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Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using total diet replacement products: a protocol for a randomised controlled trial

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1 **Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using**
2 **total diet replacement products: a protocol for a randomised controlled trial**^a

4 Susan A Jebb¹

5 Nerys M Astbury¹

6 Sarah Tearne¹

7 Alecia Nickless¹

8 Paul Aveyard¹

9

10 *Corresponding Author: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary
11 Care Building, Woodstock Road, Oxford, OX2 6GG, email: nerys.astbury@phc.ox.ac.uk,
12 tel: 01865 617871

13

14 ¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford UK

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16 ^a This trial is sponsored by the University of Oxford, Clinical Trials and Research Governance, Joint
17 Research Office, Block 60, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, UK.

18

19 Keywords: Obesity, diet, weight loss, primary care

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2
3 20 **ABSTRACT**

4
5 21 **Introduction**

6 22 The global prevalence of obesity has risen significantly in recent decades. There is a pressing need to
7
8 23 identify effective interventions to treat established obesity that can be delivered at scale. The aim of
9
10 24 the DROPLET study is to determine the clinical effectiveness, feasibility and acceptability of referral
11
12 25 to a low-energy total diet replacement programme compared with usual weight management
13
14 26 interventions in primary care.

15 27 **Methods and Analysis**

16 28 The DROPLET trial is a randomised controlled trial comparing a low-energy total diet replacement
17
18 29 programme with usual weight management interventions delivered in primary care. Eligible patients
19
20 30 will be recruited through primary care registers and randomised to receive a behavioural support
21
22 31 programme delivered by their practice nurse or a referral to a commercial provider offering an initial
23
24 32 810 kcal/d low-energy total diet replacement programme for 8 weeks, followed by gradual food
25
26 33 reintroduction, along with weekly behavioural support for 24 weeks. The primary outcome is weight
27
28 34 change at 12 months. The secondary outcomes are weight change at 3 and 6 months, the
29
30 35 proportion of participants achieving 5% and 10% weight loss at 12 months and change in fat mass,
31
32 36 HbA1c, LDL cholesterol and systolic and diastolic blood pressure at 12 months. Data will be analysed
33
34 37 on the basis of intention to treat. Qualitative interviews on a sub-sample of patients and healthcare
35
36 38 providers will assess their experiences of the weight loss programmes and identify factors affecting
37
38 39 acceptability and adherence.

39 40 **Ethics and dissemination**

40 41 This study has been reviewed and approved by NHS/HRA Research Ethics Committee (Ref:
41
42 42 SC/15/0337). The trial findings will be disseminated to academic and health professionals through
43
44 43 presentations at meetings and peer reviewed journals and to the public through the media. If the
45
46 44 intervention is effective, the results will be communicated to policymakers and commissioners of
47
48 45 weight management services.

49 46 **Trial registration number**

50 47 ISRCTN75092026
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3 48 **STRENGTHS & LIMITATIONS**

- 4 49 • This study is the first randomised controlled trial of a low-energy total diet replacement
5 programme for weight management in routine primary care and the largest randomised
6 50 controlled trial to date of low-energy total diet replacement programmes for weight loss.
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10 52 • This intervention is based on a model of care where GPs refer patients to a programme
11 delivered in the community by a commercial provider, which, if successful, could be readily
12 53 adopted into practice without the need for specialist training.
13 54
14 55 • The primary outcome is weight at one year. Although this is 9 months after the low-energy
15 total diet replacement, epidemiological evidence suggests that any weight lost will continue
16 56 to be regained beyond one year.
17 57
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19 58 • The intention of obesity treatment programmes is to improve long-term health but this
20 study does not include morbidity or mortality outcomes.
21 59
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23 60 • The counsellors delivering the low-energy total diet replacement programme are trained to
24 a standard protocol, whereas practice nurses delivering the comparator are not; this may
25 61 introduce heterogeneity in the comparator 'usual-care' intervention.
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63 INTRODUCTION

64 The prevalence obesity worldwide has more than doubled since 1980¹. According to the latest
65 estimates from the World Health Organization (WHO) more than 1.9 billion adults were overweight,
66 of whom 600 million were obese, representing 39% and 13% of the world's adult population,
67 respectively². Obesity is associated with premature mortality³ but also substantial morbidity,
68 including significantly increased risks of diabetes, cardiovascular disease and most non-smoking
69 related cancers, as well as physical impairments linked to excess weight such as breathlessness, joint
70 problems and back pain⁴. Collectively this creates a burden of ill-health and reduced quality of life
71 for individuals, additional treatment costs to the NHS and reductions in economic productivity⁵.
72 While high priority must be given to prevent future cases of obesity, in the short term there is a
73 pressing need to identify effective interventions to treat established obesity. Research has shown
74 that even modest reductions in weight can bring significantly reduced risks of disease. For example,
75 in the US Diabetes Prevention Program (DPP) individuals randomised to an intensive lifestyle
76 intervention lost 7kg by the end of the first year. Although some of this weight was regained, the
77 intensive lifestyle group remained 4 kg lighter than the usual care group at four years and this
78 reduced the incidence of diabetes by 58% relative to usual care⁶ with benefits persisting to at least
79 15 year follow-up despite weight regain⁷.

80 Primary care is an important setting for weight management interventions to reduce multi-
81 morbidity. However, although a number of interventions have been shown to be effective in
82 intensive research studies, this success has not always been replicated in routine settings. For
83 example, there was no significant reduction in weight when a weight loss programme adapted from
84 the DPP was delivered by primary care teams⁸. Our recent review of interventions suitable for use in
85 routine care⁹ and a second review, using slightly different inclusion criteria, of interventions
86 specifically delivered in primary care¹⁰ both concluded that behavioural weight management
87 interventions led by primary care practitioners were ineffective. This may relate in part to the
88 complexity of advice needed for successful dietary change and the need for frequent contact to
89 provide support which exceeds the capacity of routine primary care systems. Currently, the most
90 effective option for weight management in primary care is GP referral to a commercial provider
91 offering group-based support, and our meta-analysis showed a mean reduction in weight of 2.3 kg
92 over no intervention at one year⁹. However, greater weight losses would be expected to bring
93 greater health gains.

