisted reproduction;  
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49 142 OR, odd ratio;  
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51 143 PCOS, polycystic ovary syndrome;  
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54 144 PRECIS, PRagmatic-Explanatory Continuum Indicator Summary;  
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56 145 PRL, prolactin;  
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3 146 PSQI, Pittsburg Sleep Quality Index;  
4  
5 147 PV, Pregnancy visit;  
6  
7 148 QALY, Quality-Adjusted Life Years;  
8  
9 149 REDCap, Research Electronic Data Capture;  
10  
11 150 RCT, randomized controlled trial;  
12  
13 151 REB, Research Ethics Board;  
14  
15 152 SAE, Serious Adverse Events;  
16  
17 153 SF-6Dv2, Short Form-6 Dimensions – version 2;  
18  
19 154 SHBG, sex hormone-binding globulin;  
20  
21 155 SMART, Specific, Measurable, Attainable, Realistic and Timely;  
22  
23 156 TSH, thyroid-stimulating hormone;  
24  
25 157 V0, baseline research visit at time 0; and  
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27 158 WHO, World Health Organization.  
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5 161 **Introduction**

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10 163 *Women with obesity and infertility*

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14 165 Infertility affects approximately 10-15% of couples in Canada and the rest of North  
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16 166 America [1]. According to the International Glossary on Infertility and Fertility Care,  
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18 167 infertility is “a disease characterized by the failure to establish a clinical pregnancy after  
19  
20 168 12 months of regular, unprotected sexual intercourse or due to an impairment of a  
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22 169 person’s capacity to reproduce either as an individual or with his/her partner” [2]. For the  
23  
24 170 purpose of this study, subfertility is defined as an infertility with a reasonable probability of  
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26 171 spontaneous pregnancy without medical intervention, which excludes couples with sterility  
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28 172 or severe infertility (such as bilateral irreversible tubal factor or severe male factor).  
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30 173 Medically assisted reproduction (MAR), including ovulation induction, ovarian stimulation,  
31  
32 174 intra-uterine insemination and assisted reproductive technology (ART) [2] are part of the  
33  
34 175 current clinical management of infertility and have become more and more used and  
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36 176 effective in helping infertile couples to achieve a pregnancy [3]. Unfortunately, these  
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38 177 procedures are costly and carry risks for both women and infants. These risks can occur  
39  
40 178 at different stages of ART: ovarian stimulation (ovarian hyperstimulation syndrome,  
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42 179 thromboembolism, and ovarian torsion), oocyte retrieval (infection and bleeding) and early  
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44 180 pregnancy (ectopic or heterotopic pregnancy, and multiple gestations[4]). Although these  
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46 181 risks are rare, they can have significant consequences. Furthermore, some studies have  
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48 182 suggested that ART procedures may have negative neonatal consequences, such as  
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3 183 higher frequencies of alterations in DNA methylation patterns associated with DNA  
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5 184 imprinting disorders in children conceived through ART [5].  
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10 186 Obesity (defined operationally as a BMI  $\geq 30$  kg/m<sup>2</sup> [6]), is a known modifiable risk  
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12 187 factor associated with female infertility [7] and the population affected worldwide is high  
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14 188 enough for obesity to be recognized as a global epidemic by the World Health  
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16 189 Organization since 2000 [8]. The prevalence of obesity has been estimated to be as high  
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18 190 as 30% in Canadian and 38% in American populations, respectively [9]. More precisely,  
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20 191 21% of Canadian women of reproductive age had obesity in 2015 [10]. Women who plan  
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22 192 to get pregnant are currently more likely to be affected by obesity [11], which can  
23  
24 193 significantly affect their fertility. For instance, a very large cohort study including more than  
25  
26 194 40,000 couples estimated that women with obesity display a 78% higher risk of having  
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28 195 infertility compared to women with a normal BMI (18.50-24.99 kg/m<sup>2</sup>) (odd ratio [OR] with  
29  
30 196 95% confidence interval [CI]: 1.78 [1.63-1.95]) [12]. Women with obesity are also more  
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32 197 likely to develop polycystic ovary syndrome (PCOS), which is the leading cause of  
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34 198 anovulatory infertility, affecting 6-10% of women of childbearing age [13]. Furthermore, a  
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36 199 higher BMI has been associated with reduced pregnancy rates even in women with  
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38 200 ovulatory cycles, equating to a 4% decrease in pregnancy rate per kg/m<sup>2</sup> of BMI increase  
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40 201 in women with a BMI  $\geq 29$ kg/m [14].  
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48 202 Moreover, studies assessing MAR procedures have reported that women with  
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50 203 obesity: i) require higher doses and a longer duration of clomiphene [15] and  
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52 204 gonadotrophins [16-19] to achieve ovulation, ii) display a lower pregnancy rate per cycle  
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54 205 [18], and iii) are at a higher risk of cycle cancellation [16,18] and miscarriage [20,21].  
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3 206 Obesity also increases the risk of complications during pregnancy, such as gestational  
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5 207 diabetes, pre-eclampsia, caesarean section and intrauterine death [22,23]. In keeping with  
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7 208 the Developmental Origins of Health and Disease paradigm, maternal pre-pregnancy BMI  
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10 209 and excessive gestational weight gain are consistently associated with the early  
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12 210 development of obesity and diabetes in the offspring [24]. Obesity in childhood is closely  
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14 211 linked to adult obesity [25,26], perpetuating the intergenerational cycle of obesity [27-29].  
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16 212 Adopting a healthy lifestyle before conception and restoring of a healthy metabolic  
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18 213 environment early during pregnancy likely represents the best approach to break the  
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20 214 vicious circle of intergenerational propagation of obesity and diabetes.

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25 215 Accordingly, targeting women with obesity prior to conception may be essential to  
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27 216 reduce the burden of infertility and MAR costs, as well as obesity and cardiometabolic  
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29 217 diseases in our societies.

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### 34 35 219 *Infertility management in women with obesity seeking fertility treatments*

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40 221 To prevent the adverse effects of obesity on female fertility and on gestational and  
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42 222 neonatal health, many organizations have recommended that women with obesity should  
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44 223 be assisted, before conception, to lose weight (5 to 10 % of their initial weight) and adopt  
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46 224 a healthy lifestyle, and maintain that healthy lifestyle during pregnancy [30-33]. Results  
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48 225 from a recent systematic review support lifestyle modification prior to ART in women with  
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50 226 overweight or obesity [34]. The authors pointed out that despite the lack of RCTs in the  
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52 227 area, pre-conception weight loss in women with overweight or obesity can help improve  
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54 228 fertility and pregnancy outcomes. Out of the 7 RCTs assessing non-surgical methods of



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3 229 weight loss, including some form of lifestyle intervention, the most methodologically  
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5 230 rigorous study was a RCT published in the *New England Journal of Medicine* in 2016 [35].  
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7 231 This study compared 287 women with obesity and subfertility who were randomized to a  
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9 232 6-month structured lifestyle intervention (including 6 outpatient visits and 4 telephone  
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11 233 consultations with a nurse or dietician) and 285 women assigned to prompt fertility  
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13 234 treatments. The lifestyle intervention lasted only 6 months and was not continued during  
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15 235 fertility treatments or pregnancy. After a follow-up of 24 months, the lifestyle program did  
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17 236 not improve the live birth rate, but resulted in a significant increase in the rate of  
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19 237 spontaneous pregnancies (rate ratio [95% confidence]: 1.61 [1.16-2.24]) and reduced the  
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21 238 need for fertility treatments (rate ratio [95% confidence]: 0.78 [0.70-0.86]) [36]. In a follow-  
22  
23 239 up article, the same group of authors observed, from a hospital perspective, an  
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25 240 incremental cost-effectiveness ratio (ICER) of €15,845 per additional point of percentage  
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27 241 in the healthy live birth rate resulting from the lifestyle program compared to usual care.  
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29 242 The authors concluded that their intervention may be deemed as cost-effective, especially  
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31 243 for longer follow-up timelines, in anovulatory women, women who completed the study or  
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33 244 women  $\geq 36$  years of age [37].  
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42 246 Interestingly, in a survey asking women with obesity or overweight and considering  
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44 247 pregnancy if they were interested in adopting a healthier lifestyle prior to conception, 91%  
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46 248 reported their willingness to participate in a lifestyle program [38]. However, despite the  
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48 249 patients' motivation and the international recommendations to encourage women to  
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50 250 optimize their lifestyle before starting fertility treatments, most women with obesity do not  
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52 251 have access to such targeted lifestyle programs integrated within their fertility care.  
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55 252 Therefore, our objective is to give these women access to the Fit-For-Fertility Program  
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3 253 (FFFP), an interdisciplinary lifestyle intervention, integrated into the fertility clinic care  
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5 254 pathway. This program supports participants in adopting sustainable healthy behaviours,  
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7 255 in pre-conception, throughout fertility treatments, and during pregnancy. In response to  
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9 256 the national priority to improve the quality and costs of reproductive and perinatal care  
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11 257 established by our *Canadian network on reproductive and maternal health of women with*  
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13 258 *obesity and infertility*, we will conduct a multicentre RCT assessing the FFFP in women  
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15 259 with subfertility and obesity.  
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21 261 *Research question and hypotheses*  
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26 263 For this RCT, our research question is: Compared to usual care, does the FFFP  
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28 264 cost-effectively improve i) the live birth rate and other fertility outcomes and ii) pregnancy  
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30 265 and neonatal outcomes, in women with obesity and subfertility who seek fertility  
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32 266 treatments. We hypothesize that in comparison to prompt initiation of usual fertility care,  
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34 267 participation in the FFFP, alone for 6 months and then in combination with usual care for  
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36 268 infertility, will: 1) improve the fertility of women with obesity, 2) reduce costs associated  
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38 269 with fertility treatments, and 3) decrease the occurrence of some complications related to  
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40 270 maternal weight during the pregnancy and for their offspring.  
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47 272 *Study objectives*  
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51 274 The primary objective of this study is to assess the effectiveness of the FFFP on  
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53 275 fertility outcomes in a diverse Canadian population of women with obesity and subfertility  
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55 276 who are seeking fertility treatments. Secondary objectives are to assess the FFFP's 1)  
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3 277 cost-effectiveness, primarily in terms of costs per live birth, as well as other measures of  
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5 278 the program's costs and effectiveness measures, and 2) impacts on maternal and  
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7 279 neonatal health.  
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## 11 281 **Methods and Analysis**

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### 13 283 ***Study design***