94 Very low energy diets (VLEDs) have been used for weight loss over many years in specialist settings.
95 A VLED is defined as a diet providing ≤ 800 kcal a day, based on the use of specially formulated
96 products designed as the sole source of nutrition during periods of total diet replacement. When

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3 97 used as directed, these formula products meet 100% of the dietary reference values for vitamins,
4 98 minerals and trace elements and are enriched with high biological-value protein. A recent systematic
5 99 review and meta-analysis of the available randomised controlled trials showed that behavioural
6
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8 100 weight management interventions incorporating a VLED led to 3.9 kg greater weight loss at one year
9
10 101 compared with intensive specialist-delivered behavioural programmes¹¹. However, most of the trials
11 102 included in this review were small, typically including only 50-100 participants that were treated by
12 103 obesity specialists and many trials had methodological limitations.

14 104 UK guidance from the National Institute for Health and Care Excellence (NICE) recommends that
15 105 VLEDs may only be used for a maximum of 12 weeks in people who have a clinical need to lose
16 106 weight rapidly, such as prior to a knee replacement surgery or those seeking fertility services, but
17 107 recommends against their routine use to manage obesity¹². Clinical guidance in the USA does not
18
19 108 recommend the routine use of VLEDs, but rather suggests that their use “*may* be reasonable in
20 109 limited circumstances, but only when provided by trained practitioners in a medical care setting
21 110 where medical monitoring and high intensity lifestyle intervention can be provided”¹³.

22 111 Nevertheless, there has been growing interest in the potential for routine use of weight loss
23 112 programmes similar to traditional VLEDs, in so far as they incorporate a period of total diet
24 113 replacement using specially formulated products as the sole source of nutrition, but where the
25 114 energy content is more than 800kcal/day but less than 1600 kcal/day. The NICE guidelines suggest
26 115 that this type of low-energy diet could be considered for weight management, providing care is
27 116 taken to ensure they are nutritionally complete¹². There is one observational report (n = 91) on the
28 117 use of these low-energy total diet replacement programmes in primary care which found that 64%
29 118 of participants completed the 810kcal/day dietary programme, defined as either 12 weeks or
30 119 reaching 20kg weight loss, with a mean weight loss of 16.9 kg (standard deviation (SD) = 6.0 kg). One
31 120 third of participants starting the programme maintained a weight loss of ≥ 15 kg at 12 months¹⁴. A
32 121 large randomised controlled trial, the DiRECT study, is currently underway to investigate whether
33 122 this type of low-energy total diet replacement programme can be used to treat type 2 diabetes
34 123 among people who are also overweight¹⁵. It will compare the health effects of the current best-
35 124 available type 2 diabetes care with those achieved through weight management based on a low-
36 125 energy total diet replacement programme. While this will provide important mechanistic evidence
37 126 on the links between weight loss and diabetes risk, it will be delivered by specialist staff with specific
38 127 training and will not address the wider challenges associated with the use of such programmes for
39 128 routine weight management programmes led by non-specialists in routine care.

40 129 To fill this evidence gap we will conduct a randomised controlled trial to specifically test the
41 130 effectiveness of a GP referral to a community-based low energy total diet replacement programme

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3 131 for patients who are obese and likely to benefit from weight loss. It will assess the clinical
4 132 effectiveness of a weight loss intervention by measuring weight loss and the change in biomarkers of
5 133 cardiovascular risk at 12 months relative to weight loss advice provided by practice nurses. This
6 134 comparator is intended to represent 'usual care', though in practice most patients who are obese
7 135 are not offered support to lose weight.

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11 136 The context for this trial follows the established model for GP referral to community group-based
12 137 weight loss programmes¹⁶. This uses the generic authority and credibility of health professionals to
13 138 motivate patients to consider weight management and the specialist knowledge of the commercial
14 139 provider to guide the intervention and offer frequent contact and behavioural support to the
15 140 patient. If successful, it will provide another option for weight management that can be offered to
16 141 patients in primary care, and GPs will be able to guide patients towards the treatment which best fits
17 142 their circumstances and preferences. This trial will specifically test whether a partnership between
18 143 GPs and providers will allow for the safe provision of low energy total diet replacement programmes
19 144 even for patients with multi-morbidity who may gain the greatest benefits from such interventions
20 145 but who may also need clinical oversight and adjustments to some of their medications as they lose
21 146 weight. It will provide the opportunity for qualitative research to investigate the perspectives of
22 147 patients and health care practitioners on this type of treatment.
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33 149 **OBJECTIVE:**

34 150 The aim of the DROPLET trial is to determine the clinical effectiveness, feasibility and acceptability of
35 151 referral to a low-energy total diet replacement programme compared with usual weight
36 152 management interventions in primary care.
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3 153 **METHODS:**

4 154 **Design and Setting**

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6 155 The study will take place in general practices in England. Designed as an individually randomised,
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8 156 two arm and parallel group superiority trial with the primary endpoint as objectively measured
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10 157 changes in body weight from baseline to 12 months. Due to the nature of the intervention it will not
11
12 158 be possible to blind participants, clinicians or some of the study team to the treatment allocation
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14 159 after randomisation.
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16 161 **Recruitment**

17 162 Around 10 general practices will be identified to take part through the clinical research networks.
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19 163 Recruited practices will be asked to conduct a search of their electronic health records in order to
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21 164 identify suitable patients for the DROPLET study. As a result of this search, eligible patients will be
22
23 165 sent an invitation letter from their GP as part of a staggered mail out. Patients will be encouraged to
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25 166 call the research team if they are interested in taking part.
26
27 167 GPs may also identify eligible patients during routine consultations. The GP will provide the patient
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29 168 with an invitation letter and suggest that the patient ring the study team. The study team will
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31 169 provide the potential participants with information on what taking part in the study will entail, and
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33 170 an initial assessment of suitability to take part. Those who make contact and self-report meeting the
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35 171 eligibility criteria will be scheduled for a baseline/enrolment appointment.

34 172 **Inclusion Criteria:**

- 35 173
- 36 174 • Participant is willing and able to give informed consent for participation in the study.
 - 37 175 • Aged 18 years or above.
 - 38 176 • Body Mass Index ≥ 30 kg/m².
 - 39 177 • Likely to benefit from weight loss in the GP's opinion.

42 178 **Exclusion criteria:**

- 43 179
- 44 180 • Unable to understand English
 - 45 181 • Currently or recently (within 3 months of study entry) attended a weight management
46 182 programme or currently participating in another weight loss study.
 - 47 183 • Had bariatric surgery, or scheduled bariatric surgery.
 - 48 184 • Pregnant, breastfeeding, or planning to become pregnant during the course of the study.
 - 49 185 • Receiving insulin therapy
 - 50 186 • Heart attack or stroke within the last 3 months,
 - 51 187 • Heart failure of grade II New York Heart Association and more severe
 - 52 188 • Angina, arrhythmia, including atrial fibrillation or prolonged QT syndrome
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- 187 • Taking MAOI medication
- 188 • Taking anticoagulant medication (e.g. warfarin)
- 189 • Taking varenicline (smoking cessation medication)
- 190 • Chronic renal failure of stage 4 or 5
- 191 • Active liver disease (except NAFLD) a past history of hepatoma or within 6 months of onset
- 192 of acute hepatitis.
- 193 • People having active treatment for cancer other than skin cancer treated with curative intent by
- 194 local treatment only or people taking hormonal or other long-term secondary prevention
- 195 treatment after initial cancer treatment.
- 196 • Active treatment or investigation for possible or confirmed gastric or duodenal ulcer.
- 197 Maintenance treatment with acid-suppression is not a contra-indication.
- 198 • Porphyria
- 199 • Scheduled for surgery within 12 months
- 200 • A member of household is already enrolled in the study
- 201 • Unwilling to provide blood samples
- 202 • Patients that the GP judges not able to meet the demands of either treatment programme
- 203 or measurement schedule. This may include severe medical problems not listed above or
- 204 severe psychiatric problems including substance misuse that make following the treatment
- 205 programme or adhering to the protocol unlikely.

206

207 **Participant Flow**

208 The baseline/eligibility assessment will be scheduled with a practice nurse or health care assistant at
209 their own GP practice, where informed consent for participation in the study will be obtained before
210 eligibility will be formally assessed. After demographic information and all baseline measurements
211 have been collected the participant will be randomised to the allocated treatment group using the
212 online randomisation system. The patients' own GP will be notified by letter of the enrolment and
213 randomisation of their patient, so that it may be documented on their medical record. Participants
214 allocated to the low-energy total diet replacement programme and taking medications for type 2
215 diabetes, hypertension or high cholesterol will have their medications reviewed by a prescribing
216 member of the clinical care team. During this medication review the clinician will decide what
217 changes to medications are required at the time the participant commences the low energy total
218 diet replacement programme, with guidance provided by the study team (Supplementary Figure 1).
219 In addition, participants randomised to the low-energy total diet replacement group and who take
220 anti-hypertensive medications will be provided with a home blood pressure monitor and asked to

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3 221 record blood pressure once daily during the weight loss phase (weeks 1-12). These readings can be
4 222 used to guide clinicians with any further changes in hypertension medications.
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6 223 All participants will be invited to attend a 4 week follow-up appointment with the practice nurse.
7
8 224 The main purpose of the visit is a clinical review of medication, including any adjustments required.
9
10 225 Any changes in medication will be recorded on the concomitant medication log. Participants will be
11 226 invited to attend further follow-up visits with a member of the trial team at the GP practice at 12
12 227 weeks, 6 months and 12 month following randomisation. Participant flow through the study is
13
14 228 outlined in **Figure 1**.
15
16 229

17 230 **Sample size**

18
19 231 The total number of participants to be recruited for this study is 270. This is based on a sample size
20 232 calculation for the primary outcome using equal variance independent samples t-test assuming a
21 233 difference between groups at 12 months of 4kg with a standard deviation in both groups of 9kg;
22 234 obtained from a meta-analysis of published studies¹¹. The sample size has been inflated by 20%, to
23 235 account for attrition, and assumes 90% power and two-sided alpha of 5%.
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27 237 **Randomisation**

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29 238 All eligible, consenting participants will be randomised with an allocation ratio of 1:1 to low-energy
30 239 total diet replacement or usual care programmes using an online program which reveals group
31 240 allocation as per a computer-generated randomisation list. The randomisation criteria will be
32 241 validated by an independent statistician. Allocation will be stratified by GP Practice and baseline BMI
33 242 ($\leq 35\text{kg}/\text{m}^2$ or $> 35\text{kg}/\text{m}^2$) using stratified block randomisation with randomly varying block sizes of
34 243 size 2, 4, and 6. The randomisation software ensures full allocation concealment, with the allocation
35 244 group only revealed to the person performing the randomisation once a study identifier and
36 245 required stratification details have been entered.
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3 246 **Interventions**

4 247 **Low-energy total diet replacement**

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6 248 The programme offered to participants randomised to the active intervention will be provided by
7
8 249 Cambridge Weight Plan Ltd.™ Northants., United Kingdom.