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21 285 This study is a multicentre, two-arm, parallel pragmatic RCT comparing the FFFP to  
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23 286 usual fertility care, using quantitative and qualitative assessments (ClinicalTrials.gov:  
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25 287 NCT03908099). More specifically, we developed a pragmatic RCT based on the PRECIS-  
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27 288 2 principles [39].  
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### 31 290 ***Patient and Public Involvement***

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37 292 Our study relies on the early and regular involvement of engaged patients,  
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39 293 knowledge users and decision-makers to ensure their appropriation of the results. Policy-  
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41 294 makers and professional or patient organizations of all relevant provinces provided their  
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43 295 support to the project and partnered with the research team to facilitate the feasibility of  
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45 296 the trial and dissemination of the results. Importantly, three patient organizations  
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47 297 partnered with our team and provided strong support letters: Obesity Canada, the  
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49 298 *Association des couples infertiles du Québec* and *Conceivable Dreams*. Engaged patients  
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51 299 have been implicated early in the development of this protocol to ensure that the results  
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53 300 will be relevant for the target population and that the methods are appropriate for the  
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3 301 participants. Two previous participants from the pilot study conducted in Sherbrooke are  
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5 302 actively acting as engaged participants and have participated to each step of the trial  
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7 303 development. Before submission of the grant proposal to the funding agency, they  
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9 304 approved the research question and general objectives of the study, as well as the  
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11 305 acceptability of intervention and research visits' burden. Thereafter, they were regularly  
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13 306 consulted by the Sherbrooke research team, and they partnered with the team during  
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15 307 dedicated research meetings. Among other contributions, they have given precious input  
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17 308 on recruitment approaches, data collection's tools and timing, intervention upgrades from  
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19 309 the pilot study, as well as participants' newsletters. Other fertility clinics have committed  
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21 310 to include 1 or 2 engaged patients, who will participate at research meetings at each site.

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26 311 Engaged patients and patient organizations will also be instrumental to disseminate  
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28 312 the results of the trial to the public, in particular young women with obesity and infertility.  
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30 313 This will be performed through patient organizations' network, social media, as well as lay  
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32 314 public press conferences and "*Café scientifique*"-like activities in which our engaged  
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34 315 patients will be implicated. Such involvement of decision makers and patients increases  
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36 316 the potential impact on the public and scientific community, and use of the findings to  
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38 317 influence policies and priorities of institutions and governments.  
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### 43 44 319 ***Setting and recruitment***

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49 321 The study will be conducted in seven Canadian fertility clinics from coast to coast  
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51 322 and in an ethnically diverse population of women: Olive Fertility Centre in Vancouver  
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53 323 (British-Columbia), with its Asian population; Mount Sinai Hospital in Toronto (Ontario)  
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55 324 and *Centre hospitalier de l'Université de Montréal* (CHUM), with large multiethnic  
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3 325 communities; *Centre hospitalier universitaire de Sherbrooke* (CHUS) and *Centre*  
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5 326 *hospitalier universitaire de Québec de l'Université de Laval* (CHU de Québec-UL)  
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7 327 (Québec), which are smaller centres with mainly a Caucasian population; and Atlantic  
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9 328 Assisted Reproductive Therapies Clinic in Halifax (Nova Scotia) that has a Caucasian and  
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11 329 Afro-American populations. We are also in the process of recruiting a 7<sup>th</sup> centre, ideally in  
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13 330 the province of Manitoba.  
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19 332 Potentially eligible patients can be approached in one of two ways: 1) by a member  
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21 333 within their circle of care (nurse, physician, receptionist, etc.) who then provides contact  
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23 334 info to research staff, or 2) by responding to an advertisement indicating their interest to  
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25 335 learn more about the study. Written informed consent (see supplemental material) is  
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27 336 obtained individually for each patient during the baseline research visit (V0), after a full  
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29 337 explanation of the study's protocol and answers to the patient's questions by the research  
30  
31 338 staff, and before any data collection or study procedures. The following screening and  
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33 339 baseline data are obtained during this visit: eligibility assessment (inclusion/exclusion  
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35 340 criteria), medical history, concomitant medications, patient demographics and a baseline  
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37 341 evaluation of study outcomes. Eligibility is confirmed by the site investigator before  
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39 342 randomization.  
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### 47 344 ***Participant eligibility***

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51 346 Patients who meet the following inclusion criteria can participate in the study:

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53 347 1) Being infertile, defined as (a) failure to achieve a clinical pregnancy after  $\geq 12$   
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55 348 months of regular unprotected sexual intercourse, (b) not conceiving after having  
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3 349 attempted  $\geq 6$  months in women with irregular menstrual cycles or  $\geq 35$  years of age;  
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5 350 or (c) women with an established cause of infertility;  
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8 351 2) Aged between 18 and 40 years (since initiation of fertility treatments should not be  
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10 352 delayed in women above 40 y.o.); and  
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12 353 3) With obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or 27 kg/m<sup>2</sup> for Asian and Latin American, based on  
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14 354 WHO 2004 [40]), or with a BMI  $\geq 27$  kg/m<sup>2</sup> for women with PCOS. These women  
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16 355 display the metabolic consequences of non-PCOS women with obesity at a lower  
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18 356 BMI, and benefit more from lifestyle modifications.  
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24 358 Women presenting at least one the following exclusion criteria will not be eligible to  
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26 359 enroll in the study:

- 27  
28 360 1) Any uncontrolled medical or mental condition that contra-indicates fertility  
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30 361 treatments, based on clinical judgment of the fertility specialist;  
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33 362 2) Natural conception is impossible or highly unlikely (e.g., bilateral tubal factor,  
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35 363 severe male factor defined as a total motile sperm count  $< 5$  million on the most  
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37 364 recent partner's seminal analysis), where the only indicated MAR procedures are  
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39 365 IVF or donor sperm insemination (this exclusion criteria defines subfertility, such  
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41 366 that only subfertile couples are enrolled);  
42  
43  
44 367 3) History of recurrent spontaneous abortions ( $> 2$  miscarriages at less than 22 weeks  
45  
46 368 of gestation), with evidence of conception (such as positive  $\beta$ -hCG), within the last  
47  
48 369 12 months (since these women are more likely to have a defect that cannot be  
49  
50 370 improved by lifestyle);  
51  
52  
53 371 4) Previously diagnosed uncontrolled eating disorder or major depression that would  
54  
55 372 contra-indicate the initiation of a lifestyle intervention;  
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3 373 5) A high level of depressive state, as determined by a score for depression on the  
4  
5 374 Hospital Anxiety and Depression Scale (HADS)  $\geq 15$  [41,42], which is not a  
6  
7 375 diagnostic of depression but would also contra-indicate the initiation of a lifestyle  
8  
9 intervention;  
10 376  
11  
12 377 6) Planning for or past history of bariatric surgery, which would confound the impact  
13  
14 378 of the lifestyle intervention tested;  
15  
16  
17 379 7) Planning for or engaging in another lifestyle intervention that would be similar to  
18  
19 380 the intervention tested, e.g., including individual visits every 8 weeks or less, which  
20  
21 381 would also confound the impact of the FFFP;  
22  
23  
24 382 8) Inability to understand the language in which group sessions is provided in the  
25  
26 383 participating centre, i.e., French in the province of Quebec and English in other  
27  
28 384 provinces; and  
29  
30  
31 385 9) Unable to attend research visits at the participating centre for the next 18 months.  
32

33 386

34  
35 387 **Randomization**  
36

37 388

38  
39  
40 389 Randomization to the FFFP or control group occurs after completion of the V0 and  
41  
42 390 the eligibility assessment. Group allocation is concealed using online computerized  
43  
44 391 randomization using REDCap (Research Electronic Data Capture tool hosted at the  
45  
46 392 Université de Sherbrooke) [43] with permuted blocks of variable block sizes (2 to 6),  
47  
48 393 stratified by centre and PCOS status (yes/no). PCOS is an important potential confounder  
49  
50 394 or modifier since it decreases fertility and may affect the response to the lifestyle  
51  
52 395 intervention [13]. The randomization list has been generated by an independent  
53  
54 396 statistician and participants are randomized in one of two arms using a 1:1 ratio. The  
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3 397 randomization process is initiated by the site investigator or delegate who accesses the  
4  
5 398 web-based system and confirms patient's eligibility and informed consent. The patient's  
6  
7 399 unique study identifier and open-label study treatment allocation is then automatically and  
8  
9  
10 400 electronically delivered to the local site investigator or delegate.  
11

12 401  
13  
14 402 Following randomization, the research staff informs the fertility care team of the  
15  
16 403 patient's allocation group. On the one hand, if the participant is randomized to the control  
17  
18 404 group, the fertility care team is informed that their patient can undergo fertility treatments  
19  
20 405 immediately, according to their usual care. On the other hand, if the participant is  
21  
22 406 randomized to the intervention group, the fertility clinic will be notified that the patient has  
23  
24 407 to postpone any MAR procedures for the following 6 months, during which the patient is  
25  
26 408 enrolled in the FFFP. At the end of this first 6-month period, if the participant failed to  
27  
28 409 conceive, the research staff contacts the fertility clinic team to inform them that the  
29  
30 410 participant can now undergo usual fertility care, in combination with the FFFP.  
31  
32

33 411

## 34 412 ***Interventions***

35 413

### 36 414 Control Arm

37 415

38 416 Participants randomized to the control group are provided immediate access to the  
39  
40 417 usual fertility care, as recommended by their fertility specialist, for a maximum of  
41  
42 418 24 months. This may include lifestyle counselling by their fertility specialist and usual  
43  
44 419 fertility treatments. Since this is a pragmatic trial, they may undergo any lifestyle  
45  
46 420 approaches or consult any professionals they want on their own, but are discouraged to  
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3 421 engage in a lifestyle program similar to the FFFP, as they agreed when recruited for the  
4  
5 422 study, in order to avoid such an important contamination between intervention arms.  
6  
7

8 423

9  
10 424 Experimental Arm  
11

12 425

13  
14 426 Participants randomized to the intervention group follow the FFFP alone for the first  
15  
16 427 6 months, then in combination with usual fertility care for an additional 12 months if not  
17  
18 428 pregnant. After these 18 months, usual fertility care can continue to be provided alone for  
19  
20 429 a maximum follow-up of 24 months. The FFFP is also provided throughout gestation for  
21  
22 430 participants who achieve a successful pregnancy. Accordingly, the lifestyle program is  
23  
24 431 provided for a maximum of 18 months if there is no pregnancy, or otherwise, up to the end  
25  
26 432 of pregnancy or to a total study follow-up of 24 months (whichever comes first).  
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29

30 433

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32  
33 434 The FFFP was initially developed based on 2007 Canadian clinical practice  
34  
35 435 guidelines [44]and the approach implemented by our group at the CHUS obesity clinic  
36  
37 436 [45], and was then improved and adapted based on the experience gained from our  
38  
39 437 completed pilot study [46] and focus groups with study participants. This intervention is  
40  
41 438 aimed at supporting participants to implement progressive and sustainable lifestyle  
42  
43 439 changes. Participants attend 30-minutes individual sessions with a dietitian and a  
44  
45 440 kinesiologist, respectively, every 6 weeks for the first 6 months, then every 8 weeks for  
46  
47 441 the following 6 months, and then every 12 weeks until the end of the treatment period.  
48  
49 442 These individual meetings take place in person with the participant, or virtually using an  
50  
51 443 authorized system of telemedicine in the event that face-to-face meetings are not possible  
52  
53 444 (e.g., due to public health rules such as during the COVID-19 pandemic). Personal remote  
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3 445 contact (e.g., by phone, e-mail) is offered between in-person meetings. Patients are  
4  
5 446 guided by the dietitian and kinesiologist to formulate SMART goals (Specific, Measurable,  
6  
7 447 Attainable, Realistic and Timely) [47]. These professionals are trained in evidence-based  
8  
9 448 motivational communication skills [48], with emphasis placed on how to arm women with  
10  
11 449 the knowledge, motivation, and skills to achieve sustainable lifestyle changes. To ensure  
12  
13 450 equitable delivery of the intervention, we will implement an internal quality control and  
14  
15 451 training process. Therefore, after receiving training in motivational communication by our  
16  
17 452 leading expert (KLL), each professional will audio-record their first three individual  
18  
19 453 meetings. These recordings will be evaluated by an expert in motivational communication  
20  
21 454 using a coding scheme to verify fidelity. Feedback regarding the professional's application  
22  
23 455 of motivational communication techniques will be provided as needed, and additional  
24  
25 456 recordings may be necessary based on the trainer's assessment. After 6 and 12 months,  
26  
27 457 three more individual sessions are recorded and used to analyze the quality and fidelity  
28  
29 458 of the intervention from a research perspective. Consent for recording individual meetings  
30  
31 459 is a specific question in the informed consent form and participants have the opportunity  
32  
33 460 to revoke their agreement at any time during the course of their participation in the study.  
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40 461  
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42 462 Participants also benefit from weekly group sessions divided into 2 parts of 45  
43  
44 463 minutes each [46] (see Table 1 for group sessions' topics): 1) Workshops that cover 8  
45  
46 464 different topics addressing nutritional aspects and relevant healthy lifestyle habits  
47  
48 465 (alcohol, tobacco and motivational issues) and 2) Supervised classes of physical activity  
49  
50 466 where one of 8 different types of exercise are practiced. Women are invited to participate  
51  
52 467 in group sessions every week throughout the study, but are required to attend all 8  
53  
54 468 different sessions within the first 6 months. The spouses of participants are highly  
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469 encouraged to participate in all activities, as lifestyle modification is also important for the  
 470 partner to improve a couple's fertility [49,50].

471

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

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

472

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

478

479 **Data collection**

480

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

488

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

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

489

490

491 Participants are instructed to contact the study team between visits or phone calls

492 if they become pregnant or if any relevant situations occur (e.g., miscarriage, accident,

493 moving, changing phone number). Importantly, all clinical outcomes are ascertained with

494 participants and their medical records 24 months after participants' randomization,

495 regardless of the timing of their last research visit and the occurrence of a pregnancy.

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3 496 Pregnancy and neonatal outcomes occurring 24 months after randomization will not be  
4  
5 497 included in the primary analysis of the primary outcome, but are recorded for secondary  
6  
7 498 analyses.  
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9

10 499

11  
12 500 ***Outcome measures and their assessment***  
13

14 501

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16  
17 502 *Fertility outcomes:* The primary outcome is the cumulative incidence of live birth at  
18  
19 503 24 months. Secondary fertility outcomes are also collected from medical records at  
20  
21 504 24 months and include: the rate of biochemical pregnancy (confirmed by a positive serum  
22  
23 505  $\beta$ -hCG), ongoing confirmed pregnancy (viable pregnancy at  $\geq 10$  weeks of gestation),  
24  
25 506 spontaneous miscarriage of a confirmed pregnancy ( $< 22$  gestational weeks), multiple  
26  
27 507 gestation, spontaneous pregnancy, pregnancy following MAR procedures, doses of  
28  
29 508 fertility medications, number of MAR and/or ART cycles, number of embryo transfers, and  
30  
31 509 complications due to MAR procedures.  
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37 511 *Pregnancy outcomes (all secondary outcomes):* Total gestational weight gain,  
38  
39 512 calculated by subtracting weight at the research visit closest to the onset of pregnancy  
40  
41 513 from the last weight available in the antenatal record. Weekly gestational weight gain,  
42  
43 514 calculated by dividing total weight gestational gain by the number of weeks between the  
44  
45 515 first and last measure of weight. Pregnancy complications, which are retrieved from  
46  
47 516 medical records, include gestational diabetes, gestational hypertensive disorders,  
48  
49 517 thromboembolism, preterm birth, late fetal loss, stillbirth and post-partum hospital stay  
50  
51 518  $> 7$  days.  
52  
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3 520 *Neonatal outcomes (all secondary outcomes):* Birth weight, Apgar scores,  
4  
5 521 hypoglycemic episodes, hyperbilirubinemia, birth trauma, admission to neonatal intensive  
6  
7 522 care unit and neonatal death (up to 28 days of life), which are retrieved from medical  
8  
9 523 records.

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12 524  
13  
14 525 *Anthropometric measures and vital signs (all secondary outcomes):*  
15  
16 526 Anthropometric measures are collected at each research visit. Weight is measured with a  
17  
18 527 standard calibrated scale and height is measured with a stadiometer, based on the models  
19  
20 528 available at each centre. Foot-to-foot bioelectrical impedance analysis technology is used  
21  
22 529 to estimate the percentage of fat mass and fat free mass [52] in most, but not all centres  
23  
24 530 (models depend on each centre). Waist circumference measurement is done with a  
25  
26 531 measuring tape according to the National Institutes of Health [53]. Heart rate and blood  
27  
28 532 pressure are measured after a five-minute rest period in a sitting position. Two  
29  
30 533 measurements are taken for waist circumference and vital signs, with the average being  
31  
32 534 used for analyses.

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35 535  
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39 536 *Endocrine and metabolic blood markers (all secondary outcomes):* A blood sample  
40  
41 537 is taken at each research visit to measure different hormonal and metabolic biological  
42  
43 538 markers: luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid-stimulating  
44  
45 539 hormone (TSH), prolactin (PRL), human chorionic gonadotropin ( $\beta$ -hCG), serum  
46  
47 540 progesterone, androstenedione, estradiol, total and calculated free testosterone, sex  
48  
49 541 hormone-binding globulin (SHBG), glycated hemoglobin (HbA1c), total cholesterol,  
50  
51 542 triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein  
52  
53 543 cholesterol (LDL), cholesterol ratio, glucose, alanine amino transferase (ALT) and  
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55  
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3 544 creatinine (at initial research visit only). All markers are assessed at local laboratories,  
4  
5 545 since they are clinically indicated. Additional plasma samples are shipped to CHUS and  
6  
7 546 stored for future analyses relevant to this study's objectives, when further funding  
8  
9  
10 547 becomes available.

11  
12 548  
13  
14 549 *Lifestyle outcomes (all secondary outcomes):* Lifestyle outcomes are assessed at  
15  
16 550 each research visit. Nutritional intake is evaluated using the validated web version of the  
17  
18 551 Food Frequency Questionnaire (FFQ web), referring to the patient's nutritional  
19  
20 552 consumption of the last month. This questionnaire enables to extract data on specific food  
21  
22 553 groups and micro- or macronutrients. This questionnaire has been shown to have a  
23  
24 554 moderate validity and a good reproducibility for assessing nutrient intakes in healthy adults  
25  
26 555 [54]. Participants complete the questionnaire at the research centre at their first research  
27  
28 556 visit to ensure good understanding of the questions. For subsequent research visits,  
29  
30 557 participants have the possibility to receive a link to complete the FFQ web electronically  
31  
32 558 from home. Sleep duration and quality are evaluated by the Pittsburg Sleep Quality Index  
33  
34 559 (PSQI) questionnaire, which has been shown to have a strong reliability and validity, as  
35  
36 560 well as a moderate structural validity in the context of screening for sleep dysfunction [55].  
37  
38 561 The International Physical Activity Questionnaire (IPAQ) – short version – is used to  
39  
40 562 assess physical activity practice over the past 7 days: it was shown to have a good  
41  
42 563 repeatability of data and is as reliable as other self-administered physical activity  
43  
44 564 questionnaires [56]. Furthermore, participants are asked to wear after the research visit a  
45  
46 565 Fitbit© Flex 2 monitor during 7 consecutive days, 24 hours/day, in order to objectively  
47  
48 566 assess physical activity levels (energy expenditure, number of steps, distance walked,  
49  
50 567 time spent being inactive, lightly active, active and very active), as well as sleep data  
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3 568 (minutes spent asleep, awake and restless (when moving while sleeping)). Fitbit© devices  
4  
5 569 have been shown to accurately estimate the daily number of steps and the time spent in  
6  
7 570 bed and sleeping, while overestimating the time spent doing highly intense activities [57].  
8  
9  
10 571 However, data extracted will be mainly used to assess the change of physical activity  
11  
12 572 levels and sleep over time and not whether physical activity recommendations are met.  
13  
14 573 This estimation bias should be consistent at each measurement time point and will be  
15  
16 574 adjusted for baseline measures. The participant's physical fitness level is assessed using  
17  
18 575 the 6-minute walk test (6mWT), which has shown to be a simple, safe and low-cost test  
19  
20 576 to assess the effect of an intervention on the physical performance and walk capacity  
21  
22 577 beyond weight loss [58]. Other lifestyle habits, such as alcohol, tobacco and drugs  
23  
24 578 consumption, are measured by a study-specific self-reported questionnaire.  
25  
26  
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30  
31 580 *Quality of life (secondary outcome):* Participants' quality of life specifically related  
32  
33 581 to infertility and its treatments are assessed using the Fertility Quality of Life questionnaire  
34  
35 582 (FertiQoL) [59]. Moreover, the Short Form-6 Dimensions – version 2 (SF-6Dv2) is used to  
36  
37 583 determine Quality-Adjusted Life Years (QALY), which is an important variable for the  
38  
39 584 economic evaluation of the intervention, and to assess the general quality of life of our  
40  
41 585 participants, as well as the impact of our intervention on dimensions of quality of life.  
42  
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45 586  
46  
47 587 *Patients' perceptions and satisfaction (all secondary outcomes):* Based on  
48  
49 588 experience from previous studies [46,60,61], we will evaluate the expectations,  
50  
51 589 perceptions and satisfaction towards care provided for fertility and weight management in  
52  
53 590 all participants with a questionnaire, and will further assess these aspects in a small  
54  
55 591 sample (from both groups) using focus groups. The satisfaction questionnaire is given at  
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3 592 the 18-month research visit (V18) or at the second pregnancy research visit (PV2) if  
4  
5 593 pregnant. Focus groups will take place at 2 time points: 1) after completion of the study  
6  
7 594 by half of the participants and 2) close to the end of the trial. A total of 168 patients (27%  
8  
9 595 of all participants) will participate in the focus groups across all 7 centres, each centre  
10  
11 596 evaluating two separate sub-groups of 6 patients from the intervention and control groups.  
12  
13  
14 597 The number of participants for the second series of focus groups may be adjusted to reach  
15  
16 598 data saturation. See below under “Methodology and analyses of qualitative substudy” for  
17  
18 599 more details.  
19  
20  
21  
22