9
10 250 Following randomisation participants allocated to this group will be referred to a local Cambridge
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12 251 Weight Plan Counsellor who will invite the participant to attend regular appointments for 24 weeks.
13
14 252 These appointments consist of motivational support, encouragement, reassurance and problem-
15
16 253 solving.

17 254 During the first 12 weeks the participant will meet with their counsellor weekly. Patients will be
18
19 255 asked to follow a programme based on using formula meal replacement products (soups, shakes and
20
21 256 bars) and milk comprising 810kcal/day (3389kJ/d). For the first eight weeks patients will be advised
22
23 257 to replace *all* their usual foods and drinks with four of the formula products daily, 750ml of skimmed
24
25 258 milk, 2.25L of water or other non-calorific drinks and a fibre supplement (total diet replacement
26
27 259 stage). During the first two weeks, the formula products will be limited to liquid products (soups and
28
29 260 shakes), but from week 3 onwards participants will have the option to include meal replacement
30
31 261 bars as part of the formula product allowance. After eight weeks there will be a four week stepwise
32
33 262 reduction in the use of formula meal replacement products and a gradual re-introduction of food-
34
35 263 based meals. The weight maintenance phase from week 12 to 24 will involve consuming only one
36
37 264 formula product a day, with the remainder of diet provided by food. This weight maintenance phase
38
39 265 will include a recommendation to return to the total diet replacement stage for periods of up to 4
40
41 266 weeks if a participant regains 1kg or more than their weight measured at 12 weeks.

42 267 All consultations with consultants and formula products will be provided to participants by their
43
44 268 nominated consultant and will be free of charge for the first 24 weeks, after which the intervention
45
46 269 will end. Participants in both groups will be free to choose whether or not to continue with the
47
48 270 programme, but at their own cost.

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50 272 **Comparator**

51 273 The comparator intervention will consist of the usual weight management programme provided by a
52
53 274 member of the practice nurse team who has been trained to offer a weight loss programme. The
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55 275 trial will take place only in practices where this is routine care. Participants allocated to the usual
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57 276 care group will not be prevented from attending other weight management groups if they choose to
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59 277 do so, but no NHS referrals to these schemes will be offered during the trial. The practice nurse will
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278 give participants a copy of the booklet " So you want to lose weight ... for good" ¹⁷. This 47 page
279 booklet provides advice akin to a behavioural weight management programme. The aim is to

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3 280 produce a weight loss goal of 0.5 to 1kg/week. It includes goal setting, advice on portion control and
4 281 physical activity, other behavioural strategies, and monitoring and feedback on progress. Nurses will
5 282 be asked to offer a programme for 12 weeks, at a frequency that is usually used in the practice (e.g.
6 283 weekly or bi-weekly).
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11 285 **Outcomes:**

12 286 **Primary outcome**

- 13
14 287 • Change in body weight from baseline to 12 months

15 288 **Secondary outcomes**

- 16 289 • Change in body weight from baseline at 3 and 6 months
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18 290 • Proportion of participants achieving 5% and 10% weight loss at 12 months
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20 291 • Change in fat mass between baseline and 12 months
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22 292 • Change in LDL cholesterol concentrations between baseline and 12 months
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24 293 • Change in HbA1c between baseline and 12 months
25
26 294 • Change in systolic and diastolic blood pressure between baseline and 12 months
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28 295 **Exploratory outcomes**

- 29 296 • Change in fat mass from baseline to 12 weeks and from baseline to 6 months.
30 297 • Change in waist circumference from baseline to 3, 6, and 12 months.
31
32 298 • Change in triglyceride and HDL cholesterol concentrations between baseline and 12 months.
33 299 • Change in fasting glucose and insulin concentrations and change in HOMA-IR, HOMA-%S and
34 300 HOMA-%B between baseline and 12 months.
35
36 301 • Change in systolic and diastolic blood pressure between baseline and 3 months and between
37 302 baseline and 6 months.
38
39 303 • Change in QRISK between baseline and 12 months.
40
41 304 • Change in the EQ-5D scale between baseline and 12 months
42
43 305 • Change in obesity related quality of life measured with the OWLQOL between baseline, 3, 6, and
44 306 12 months.
45
46 307 • Proportion of people continuing their weight loss attempt and following the prescribed
47 308 programme at 4, 8, and 12 weeks.
48
49 309 • The number of weight control behaviours that participants are using assessed using the OxFAB
50 310 questionnaire¹⁸ at 3 and 6 months.
51
52 311 • Qualitative interviews with a sub-sample of participants at 6 and 12 months
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54 312 • Adverse Event reports up to 12 weeks, the end of the weight loss intervention or 6 months for
55 313 AE's known or presumed to be related to gallstones.
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3 314 **Measurements**

4 315 Figure 2 provides a summary of the measurements collected.

5 316 *Socio-demographic characteristics*; Participants' will be asked to self-report age, sex, ethnicity
6
7 317 *Medical History*; Relevant medical history and all concomitant medication will be recorded and
8
9 318 checked against the participants' medical record. Participants will also be asked to self-report items
10
11 319 required to determine cardiovascular risk score using QRISK2¹⁹.