23  
24 601 *Health-related costs (secondary outcomes):* Data is collected from both the patient  
25  
26 602 and the health care system perspectives for each mother/child dyad. Costs of interest  
27  
28 603 include costs related to the FFFP, fertility treatments, adverse events or complications,  
29  
30 604 pregnancy-related visits and hospital admissions, and patient out-of-pocket expenses.  
31  
32 605 Data collection for this component will be done through patient questionnaires, charts  
33  
34 606 reviews, administrative data, and interviews with healthcare providers and fertility clinic  
35  
36 607 staff for the description of care procedures.  
37  
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40 608  
41  
42 609 *Medical history and physical health (all secondary outcomes):* A study-specific self-  
43  
44 610 administered questionnaire will be used to evaluate participant’s relevant medical history,  
45  
46 611 use of medications or natural products, and physical health during daily activities. It will  
47  
48 612 be possible with the data of this questionnaire to use the Edmonton Obesity Staging  
49  
50 613 System (EOSS), which has been shown to be an effective classification tool for obesity  
51  
52 614 risk assessment, including in the context of obesity and infertility [62].  
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3 616 **Data management, monitoring and quality assessment**  
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5 617  
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7 618 Research measures and outcomes are recorded through printed or online versions  
8  
9  
10 619 of the questionnaires and paper Case Report Forms at each relevant timepoint. These  
11  
12 620 are checked for integrity by each site's research assistant before being entered into the  
13  
14 621 centralized web-based database REDCap.  
15  
16

17 622  
18  
19 623 The central coordinator at the CHUS is responsible for training of the research staff  
20  
21 624 and health professionals (dietitians and kinesiologists), and the monitoring at all centres.  
22  
23 625 The central coordinator is also responsible for ensuring that patient safety, study  
24  
25 626 procedures and data collection are performed at each centre according to the research  
26  
27 627 protocol and Good Clinical Practice guidelines [63]. The central coordinator sends regular  
28  
29 628 queries to site coordinators to resolve discrepancies identified in the database and  
30  
31 629 performs regular onsite visits. These visits will begin after the site research teams have  
32  
33 630 recruited their first 35 participants (corresponding to one-third of participants to be  
34  
35 631 recruited per sites). Then they will be held at every 6-month intervals to assess protocol  
36  
37 632 adherence, intervention standardization, as well as data completeness and quality. During  
38  
39 633 onsite monitoring visits, approximately 10% of participants' records will be reviewed.  
40  
41 634 Concordance with the original data entered by the site will be assessed using the Cohen's  
42  
43 635 kappa statistics. A kappa coefficient below 0.60 for one site at the time of a visit, which is  
44  
45 636 considered as less than a moderate concordance [64], will require repeating the training  
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47 637 of research staff at this site and, if necessary, revising of all records of participants who  
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49 638 completed the study at this site, if possible.  
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3 640 The trial steering committee of this projects includes JPB, RB, AG, EG, WK, BCM,  
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5 641 ASM, CKN, MHP, BT, and their key research team members. An advisory committee is  
6  
7 642 also in place and includes JPB, WF, FG, MFL, KL, TP, ASM, SNR, KA, NC, PS, SL, Becky  
8  
9 643 Attenborough, now retired from the Reproductive Care Program of Nova Scotia, Celine  
10  
11 644 Braun, president of the *Association des couples infertiles du Québec*, Rahda Chari, now  
12  
13 645 retired from the Maternal Newborn Child & Youth Strategic Clinical Network, Alberta, Anne  
14  
15 646 Hayes from the Ministry of Health and Long-Term Care of Ontario, Tamil Kendall, past  
16  
17 647 provincial executive director of perinatal services BC, Martine Pageau, *Directrice du sport,*  
18  
19 648 *du loisir et de l'activité physique* at *Ministère de l'Éducation et de l'Enseignement supérieur*  
20  
21 649 *du Québec*, Daniel Riverin, past director of Mother-Child Services of Quebec Ministry of  
22  
23 650 Health and Danielle Xavier, past president of Conceivable Dream. The steering and  
24  
25 651 advisory committees meet periodically to support the coordination of the FFF study, and  
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27 652 their implication had already started at the protocol design stage.  
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### 33 653

### 35 654 **Safety measurement**

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39 656 Due to the relatively short duration of recruitment and follow-up of participants, it  
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41 657 will not be relevant to perform formal interim efficacy analyses for fertility or superiority and  
42  
43 658 interim safety analyses. Furthermore, it is very unlikely that the proposed lifestyle  
44  
45 659 intervention, which is already recommended during preconception and pregnancy in  
46  
47 660 women with obesity, would cause any safety issues. For these reasons, a Data and Safety  
48  
49 661 Monitoring Board (DSMB) will not be required for this trial, and no interim analyses will be  
50  
51 662 performed. However, Adverse Events of Special Interest (AEoSI) and Serious Adverse  
52  
53 663 Events (SAE) will be closely monitored throughout the study (see Table 3). These potential  
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664 events will be evaluated according to their causality and severity. Furthermore, after  
 665 randomization of the first 50 patients, the trial's steering committee will produce a quarterly  
 666 blinded report of AEoSI and SAE for each treatment group, including the grades of  
 667 causality with the intervention. If SAE occur, these events will be reported to the  
 668 coordination centre and local Research Ethics Board (REB), as well as the central REB  
 669 of the Province of Quebec.

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

| <b>AEoSI</b>   |
|--|
| 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 <10 <sup>th</sup> percentile of the sex-specific birth weight for gestational age reference)   |
| Newborn large for gestational (birth weight >90 <sup>th</sup> percentile of the sex-specific birth weight for gestational age reference)   |
| <b>SAE</b>   |
| 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 |

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## 673 ***Statistical analyses and sample size***

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### 675 ***Sample size calculation***

676 Experts from our *Canadian network on reproductive and maternal health of women*

677 *with obesity and infertility* agreed that for a study using a lifestyle intervention and following

678 intent-to-treat (ITT) principles, the minimal clinically important difference (MCID) in the trial

679 primary outcome, i.e., cumulative life birth rates, would be 15% between groups.

680 Therefore, a sample size of 293 women per group is required to detect a 15% absolute

681 difference between groups, with a power of 95% and alpha level of 5%, from an estimated

682 live birth rate of 35% in the control group (based on our previous pilot RCT [46]) to 50%

683 in the intervention group (nQuery advisor 4.0). Assuming a withdrawal rate of 5% (eligibility

684 criteria violation and loss to follow up), the total recruitment target is 616 women. A 95%

685 power is sufficient for most of our secondary outcome analyses. To recruit a total of 616

686 participants in 18 months, the two clinics with smaller practices (CHUS and CHUQ) will

687 need to recruit 53 participants (i.e., 39 per year), and the other 5 clinics will have to recruit

688 102 participants (i.e., 68 per year). These recruitment rates are feasible given the data

689 from our pre-trial survey of participating fertility clinics that showed that smaller practices

690 (CHUS, CHUQ) evaluate 80 to 315 new women with obesity per year, and larger

691 practices, between 265 and 810.

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3 693 *Statistical analyses of quantitative data*  
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5 694 The primary outcome is 24-month live birth cumulative incidence and the primary  
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8 695 analyses of interest will be ITT, including all randomized participants with available data  
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10 696 and no violation of eligibility criteria. The ITT analyses will be supplemented by  
11  
12 697 per-protocol analyses that will exclude women who dropped out of the study during their  
13  
14 698 first 6 months in both groups, i.e. who signified their desire to stop participating in the  
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16 699 study and/or intervention visits, or were unreachable from that period up to the end of the  
17  
18 700 trial. The per-protocol analyses will keep all women who persevered in the study for at  
19  
20 701 least 6 months and were therefore appropriately exposed to the intervention (intervention  
21  
22 702 group) and adherent to the 6-month study visit (both group). The 24-month cumulative  
23  
24 703 incidence of live birth will be compared between the two arms using the Mantel-Haenszel  
25  
26 704 test with stratification by centre and PCOS status. This analysis will be supplemented by  
27  
28 705 a survival analysis (log rank test) where the time to live birth will be used. Randomized  
29  
30 706 groups will be examined at baseline to ensure demographic and clinical data are  
31  
32 707 comparable. If substantial imbalance is found, which is very unlikely, additional analyses  
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34 708 will be carried out to assess the potential confounding effects of this imbalance, using  
35  
36 709 multiple logistic regression and Cox proportional hazards model. Similar analyses will be  
37  
38 710 used for the other clinical outcome variables that are categorical. Continuous outcome  
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40 711 variables will also be compared between groups based on either ITT or per-protocol  
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42 712 analyses, using linear mixed models with repeated measures.  
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49 713 We will also analyze the impact of the FFFP on lifestyle and anthropometric  
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51 714 outcomes, as well as other outcomes measured during a research visit, at 6 months  
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53 715 (including research visits occurring  $6 \pm 1$  months after randomization), as frequently  
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3 716 reported in previous and similar trials. For these analyses, continuous variables will be  
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5 717 compared between groups using unpaired *t* tests and categorical variables will be  
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7 718 examined using chi-square tests. Missing data due to missed research visits or incomplete  
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9 719 data collection will not be imputed, due to the relatively small sample size, such that these  
10  
11 720 analyses might be subjected to non-random missing data differing between groups.  
12  
13 721 Therefore, these tests will be corrected for potential baseline imbalances and confounding  
14  
15 722 effects as mentioned above. Variables that are not normally distributed will be  
16  
17 723 mathematically transformed to fit a normal distribution allowing their use in these models.  
18  
19 724 Subgroup analyses will be performed for all outcomes based on baseline age, level of  
20  
21 725 obesity (BMI  $\geq 35$  vs  $< 35$  kg/m<sup>2</sup>), ethnic origins, socio-economic status, the cause of  
22  
23 726 subfertility and polycystic ovary syndrome status. A 5% level of significance will be used  
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25 727 for all analyses.  
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### 33 729 *Economic evaluation*