12 320 *Physical measurements*; Height will be measured to the nearest 1cm using stadiometers available in
13
14 321 the practice. Weight will be recorded to the nearest 0.1kg using an electronic scale (SC240 MA,
15
16 322 Tanita Japan) which will also record the proportion of body fat using bioelectrical impedance. Waist
17
18 323 circumference will be measured in the horizontal plane at the upper border of the iliac crest at the
19
20 324 end of expiration²⁰ using a fibreglass non-stretch tape measure fitted with a tensioning device (Gulik
21
22 325 II Tape Measure, Fitness Mart USA). Seated blood pressure will be measured in triplicate with 1 min
23
24 326 between each measure. All physical measures are performed by assessors trained according to the
25
26 327 study manual of procedures.

27 328 *Fasting blood sample*; A fasting venous blood sample will be collected (to be analysed for glucose,
28
29 329 insulin, HbA1c, HDL and LDL cholesterol, triglycerides). When baseline/enrolment appointments are
30
31 330 scheduled at times when it may be inappropriate to fast, participants will be asked to arrange for a
32
33 331 fasting blood sample to be collected at an alternative appointment within 7 days of the enrolment
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35 332 visit and before the participant commences the allocated weight loss programme.

36 333 *Questionnaires*; Participants will be provided with a questionnaire booklet which they will be asked
37
38 334 to complete and return to the trial team in a postage paid envelope provided. The questionnaire
39
40 335 booklet contains the following measures:

41 336 *Obesity specific quality of life (OWLQOL)*; a weight-specific instrument intended to be used to assess
42
43 337 obesity specific symptoms and quality of life, general functional status and well-being, and person-
44
45 338 specific preference measurement²¹.

46 339 *Quality of Life*; EQ-5D will be used as a standardised validated instrument used for measuring
47
48 340 general health status²².

49 341 *Programme adherence*; Self-reported adherence to the allocated programme and methods
50
51 342 participants are using to attempt to lose weight will be recorded by questionnaire.

52 343 *Programme feedback*; will be assessed using several 5-point Likert scales, including whether there is
53
54 344 an aim to continue with the programme.

55 345 *Oxford Food and Activity Behaviours (OxFAB)*: a questionnaire to assess personal strategies used by
56
57 346 individuals for the purposes of weight loss¹⁸.

Retention and withdrawal

We will seek to follow up all participants except those who expressly withdraw from the study. Participants who decide to withdraw from or discontinue the intervention allocated as part of the study will be asked to return for follow-up visits to collect outcome measures. To promote participant retention and complete follow-up participants will be offered a £10 gift card for attending each of the 6 month and 12 month follow-up visits.

Adverse Events

Adverse events are of relevance in this trial because many practitioners feel these programmes are poorly tolerated and unsuitable for routine use in primary care. We will record AEs following Good Clinical Practice (GCP). All serious and non-serious AE's that occur during the first 12 weeks of the study or until the termination of the weight loss programme will be recorded in participants who initiate one of the weight loss interventions. We will also record all AEs that are presumed to be or known to be related to gallstones up to 6 months.

Data management

Data will be recorded in a web-based data capture system (OpenClinica), which is hosted by the Primary Care Clinical Trials Unit of the University Oxford. This system is customised and has an audit trail facility. Ranges and programmed validation checks are implemented in the system in order to aid reliable data entry.

Statistical Analysis

The primary and secondary outcomes will be assessed using an intention-to-treat (ITT) analysis by an independent statistician. Each continuous outcome will be assumed to follow the normal distribution and be analysed by means of a linear mixed effects model, adjusted for outcome at baseline. The model will include fixed effects terms for randomised group, visit, interaction between randomised group and visit, and baseline BMI (for non-weight outcomes only), and random effects to account for repeated measures on the same participant at 3, 6 and 12 months. No adjustment will be made for baseline BMI in the analysis of the weight outcomes due to its strong collinearity with baseline weight. A random effect will also be included for individual practice. An unstructured variance covariance matrix will be specified between repeated measurements on the same individual and the random effects for patient and practice will be assumed to be independent. The adjusted treatment effect together with the 95% confidence interval and p-value will be reported. The analysis will be performed using PROC MIXED in a current version of SAS. The proportion of

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3 381 participants who lose 5% and 10% of their initial weight at 12 months respectively will be presented
4 382 and the adjusted difference between two arms and 95% confidence interval will be reported. The
5 383 binary outcome will be analysed by means of a logistic mixed effects model, adjusting for baseline
6 384 BMI (fixed effect) and practice (random effect). The number needed to treat (NNT) to achieve 5 or
7 385 10% weight loss, defined as the inverse of the absolute difference in proportions, will be reported if
8 386 the differences between the treatment and control groups are statistically significant. A full
9 387 statistical analysis plan will be prepared prior to any data analysis.

14 388 **Qualitative sub-study**

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17 389 The purpose of this study is to examine participants' views of the programmes. In particular, we aim
18 390 to examine the features that helped or hindered adherence to the programme and participants'
19 391 views of the behavioural support provided in the respective programmes. We will therefore
20 392 purposively sample participants based on their responses to the satisfaction questionnaire,
21 393 reflecting positive, neutral and negative evaluations. Where possible, we will select participants to
22 394 reflect both genders, socioeconomic status, and ethnic group differences. We anticipate
23 395 interviewing around 20 participants in the intervention group and 10 in the control group but
24 396 sampling will continue until saturation is reached, evidenced by no new themes occurring.
25 397 We will develop a semi-structured topic guide for the interviews. The interviewer will encourage
26 398 respondents to discuss their perceptions and experiences freely and in depth. The interview will set
27 399 the context by asking about previous experience of weight management. Thereafter, we will ask for
28 400 participants' views on which component parts of their treatment they felt were effective and which
29 401 they felt were not effective; thoughts about ability to continue to manage their weight when
30 402 treatment has ended; and their views on medication adjustments where these occurred. The
31 403 acceptability of the weight management treatment programmes and any preference they initially
32 404 had for the total diet replacement programme or the usual care programme will be explored.
33 405 Data from participants will be collected in a confidential, telephone interview which will be audio
34 406 recorded. All interviews will be transcribed. To examine saturation, analysis will proceed
35 407 concurrently with interviewing.

36 408 37 409 **Trial oversight**

38 410 An independent Trial Steering Committee (TSC) will provide oversight of all matters relating to
39 411 participant safety and data quality and value to the public. Due to the low risk nature of the
40 412 DROPLET trial and that it is an open label trial, the TSC also has the role of the Data Monitoring

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3 413 Committee in addition to their role as the TSC. However, there are no early stopping rules and all
4 414 AEs are evaluated un-blinded to allocation by the trial management group as well as the TSC.
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6 415 The TSC includes an independent clinician, dietitian, statistician and two patient representatives.
7
8 416 The TSC has reviewed the trial protocol, statistical analysis plan and the suitability of the proposed
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10 417 safety data to be collected. No interim analysis is planned for this trial due to the short recruitment
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12 418 period and low risk nature of the two dietary approaches¹¹. The trial may be subject to inspection
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14 419 and audit by University of Oxford, under their remit as sponsor, the trial coordinating centre as the
15
16 420 Sponsor's delegate and other regulatory bodies.
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18 421

422 **Ethics and dissemination**

19 423 The study protocol (Version: 4.0 Date: 5th October 2016) was reviewed and approved by the South
20
21 424 Central Oxford B REC Committee (Ref: 157/SC/0337). Any protocol modifications will be sent for
22
23 425 review by the research ethics committee and will be amended at the trial registry.
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25 426 It is planned that results will be disseminated to academic and health professional audiences via
26
27 427 presentations at conferences and publication in peer-reviewed journals. Participants will be sent a
28
29 428 summary of the trial findings at the time when the main article is published. If the trial shows this
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31 429 intervention is effective, results will be communicated to policymakers and commissioners of weight
32
33 430 management services through briefing papers summarising the main findings. We will also provide
34
35 431 the results to all participants coincident with publication and disseminate the results to the public
36
37 432 through a press release, regardless of what the results show.
38
39 433

434 **Acknowledgements**

40 435 The low-energy total diet replacement programme including the formula meal replacement
41
42 436 products will be provided by Cambridge Weight Plan Ltd, Northants, UK.
43
44 437

438 **Funding and Sponsorship**

45 439 This research is funded by research grants from Cambridge Weight Plan Ltd and NIHR Collaboration
46
47 440 for Leadership in Applied Health Research and Care (CLAHRC) Oxford at Oxford Health NHS
48
49 441 Foundation to the University of Oxford. The sponsor of the trial is the University of Oxford.
50
51 442

52 443 **Contributions**

53 444 The protocol was initiated and designed by the investigators who have no personal financial
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55 445 relationships with the Cambridge Weight Plan Ltd. Although Cambridge Weight Plan were consulted
56
57 446 and commented on the protocol, the final decisions lay with the investigators. There are no
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3 447 restrictions on publication of results arising from this study and the contract between the funder and
4 448 the University ensures that the funding body will have no input into the decisions regarding
5 449 publication.

6
7 450 SAJ and PA designed the study and secured the funding. NA and ST helped to develop the protocol.
8 451 NA is the trial manger and AN is the trial statistician.

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11 452

12 453 **Competing interests**

13
14 454 SAJ and PA have led publicly funded trials in which the weight management intervention was
15 455 provided free of charge by other commercial companies. They receive no personal financial benefits
16 456 from these trials or from the companies. NMA, ST, and AN have no competing interests.

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20 458 **Footnotes**

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22 459 As sponsor, the University of Oxford has a specialist insurance policy in place that would operate in
23 460 the event of any participant suffering harm as a result of their involvement in the research.

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27 462 **Provenance and peer review**

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29 463 Not commissioned; external peer review for ethical approval prior to submission.

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31 464

32 465 **Data sharing**

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34 466 For access to the data set, a formal request should be sent to the DROPLET study group. The request
35 467 will only be considered when the principal results of the study have been published.

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Figure 1: Participant flow through the study