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35 730 The economic evaluation of the FFFP represents the second objective of this study.  
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37 731 The primary economic analysis will be based on the incremental cost-effectiveness ratio  
38  
39 732 (ICER), using live birth as the primary effectiveness outcome. As a secondary measure of  
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41 733 cost-effectiveness, QALYs will be calculated from the SF-6Dv2 [65,66], using the  
42  
43 734 algorithm developed by Mulhern et al [67]. QALYs will help in considering the aspect of  
44  
45 735 health-related quality of life affected by weight reduction, healthy lifestyle and  
46  
47 736 psychological impacts of subfertility. A 1.5% discount rate will be considered for periods  
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49 737 higher than one year and sensitivity analysis will be performed [68]. To estimate the  
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51 738 confidence interval on the difference in costs, we will perform non-parametric analyses  
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53 739 with 5,000 bootstrap replications. We will also perform cost-effectiveness acceptability  
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3 740 curves to compare the cost-effectiveness thresholds for different costs per unit gain  
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5 741 [68,69].  
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10 743 *Methodology and analyses of qualitative substudy*  
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12 744 In addition to the simple satisfaction questionnaire, an in-depth, qualitative iterative  
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14 745 exploration of patient's perceptions of the FFFP and medical care will be performed.  
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16 746 Purposive sampling will be used to create the two sub-groups in each clinic, based on the  
17  
18 747 technique of critical incidents using patients' characteristics (levels of satisfaction with  
19  
20 748 their care based on questionnaires, fertility or pregnancy outcomes, loss or gain of weight  
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22 749 during follow-up, ethnic group, etc.). A semi-structured interview guide will be used for the  
23  
24 750 focus groups, tailored to each trial group, with open-ended questions adapted from results  
25  
26 751 of previous studies on similar topics [70]. The 90-minute focus group meetings will be led  
27  
28 752 by a facilitator who will encourage participation and discussions [71,72]. An experienced  
29  
30 753 observer from our research group will participate remotely from Sherbrooke: he will take  
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32 754 notes and support the facilitator, by asking follow-up questions for example. Data will be  
33  
34 755 analyzed as soon as possible by a member of the research team, using Miles, Huberman  
35  
36 756 & Saldana's method. The analysis of the content of the focus groups as they are  
37  
38 757 conducted will help enrich the subsequent focus groups (iterative approach) [73]. A  
39  
40 758 preliminary analysis grid with various categories based on our previous work will be used,  
41  
42 759 to which emerging categories will be added successively. Regular discussions with the  
43  
44 760 research team will take place during the analysis process to promote a comprehensive  
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46 761 understanding of the material collected.  
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3 763 After the trial completion, health professionals' perceptions, self-efficacy,  
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5 764 inter-professional collaboration, and satisfaction toward obesity management will be  
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7 765 evaluated through a taped-recorded semi-structured focus group interviews in each clinic,  
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9 766 as we have previously done [46,60,74]. Discussions among physicians, nurses, dietitians,  
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11 767 kinesiologists, clinic administrative personnel, and directors will be encouraged. These  
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13 768 focus groups will be performed and analyzed using the same methods as described above  
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15 769 for patients.  
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3 **772 Discussion**  
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7 774 In this paper, we present the research protocol for a multicentre pragmatic RCT  
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10 775 assessing clinical and economic outcomes of an interdisciplinary lifestyle intervention  
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12 776 targeting women with subfertility and obesity (the Fit-For-Fertility program) that takes  
13  
14 777 place 6 months before initiating fertility treatments and, for the first time, continues in  
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16 778 combination with usual fertility care as well as during pregnancy. This study will highlight  
17  
18 779 the effectiveness, cost-effectiveness and transferability of such a program in a diverse  
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20 780 population.  
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25 782 Obesity has been shown to negatively impact on women's reproductive capacity  
26  
27 783 by reducing chances of pregnancy, with or without the help of fertility treatments  
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29 784 [12,16,18,19]. Women with obesity are also at a higher risk of complications during  
30  
31 785 pregnancy. Interventions supporting changes in lifestyle habits and a moderate weight  
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33 786 loss of 5-10% of the initial weight are highly recommended for women who are trying to  
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35 787 conceive [31-33]. Unfortunately, there is little evidence from large and of good quality  
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37 788 RCTs in this population supporting this recommendation. To our knowledge, there is only  
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39 789 one published RCT (the LIFESTYLE study) evaluating the impacts of a 6-month lifestyle  
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41 790 intervention on fertility outcomes among a general population of women with obesity and  
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43 791 subfertility, not specifically affected with PCOS [35]. Although the authors did not observe  
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45 792 an improvement in their primary outcome (vaginal birth of a healthy singleton) with their  
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47 793 lifestyle intervention as compared to usual care, they reported a higher proportion of  
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49 794 women in the intervention group achieving a spontaneous pregnancy (26.1% vs 16.2%,  
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51 795 RR [95% CI: 1.61 [1.16-2.24]) and a reduced total number of treatment cycles. Our trial  
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3 796 will therefore contribute significantly to the actual knowledge and levels of evidence in the  
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5 797 literature.

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10 799         Although this study uses a robust methodology, as all studies, it has a few  
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12 800 limitations. First, it is not possible to blind the intervention and data collection, either to the  
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14 801 participants nor the professionals (research or clinical), since the tested intervention is a  
15  
16 802 lifestyle program. Although a blind research study adds robustness and limits potential  
17  
18 803 bias, we do not think this represents an important stake, because the study's primary  
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20 804 outcome is life birth, which is a robust clinical outcome that is not susceptible to bias.  
21  
22 805 Secondly, data collection is done mainly using self-reported questionnaires that can result  
23  
24 806 in a desirability bias. However, most of the questionnaires used have been validated and  
25  
26 807 used in previous studies, and the bias should be similar in the intervention and control  
27  
28 808 groups. Additionally, self-reported questionnaires may introduce a recall bias when  
29  
30 809 patients have to report on previous events (e.g., costs, nutritional intake in the last month).  
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32 810 In that perspective, clear and detailed instructions are given to patients at each research  
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34 811 visit to assist them in completing the questionnaires to the best of their ability. Thirdly,  
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36 812 there may be a degree of diversity in the FFFP delivery due to the multicentre nature of  
37  
38 813 the study. In the context of a pragmatic RCT, this diversity would in fact, reflect the real-  
39  
40 814 world reality of program implementation in different fertility clinics. While we consider this  
41  
42 815 aspect to be a strength contributing to the generalizability of the results, it could also result  
43  
44 816 in a variability in the efficacy of the intervention at each centre. To mitigate this concern,  
45  
46 817 formal training is provided to all health professionals regarding motivational interviewing  
47  
48 818 techniques, with coaching for the first meetings with participants until the professional  
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50 819 masters these skills appropriately. Fidelity of the proper use of motivational  
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3 820 communication in real clinical settings will be monitored throughout the study and  
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5 821 corrective measures will be initially suggested to professionals, if needed. Furthermore,  
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7 822 some standardization in administering the core concepts of the FFFP is provided to health  
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10 823 professionals beforehand to ensure that the interventions are as effective as possible.  
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12 824  
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14 825         Despite its limitations, this study is highly relevant and uses a robust study design.  
15  
16 826 The multicentre setting allows our work to be more generalizable, because of the diversity  
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18 827 in the sub-populations and healthcare systems enrolled. The slight differences in  
19  
20 828 provincial healthcare systems in Canada will allow us to examine the potential of the FFFP  
21  
22 829 to be implemented in various health care contexts. The proposed study relies on early  
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24 830 involvement of engaged patients, key decision-makers from each province, directors of  
25  
26 831 fertility clinics, as well as professional and public health associations, which will increase  
27  
28 832 the potential impact and use of the findings to influence policies and priorities of institutions  
29  
30 833 and governments. The results of our multicentre RCT will have major scientific impact  
31  
32 834 since they will provide important data on the importance of a lifestyle program supporting  
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34 835 women with obesity seeking fertility treatments. We believe our work will promote better  
35  
36 836 fertility outcomes and response to ART as well as contribute in achieving a healthy  
37  
38 837 pregnancy and giving birth to a healthy baby. This study will also provide valuable  
39  
40 838 information on potential cost-effectiveness for individuals and the healthcare system.  
41  
42 839 Therefore, the FIT-For-Fertility study has the potential to improve the care trajectory of  
43  
44 840 women with subfertility and obesity seeking fertility treatments, and do so at an acceptable  
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46 841 cost both for patients and government-funded providers.  
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3 842 ***Ethics approval and consent to participate***  
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5 843 This research study has been approved by the Research Ethics Board (REB) of *Centre*  
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7 844 *intégré universitaire de santé et des services sociaux de l'Estrie – CHUS (CIUSSS de*  
8  
9 845 *l'Estrie – CHUS)* (research coordinating centre) on December 10, 2018 (approval number:  
10  
11 846 MP-31-2019-2802). The central REB of *CIUSSS de l'Estrie – CHUS* acts as the central  
12  
13 847 REB for centres in the Province of Quebec and individual ethics approval has been  
14  
15 848 obtained for all participating centres in the other provinces (IWM Research Ethics Board  
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17 849 (IWK-REB); approval number: #1025047, Office of Research Ethics from the University of  
18  
19 850 British Columbia; approval number: H18-03597, Research Ethics Board from Mount Sinai  
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21 851 Hospital; approval number: 19-0317-A), and will be obtained for the 7<sup>th</sup> centre to be  
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23 852 recruited. Ethics approval will be maintained annually. Informed consent is obtained from  
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25 853 participants before beginning any research procedure and supported throughout their  
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27 854 participation in the trial. The participant may withdraw at any time during the study without  
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29 855 impact on their regular medical care. If the study participant decides to leave the study,  
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31 856 the information that was collected will still be available in order to help answer study  
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33 857 research questions unless the participant provides written documentation of their wish to  
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35 858 have the data removed. All personal health information will be treated in a confidential  
36  
37 859 manner with respect to its collection, use and disclosure. Participant names or potentially  
38  
39 860 identifying personal health information will not leave the institution. A master list that links  
40  
41 861 participant identifiers to their unique participant number will be maintained at all study  
42  
43 862 sites, stored separately from all other study records according to local institutional policies,  
44  
45 863 and locked by key or password.  
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56 865 ***Consent for publication***  
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3 866 Not applicable.  
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8 868 ***Trial status***  
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10 869 Due to the widespread public health rules and restrictions implemented in the province of  
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12 870 Quebec from March 2020 due to the COVID-19 pandemic, the RCT has experienced  
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14 871 considerable delays in the initiation of the study in each centre. Furthermore, one centre  
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16 872 located in the province of Alberta had to withdraw from the trial for considerations related  
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18 873 to the pandemic. Recruitment has begun in Sherbrooke, Quebec, with its first  
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20 874 randomization in May 2019 (n=33 as of November 2021), Québec city, Quebec, in  
21  
22 875 February 2020 (n=14), Toronto, Ontario, in May 2021 (n=1), and in Montreal, Quebec, in  
23  
24 876 November 2021 (n=1). The centre in Halifax has not yet begun recruiting because of  
25  
26 877 COVID-19 restrictions in its province. Other centres are ready and allowed to start  
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28 878 recruiting at this time. We are also in the process of recruiting a 7<sup>th</sup> centre in the province  
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30 879 of Manitoba.  
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38 881 ***Availability of data and material for site investigator and their teams***  
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40 882 Only the coordinating centre (Sherbrooke, Québec, Canada) will have access to the data  
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42 883 from all centres for data management purposes. Contract agreements have been signed  
43  
44 884 specifying that participating centres will only have access at their site's dataset, except for  
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46 885 access to coded multicenter data granted by the Steering Committee to perform approved  
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48 886 specific sub-studies, in agreement with REB approvals.  
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54 888 ***Availability of data and material for other research teams***  
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3 889 Access to anonymized multicenter data can be granted to other research teams by the  
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5 890 Steering Committee to perform approved specific sub-studies, in agreement with REB  
6  
7  
8 891 approvals.  
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10 892  
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12 893 **Competing interests**  
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14 894 Ferring Inc. has provided an unrestricted grant for the trial, without influencing the design  
15  
16  
17 895 or conduct of the trial, or the analysis or dissemination of the study's results.  
18