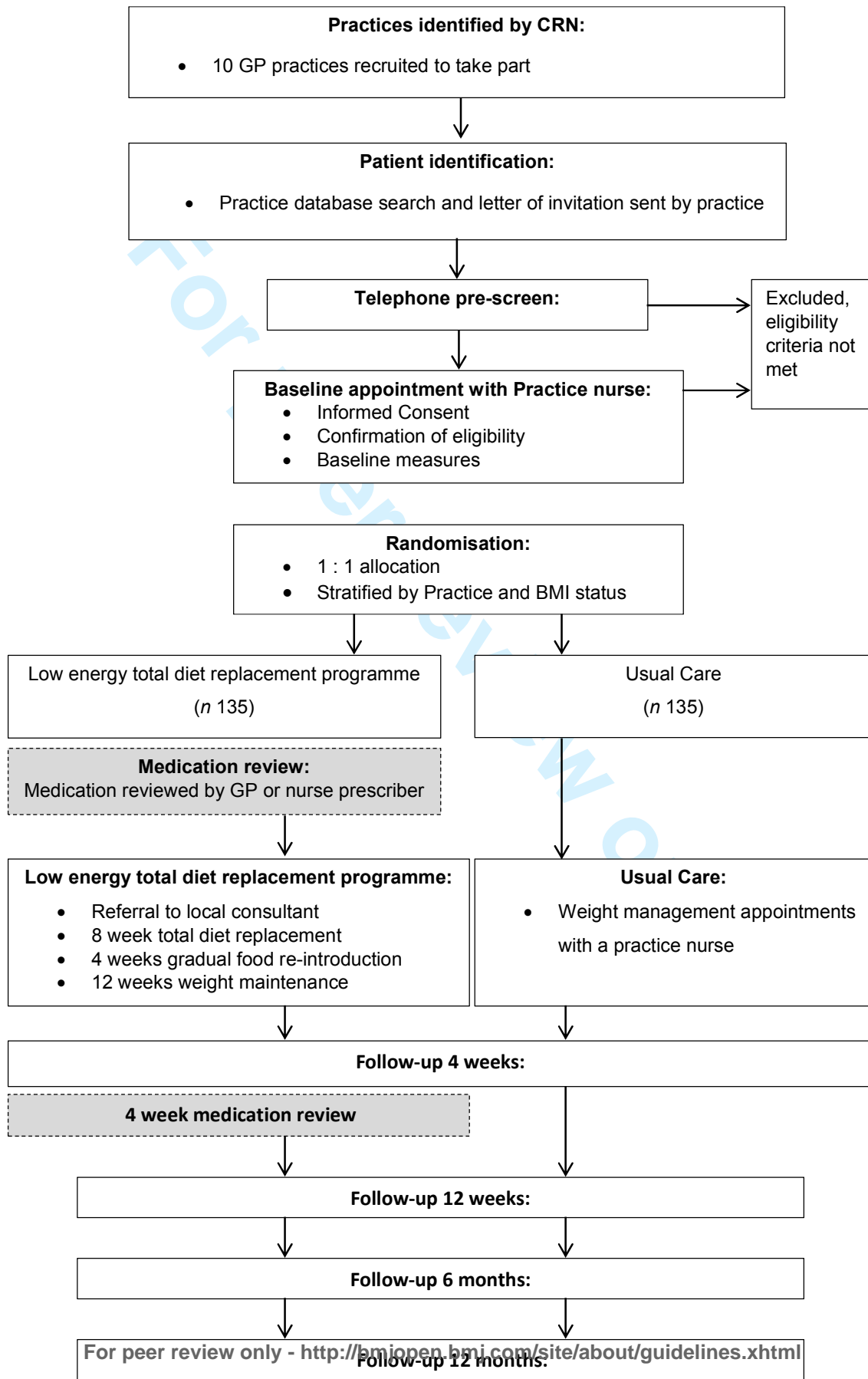


Figure 2: Schedule of measurements



VISIT					
	Enrolment	Follow-up visits			
TIMEPOINT	Baseline	4 weeks	12 weeks	6 months	12 months
ENROLMENT:					
Informed consent	X				
Eligibility screen	X				
Randomisation	X				
INTERVENTIONS:					
<i>Low energy total diet replacement programme</i>					
<i>Usual Care</i>					
ASSESSMENTS:					
<i>Demographic</i>	X				
<i>Medical History</i>	X				
<i>Concomitant Medication</i>	X	X	X	X	X
<i>Height</i>	X				
<i>Weight</i>	X	X	X	X	X
<i>Body composition</i>	X	X	X	X	X
<i>Waist circumference</i>	X	X	X	X	X
<i>Blood Pressure</i>	X	X	X	X	X
<i>Fasting blood sample</i>	X				X
<i>Medication review</i>	X	X			
QUALITATIVE INTERVIEWS			X		X
QUESTIONNAIRES:					
<i>Quality of life: (EQ-5D and OWLQOL)</i>	X		X	X	X
<i>Programme adherence</i>		X	X	X	X
<i>Programme feedback</i>		X	X	X	
<i>OXFAB¹</i>			X	X	

Figure 2: Schedule of measurements

1. Hartmann-Boyce J, Aveyard P, Koshiaris C, et al. Development of tools to study personal weight control strategies: OxFAB taxonomy. *Obesity (Silver Spring)* 2016;**24**(2):314-20 doi: 10.1002/oby.21341.

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Medication changes



Guidance on making adjustments to your patients' medications

This guidance aims to help you make medication adjustments, but if in doubt please use your clinical judgement or contact the GP lead for this study.

The adjustments detailed below should be made when commencing the low-energy total diet replacement programme.

TYPE 2 DIABETES

Patient currently takes:	Recommendation
Metformin	HALF daily dose
Sulphonylurea	STOP
Glitazone	STOP
Glinide	STOP
DPP IV inhibitor	STOP
Acarbose	STOP

At the end of the weight loss phase, re-assess patients requirements for oral diabetic therapies using

HYPERTENSION

Patient currently takes:	Current dose	Recommendation
Loop Diuretic:		
<i>Furosemide</i>	≤ 40 mg daily	STOP
	80 – 120 mg daily	REDUCE <u>by</u> 40 mg daily
	≥ 120 mg daily	REDUCE <u>by</u> 40 mg daily
<i>Bumetamide</i>	≤ 1 mg daily	STOP
	2-3 mg daily	REDUCE <u>to</u> 1mg daily
	≥ 3 mg daily	REDUCE <u>by</u> 1mg daily
Thiazide Diuretic		STOP
β Blocker	Used for hypertension	STOP
	Other uses	CONTINUE
α Blocker		HALF daily dose
Ca channel blocker		HALF daily dose
ACE inhibitors or ARBs	Used for hypertension	STOP
	Used for heart failure	HALF daily dose

LIPID DRUGS

Patient currently takes:	Recommendation
Fibrates	STOP
Statins	CONTINUE
Ezetimibe	CONTINUE



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P15
Funding	4	Sources and types of financial, material, and other support	P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	P1
	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	P15

	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)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4-6
	6b	Explanation for choice of comparators	P10-11
Objectives	7	Specific objectives or hypotheses	P6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
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	P9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P12
	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	P13
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	P13
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	P13/14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/14
	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)	P13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P15