19 896  
20  
21 897 **Funding**  
22  
23 898 The Fit-For-Fertility Study is mainly funded by the Canadian Institutes of Health Research,  
24  
25  
26 899 and to a lower extent by an investigator-initiated trial grant from Ferring Inc (Toronto,  
27  
28 900 Ontario, Canada). Université de Sherbrooke and *Centre hospitalier universitaire de*  
29  
30 901 *Québec* have also provided a financial contribution. The views expressed in this article  
31  
32 902 are those of the authors, and no official endorsement by supporting agencies is intended  
33  
34  
35 903 or should be inferred. JPB was supported by an award from the Department of medicine  
36  
37 904 of Université de Sherbrooke (N/A award number). KL is supported by a Tier 1 Canada  
38  
39 905 Research Chair in Behavioural Medicine (CIHR, N/A grant number). KA is supported by  
40  
41 906 CIHR (PJT-178360, MOP-142298) and the NSERC (RGPIN-2017-05457) for projects  
42  
43  
44 907 related to maternal health. SMR if supported by the UQTR Junior Research Chair (N/A  
45  
46 908 grant number) in physical activity and maternal and neonatal health.  
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49 909  
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51 910 **Authors' contributions**  
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53 911 JPB is the senior author of the manuscript, he designed the study and obtained funding  
54  
55 912 as principal investigator of the trial; and MB wrote the first draft of the manuscript in  
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3 913 collaboration with MG, FJD and JPB. Authors have made substantial contributions to the  
4  
5 914 conception or design of the trial (JPB, BCM, MFL, ASM, SMR, KL, KA, TGP, FG, MHP,  
6  
7 915 FJD, RB, MS , BT, NC), contribute or will likely contribute to the acquisition of data for the  
8  
9 916 study (JPB, MG, BCM, ASM, FG, MHP, FJD, RB, AG, EG, CKN, WK, SL, BT), and/or will  
10  
11 917 likely contribute to analysis or interpretation of future data (JPB, BCM, MFL, ASM, SMR,  
12  
13 918 KL, KA, TGP, FG, MHP, RB, WF, EG, CKN, MS, BT). All authors revised critically this  
14  
15 919 manuscript for intellectual content, approved the version to be published and agreed to  
16  
17 920 be accountable for all aspects of the work.  
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### 922 ***Authorship guidelines***

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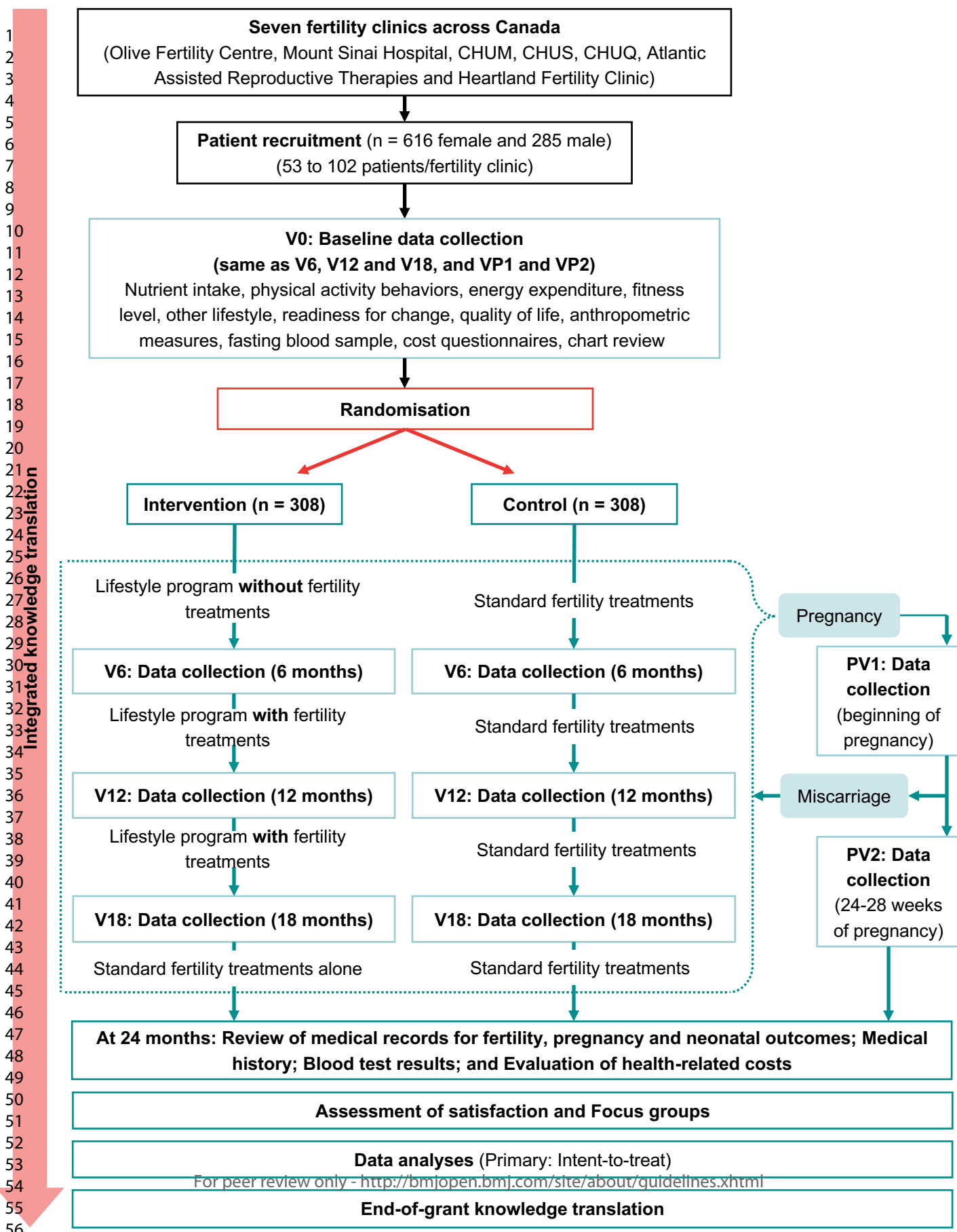
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15 1162 Figure 1 – Fit-For-Fertility's Study Flowchart.  
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## RESEARCH INFORMATION AND CONSENT FORM

**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

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**Principal investigator:** Jean-Patrice Baillargeon, Department of Medicine,  
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### For information

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

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

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

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3 46 the research project and ask them to explain any words or information you do not  
4 47 understand.

## 6 48 **NATURE AND OBJECTIVES OF THE RESEARCH STUDY**

8 49 Obesity increases the risk of developing the polycystic ovary syndrome (PCOS), which  
9 50 is characterized by the absence of ovulation, but it is also associated with fertility  
10 51 problems even in women who ovulate. In addition, obesity reduces the effectiveness of  
11 52 assisted reproduction procedures, including fertility drug treatments. It has also been  
12 53 observed that women who become pregnant and who are obese have a higher risk of  
13 54 complications during pregnancy, delivery and for the newborn. However, it has been  
14 55 shown that a slight weight loss of about 5% of total weight can restore ovulation and  
15 56 improve pregnancy rates.

17 57 The purpose of this study is to evaluate the effects of a lifestyle management program  
18 58 on fertility, the course of pregnancy and childbirth, and the health of the newborn. We  
19 59 anticipate that a total of approximately 616 patients from 7 fertility clinics across Canada  
20 60 will participate. Of this total, approximately 53 patients will be from the *CIUSSS de*  
21 61 *l'Estrie – CHUS*.

## 24 62 **STUDY PROCEDURES**

25 63 If you accept to participate in the study, you will have 2 to 5 evaluation visits at the  
26 64 Research Centre of the CHUS (RC-CHUS) (Fleurimont) over a period of about 18  
27 65 months.

28 66  
29 67 Initial visit:

- 30 68 - Measurement of your height, weight, body fat percentage (with electrical  
31 69 bioimpedance analysis) and waistline. The use of an electrical bioimpedance  
32 70 analysis in standing position involves the transmission of a very light electrical  
33 71 current through the body tissues from the soles of the feet for a few seconds.  
34 72 This electrical current causes no pain and is safe for the human health.
- 35 73 - Measurement of your blood pressure and your resting heart rate.
- 36 74 - Blood sample (approximately one tablespoon, or 15 mL).
- 37 75 - Questionnaires to fill (approximately 1 ½ hour).
- 38 76 - Walking test (walking as fast as possible for 6 minutes, going back and forth for a  
39 77 distance of 20 meters).
- 40 78 - You will be given a Fitbit monitor. You will have to wear it continuously for a  
41 79 period of 7 consecutive days. Wearing the monitor will allow us to assess your  
42 80 level of physical activity and the quality of your sleep over a week.

43 81  
44 82 The duration of this initial visit is approximately 2 ½ hours.

45 83  
46 84 After this visit, you will be assigned randomly (like at the flip of a coin) in one of the 2  
47 85 groups: the intervention group or the control group.

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3 87 **Intervention group:**

4 88 In the days following the initial visit, a second appointment will be scheduled for a one-  
5 89 hour meeting with the nutritionist and kinesiologist (30 minutes with each) to begin the  
6 90 lifestyle modification program. You will have an individualized follow-up with these  
7 91 professionals every 6 weeks (30 minutes with each) at the RC-CHUS or the first 6  
8 92 months, then every 8 weeks for the next 6 months and every 12 weeks for the last 6  
9 93 months or until delivery. During these visits, you will also be asked to fill out a short  
10 94 questionnaire concerning the costs that these meetings imply for you. In order to offer  
11 95 you more support, the nutritionist or kinesiologist will also follow up with you by phone or  
12 96 email between your appointments at the RC-CHUS. With your agreement and solely for  
13 97 the purpose of evaluating the intervention proposed in this research project, the  
14 98 individual meetings of the intervention program will be recorded.  
15 99

16 100 Participants in the intervention group will also have a group session once a week where  
17 101 different nutrition topics are discussed (8 topics, 45-minutes each), in addition to  
18 102 sessions where physical activities are practiced (8 different physical activities). You will  
19 103 be required to attend all 8 different sessions at the CHUS at Hotel-Dieu, within the first  
20 104 6 months of your participation. For the remaining duration of the project, up to 18  
21 105 months or as long as there are no contraindications during pregnancy, you are  
22 106 encouraged to continue your participation in the physical activity sessions, which last 45  
23 107 minutes.  
24 108

25 109 During the first 6 months of the program, you must agree to receive no fertility  
26 110 treatments, including fertility medications. After this period, if you are not pregnant, you  
27 111 will be seen by your fertility specialist and received required interventions according to  
28 112 standard fertility care.  
29 113

30 114 **Control group:**

31 115 From the beginning of the project, you will consult your fertility specialist and receive  
32 116 standard fertility care.  
33 117

34 118  
35 119 **For both groups:**

36 120 Evaluation visits at 6 months, 12 months and the final visit at 18 months if no  
37 121 pregnancy:

38 122 You must be fasting for the 12 hours preceding those visits. During those visits you will  
39 123 go through the same tests as the initial visit. The visits should last about 2 hours.  
40 124

41 125 **If you become pregnant, 2 visits are planned:**

42 126 1<sup>st</sup> pregnancy visit (if no evaluation visit during the last month) and final pregnancy visit  
43 127 between 24 and 28 weeks of pregnancy:

44 128 You must be fasting for the 12 hours preceding those visits. During those visits you will  
45 129 go through the same tests as the initial visit, except for the walk test that will not be  
46 130 done at the final pregnancy visit. The visits should last about 2 hours.  
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3 132 **Please refer to the calendar at the end of the present document for a global view**  
4 133 **of the tests and procedures realized during the research project.**

5 134  
6 135 In addition to these visits, we will consult your personal health records to gather  
7 136 information regarding the fertility treatments used, the progress of your pregnancy, your  
8 137 delivery and your baby. In order to obtain general health information on your baby, we  
9 138 will access his or her personal health records. We will also be able to assess some of  
10 139 the components of your health-related costs based on your hospital visits as described  
11 140 in your record. In case we need information from your personal health records in a  
12 141 hospital other than the CHUS, we will have you sign an access request.  
13 142

14 143 At the end of the project, some patients from the control and the intervention groups will  
15 144 be invited to participate in a focus group. These patients will be selected according to a  
16 145 list of criteria. The following topics will be discussed: satisfaction and perceptions of the  
17 146 care received and the impact of the program on quality of live. To ensure accurate data  
18 147 collection, the discussion will be recorded. All records will be destroyed after  
19 148 transcription.  
20 149

## 21 150 **PARTICIPANT'S COOPERATION**

22 151 We ask your collaboration to inform us as soon as possible in case of a pregnancy. For  
23 152 the participants in the intervention group, we ask that you attend all individual  
24 153 appointments in the lifestyle program and the 8 group sessions, and to notify us as soon  
25 154 as possible if you are unable to attend one of your appointments.

## 26 155 **RISKS AND INCONVENIENCES THAT MAY ARISE FROM THE SUBJECT'S** 27 156 **PARTICIPATION IN THE RESEARCH STUDY**

28 157 Your participation in this study involves minimal risk. The risks associated with having  
29 158 blood samples taken are: mild pain, dizziness, fainting, bruising, bleeding, and in rare  
30 159 cases, blood clots and infection.

31 160 For the participants in the intervention group, exercise demonstrations will be done  
32 161 under the supervision of a kinesiologist. The risk of injury is very low since the exercise  
33 162 will be done in a way to provide a gradual effort and respect your abilities. However, you  
34 163 may feel muscle aches the day after the activity, but these will be only be short-lived.

35 164 Travel is required for participation in the lifestyle program: approximately 10 meetings  
36 165 for the individual follow-ups and at least 8 group sessions.

## 37 166 **RISKS OF INFORMATION DISCLOSURE**

38 167 For the participants in the intervention group, you may feel some discomfort with the  
39 168 recording of the individual meetings with the kinesiologist and the nutritionist. In such a  
40 169 case, you will be free to ask that the recording be stopped.

41 170 For the participants in the control and intervention groups who will take part in the focus  
42 171 group, the facilitation will be designed and carried out in such a way as to make you as

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3 172 comfortable as possible, in particular by reminding everyone their right to be different.  
4 173 Furthermore, you are in no obligation to answer any questions. If you feel  
5 174 uncomfortable, you may share it with the facilitator in private or in front of the group. The  
6 175 facilitator will take the time to listen to you and see what can reassure you.  
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## 9 176 **BENEFITS RESULTING FROM YOUR PARTICIPATION IN THE RESEARCH STUDY**

10  
11 177 There may be a personal benefit to you from your participation in this research project,  
12 178 but we cannot guarantee it. Furthermore, the ensuing information from this research  
13 179 project could contribute to the advancement of knowledge in the field of infertility.  
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## 16 180 **VOLUNTARY PARTICIPATION AND RIGHT TO WITHDRAW**

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18 181 Your participation in this research project is voluntary. You are therefore free to refuse  
19 182 to participate. You may also withdraw from the project at any time, without giving any  
20 183 reason, by informing the research team.  
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22 184 Your decision not to participate in the study, or to withdraw this research project, will  
23 185 bear no consequences on your relationship with the research team.  
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25 186 Unless you inform us otherwise, if you withdraw or are withdrawn from the study, the  
26 187 information and material already collected during the study will still be stored, analysed  
27 188 or used to ensure scientific integrity of the study.  
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29 189 Any new knowledge acquired during the course of the project that could have an impact  
30 190 on your decision to continue participating in this research project will be communicated  
31 191 to you as soon as possible.  
32

## 33 192 **CONFIDENTIALITY**

### 34 193 Collection - Reason for which personal information is requested.

35 194 During your participation in this research project, the study investigator and his/her  
36 195 study staff will collect and record information about you in a study file. They will only  
37 196 collect information required to meet the scientific goals of this study.  
38 197

### 39 198 Collection – What personal information will be collected

40 199 The study file may include information from your medical chart regarding your past and  
41 200 present state of health, your lifestyle, as well as the results of tests, exams, and  
42 201 procedures that you will undergo during this research project. Your research file could  
43 202 also contain other information, such as your name, sex, date of birth and ethnic origin.  
44 203

### 45 204 Data/information storage - Protection

46 205 All the information collected will remain confidential to the extent provided by law. You  
47 206 will only be identified by a code number. The key to the code linking your name to your  
48 207 study file will be kept by the doctor in charge of this research study.  
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50 209 To ensure your safety, your participation in this research study will be mentioned in your  
51 210 medical chart. Consequently, any person or company to whom you give access to your  
52 211 medical file will have access to that information.  
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3 212 Duration of data storage

4 213 The research data will be kept during 25 years by the investigator in charge of the  
5 214 research study.  
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8 216 Dissemination of results

9 217 Results of the research could be published or discussed during scientific meetings, but  
10 218 it will be impossible to identify you.  
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14 222 Right of access for monitoring and safety

15 223 For monitoring, control, protection and safety, your study file could be examined by  
16 224 persons mandated by the institution or the Research Ethics Board. These individuals  
17 225 observe confidentiality policies.

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20 226 You have the right to access your study file in order to verify the information gathered,  
21 227 and to have it corrected if necessary.  
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23 228 **COMPENSATION**

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25 229 As compensation for the costs incurred as a result of your participation in the research  
26 230 project, you will receive an amount of 20\$ per evaluation visit. If you withdraw or are  
27 231 withdrawn from the study before its completion (or if your participation is ended), the  
28 232 compensation will be proportional to the duration of your participation.  
29 233

30 234 Your parking fees related to your evaluation visits will be covered using a prepaid code  
31 235 that we will be given for each of your research evaluation visits. This does not include  
32 236 the visits associated to the intervention program for the participants in this group.  
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35 237 **FUNDING**

36  
37 238 This project is funded mainly by the Canadian Institutes of Health Research, an agency  
38 239 of the Government of Canada responsible for investing in health research. This project  
39 240 also benefits of the support of private companies, but no amount is intended to cover  
40 241 salaries or advantages for the research team. All the financial support is dedicated to  
41 242 the realization of the study.  
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43 243 **IN CASE OF PREJUDICE**

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45 244 Should you suffer any harm as a result of your participation in the research project, you  
46 245 will receive all the care and services required by your health condition.  
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48 247 By agreeing to participate in this research project, you do not waive any of your legal  
49 248 rights nor do you release the researcher responsible for this research project and the  
50 249 establishment of their civil and professional responsibilities  
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3 250 **CONTACT PERSONS**  
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5 251 If you have any questions or problems related to the research study or if you wish to  
6 252 withdraw from the research project, you can contact the physician in charge or a person  
7 253 from the research team. Please refer to the box on page 1.

8  
9 254 If you have any questions about your rights as a participant in this research study or if  
10 255 you have any complaints, you can contact the *CIUSSS de l'Estrie – CHUS*' Office of  
11 256 Complaints and Quality of Services at [plaintes.ciusse-chus@ssss.gouv.qc.ca](mailto:plaintes.ciusse-chus@ssss.gouv.qc.ca) or at the  
12 257 following number: 1-866-917-7903.

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14 258 **MONITORING OF ETHICAL ASPECTS OF THE STUDY**  
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16 259 The Research Ethics Board of the *CIUSSS de l'Estrie – CHUS* approved this study and  
17 260 is in charge of its monitoring for the participating institutions of the Québec Health and  
18 261 Social Services Network.

19  
20 262 If you wish to contact a member of that board, you can reach the Research Ethics  
21 263 Support Services of the *CIUSSS de l'Estrie - CHUS* at [ethique.chus@ssss.gouv.qc.ca](mailto:ethique.chus@ssss.gouv.qc.ca)  
22 264 or at the following number: 819-346-1110, ext. 12856.

23  
24 265 **FOLLOW-UP STUDIES**  
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26 266 In the event that future research projects following or similar to the current project are  
27 267 conducted, would you agree to be contacted by a member of the research team to offer  
28 268 you a new participation? Of course, during this call, you would be entirely free to accept  
29 269 or refuse to participate.

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31 270  
32 271  YES  NO  
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4 273 **CONSENT**

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6 274 I have reviewed the *Information and Consent Form*. The research project and this  
7 275 information and consent form have been explained to me. My questions were answered  
8 276 and I was given the time to decide. Upon reflection, I consent to participate in this  
9 277 research study project under the conditions stated above.

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11 278 I authorize the research team to access my medical records.

12 279

13 280

14 281 I accept that the individual meetings for the purpose of the intervention program will be  
15 282 recorded.

16 283  YES  NO

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|---------------------------|--------------------------------|-------------|
| <i>Participant's name</i> | <i>Participant's signature</i> | <i>Date</i> |
| <i>(block letters)</i>    |                                |             |

32 296 I explained the research project and this Information and Consent Form to the  
33 297 participant and answered her questions.

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4 **308 CALENDAR FOR RESEARCH AND INTERVENTION VISITS**

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6 **309** Boxes marked with an X indicated tests and data collected at each visit:

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8 **310**

|   | Initial visit | 6-month visit | 12-month visit | 18-month visit (final visit) | Intervention sessions <sup>2</sup> | Weekly Group Workshops (8 weeks) <sup>2</sup> |
|---|---------------|---------------|----------------|------------------------------|------------------------------------|---|
| 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   |

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26 **311**  
27 **312** For women who become pregnant during the study:

28 **313**

|   | First pregnancy visit <sup>1</sup> | 24-28 weeks (final visit) | Intervention sessions <sup>2</sup> |
|---|------------------------------------|---------------------------|------------------------------------|
| 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                                  |

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41 **314** <sup>1</sup> Only if the last research visit > 1 month.

42 **315** <sup>2</sup> For participants in the intervention group only.



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

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

## 1 Introduction

|    |                |    |   |
|----|----------------|----|---|
| 2  |                |    |   |
| 3  | Background and | 6a | Description of research question and justification for undertaking the trial, including summary of relevant   |
| 4  | rationale      |    | studies (published and unpublished) examining benefits and harms for each intervention                        |
| 5  |                |    | <u>10-15</u>  |
| 6  |                | 6b | Explanation for choice of comparators   |
| 7  |                |    | <u>19-21</u>  |
| 8  | Objectives     | 7  | Specific objectives or hypotheses   |
| 9  |                |    | <u>14-15</u>  |
| 10 | Trial design   | 8  | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), |
| 11 |                |    | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |
| 12 |                |    | <u>15-24</u>  |

## 14 Methods: Participants, interventions, and outcomes

|    |                      |     |   |
|----|----------------------|-----|---|
| 15 |                      |     |   |
| 16 | Study setting        | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will |
| 17 |                      |     | be collected. Reference to where list of study sites can be obtained  |
| 18 |                      |     | <u>16-17</u>  |
| 19 | Eligibility criteria | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  |
| 20 |                      |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |
| 21 |                      |     | <u>17-19</u>  |
| 22 | Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be |
| 23 |                      |     | administered  |
| 24 |                      | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  |
| 25 |                      |     | change in response to harms, participant request, or improving/worsening disease)                             |
| 26 |                      |     | <u>32-34</u>  |
| 27 |                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        |
| 28 |                      |     | (eg, drug tablet return, laboratory tests)  |
| 29 |                      |     | <u>31-32</u>  |
| 30 |                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 |
| 31 |                      |     | <u>20-21</u>  |
| 32 | Outcomes             | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       |
| 33 |                      |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |
| 34 |                      |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |
| 35 |                      |     | efficacy and harm outcomes is strongly recommended  |
| 36 |                      |     | <u>24-34</u>  |
| 37 | Participant timeline | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   |
| 38 |                      |     | participants. A schematic diagram is highly recommended (see Figure)  |
| 39 |                      |     | <u>20-26 +</u>  |
| 40 |                      |     | <u>Figure 1</u>   |

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including  
 2 clinical and statistical assumptions supporting any sample size calculations 34-36

3  
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 34-36

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 6 **Methods: Assignment of interventions (for controlled trials)**

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 8 Allocation:

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 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any  
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
 13 or assign interventions 19-20

14  
 15 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,  
 16 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 19-20  
 17 mechanism

18  
 19 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to  
 20 interventions 16-17, 19-20

21  
 22 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome  
 23 assessors, data analysts), and how 40

24  
 25 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's  
 26 allocated intervention during the trial 40

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 29  
 30 **Methods: Data collection, management, and analysis**

31  
 32 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related  
 33 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
 34 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. 24-38  
 35 Reference to where data collection forms can be found, if not in the protocol

36  
 37 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be  
 38 collected for participants who discontinue or deviate from intervention protocols 35-36

|    |                                 |     |   |              |
|----|---------------------------------|-----|---|--------------|
| 1  | 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   | <u>31-33</u> |
| 2  |                                 |     |   |              |
| 3  |                                 |     |   |              |
| 4  |                                 |     |   |              |
| 5  | 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  | <u>35-38</u> |
| 6  |                                 |     |   |              |
| 7  |                                 |     |   |              |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>35-38</u> |
| 9  |                                 |     |   |              |
| 10 |                                 | 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)   | <u>35-36</u> |
| 11 |                                 |     |   |              |
| 12 |                                 |     |   |              |
| 13 |                                 |     |   |              |
| 14 | <b>Methods: Monitoring</b>      |     |   |              |
| 15 |                                 |     |   |              |
| 16 | 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 | <u>29-31</u> |
| 17 |                                 |     |   |              |
| 18 |                                 |     |   |              |
| 19 |                                 |     |   |              |
| 20 |                                 |     |   |              |
| 21 |                                 |     |   |              |
| 22 |                                 | 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   | <u>31</u>    |
| 23 |                                 |     |   |              |
| 24 |                                 |     |   |              |
| 25 | 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   | <u>31-32</u> |
| 26 |                                 |     |   |              |
| 27 |                                 |     |   |              |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>31</u>    |
| 29 |                                 |     |   |              |
| 30 |                                 |     |   |              |
| 31 |                                 |     |   |              |
| 32 | <b>Ethics and dissemination</b> |     |   |              |
| 33 |                                 |     |   |              |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>42</u>    |
| 35 |                                 |     |   |              |
| 36 |                                 |     |   |              |
| 37 | 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)  | <u>32-33</u> |
| 38 |                                 |     |   |              |
| 39 |                                 |     |   |              |
| 40 |                                 |     |   |              |
| 41 |                                 |     |   |              |
| 42 |                                 |     |   |              |
| 43 |                                 |     |   |              |
| 44 |                                 |     |   |              |
| 45 |                                 |     |   |              |
| 46 |                                 |     |   |              |

|    |                               |     |   |                            |
|----|-------------------------------|-----|---|----------------------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | <u>17</u>                  |
| 2  |                               |     |   |                            |
| 3  |                               |     |   |                            |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | <u>N/A</u>                 |
| 5  |                               |     |   |                            |
| 6  |                               |     |   |                            |
| 7  | 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  | <u>42</u>                  |
| 8  |                               |     |   |                            |
| 9  |                               |     |   |                            |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | <u>43-44</u>               |
| 11 |                               |     |   |                            |
| 12 |                               |     |   |                            |
| 13 | 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   | <u>43</u>                  |
| 14 |                               |     |   |                            |
| 15 |                               |     |   |                            |
| 16 | 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   | <u>32-33</u>               |
| 17 |                               |     |   |                            |
| 18 |                               |     |   |                            |
| 19 |                               |     |   |                            |
| 20 | 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 | <u>15-16</u>               |
| 21 |                               |     |   |                            |
| 22 |                               |     |   |                            |
| 23 |                               |     |   |                            |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | <u>45</u>                  |
| 25 |                               |     |   |                            |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | <u>N/A</u>                 |
| 27 |                               |     |   |                            |
| 28 |                               |     |   |                            |
| 29 | <b>Appendices</b>             |     |   |                            |
| 30 |                               |     |   |                            |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | <u>Supplementary files</u> |
| 32 |                               |     |   |                            |
| 33 |                               |     |   |                            |
| 34 | 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  | <u>26</u>                  |
| 35 |                               |     |   |                            |
| 36 |                               |     |   |                            |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
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 41  
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