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P15
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)	P15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P8
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	_P16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15
	31b	Authorship eligibility guidelines and any intended use of professional writers	P15-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P16
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<hr/>
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	<hr/>

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

peer review only

BMJ Open

Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using total diet replacement products: a protocol for a randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016709.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jun-2017
Complete List of Authors:	Jebb, Susan; University of Oxford, Nuffield Department of Primary Care Health Sciences Astbury, Nerys; University of Oxford, Nuffield Department of Primary Care Health Sciences Tearne, Sarah; University of Oxford, Nuffield Department of Primary Care Health Sciences Nickless, Alecia; University of Oxford, Nuffield Department of Primary Care Health Sciences Aveyard, Paul; University of Oxford, Nuffield Department of Primary Care Health Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Obesity, Diet, Weight loss, PRIMARY CARE

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Manuscripts

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1 **Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using**
2 **total diet replacement products: a protocol for a randomised controlled trial**^a

4 Susan A Jebb¹

5 Nerys M Astbury¹

6 Sarah Tearne¹

7 Alecia Nickless¹

8 Paul Aveyard¹

9

10 *Corresponding Author: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary
11 Care Building, Woodstock Road, Oxford, OX2 6GG, email: nerys.astbury@phc.ox.ac.uk,
12 tel: 01865 617871

13

14 ¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford UK

15

16 ^a This trial is sponsored by the University of Oxford, Clinical Trials and Research Governance, Joint
17 Research Office, Block 60, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, UK.

18

19 Keywords: Obesity, diet, weight loss, primary care

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2
3 20 **ABSTRACT**

4
5 21 **Introduction**

6 22 The global prevalence of obesity has risen significantly in recent decades. There is a pressing need to
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8 23 identify effective interventions to treat established obesity that can be delivered at scale. The aim of
9
10 24 the DROPLET study is to determine the clinical effectiveness, feasibility and acceptability of referral
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12 25 to a low-energy total diet replacement programme compared with usual weight management
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14 26 interventions in primary care.

15 27 **Methods and Analysis**

16 28 The DROPLET trial is a randomised controlled trial comparing a low-energy total diet replacement
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18 29 programme with usual weight management interventions delivered in primary care. Eligible patients
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20 30 will be recruited through primary care registers and randomised to receive a behavioural support
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22 31 programme delivered by their practice nurse or a referral to a commercial provider offering an initial
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24 32 810 kcal/d low-energy total diet replacement programme for 8 weeks, followed by gradual food
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26 33 reintroduction, along with weekly behavioural support for 24 weeks. The primary outcome is weight
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28 34 change at 12 months. The secondary outcomes are weight change at 3 and 6 months, the
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30 35 proportion of participants achieving 5% and 10% weight loss at 12 months and change in fat mass,
31
32 36 HbA1c, LDL cholesterol and systolic and diastolic blood pressure at 12 months. Data will be analysed
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34 37 on the basis of intention to treat. Qualitative interviews on a sub-sample of patients and healthcare
35
36 38 providers will assess their experiences of the weight loss programmes and identify factors affecting
37
38 39 acceptability and adherence.

39 40 **Ethics and dissemination**

40 41 This study has been reviewed and approved by NHS/HRA Research Ethics Committee (Ref:
41
42 42 SC/15/0337). The trial findings will be disseminated to academic and health professionals through
43
44 43 presentations at meetings and peer reviewed journals and to the public through the media. If the
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46 44 intervention is effective, the results will be communicated to policymakers and commissioners of
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48 45 weight management services.

49 46 **Trial registration number**

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48 STRENGTHS & LIMITATIONS

- 49 • This study is the largest randomised controlled trial to date of a low-energy total diet
50 replacement programme for weight management in routine primary care
- 51 • This intervention is based on a model of care where GPs refer patients to a programme
52 delivered in the community by a commercial provider using non-NHS staff, which, if
53 successful, could be readily adopted into practice without the need for specialist training for
54 the primary care workforce
- 55 • The primary outcome is weight at one year. Although this is 9 months after the low-energy
56 total diet replacement, epidemiological evidence suggests that any weight lost will continue
57 to be regained beyond one year.
- 58 • The intention of obesity treatment programmes is to improve long-term health but this
59 study does not include morbidity or mortality outcomes.
- 60 • Longer term follow-up data would be helpful to better estimate the longer health impact
61 and cost effectiveness of the intervention.

62 INTRODUCTION

63 The prevalence obesity worldwide has more than doubled since 1980¹. According to the latest
64 estimates from the World Health Organization (WHO) more than 1.9 billion adults were overweight,
65 of whom 600 million were obese, representing 39% and 13% of the world's adult population,
66 respectively². Obesity is associated with premature mortality³ but also substantial morbidity,
67 including significantly increased risks of diabetes, cardiovascular disease and most non-smoking
68 related cancers, as well as physical impairments linked to excess weight such as breathlessness, joint
69 problems and back pain⁴. Collectively this creates a burden of ill-health and reduced quality of life
70 for individuals, additional treatment costs to the NHS and reductions in economic productivity⁵.
71 While high priority must be given to prevent future cases of obesity, in the short term there is a
72 pressing need to identify effective interventions to treat established obesity. Research has shown
73 that even modest reductions in weight can bring significantly reduced risks of disease. For example,
74 in the US Diabetes Prevention Program (DPP) individuals randomised to an intensive lifestyle
75 intervention lost 7kg by the end of the first year. Although some of this weight was regained, the
76 intensive lifestyle group remained 4 kg lighter than the usual care group at four years and this
77 reduced the incidence of diabetes by 58% relative to usual care⁶ with benefits persisting to at least
78 15 year follow-up despite weight regain⁷.

79 Primary care is an important setting for weight management interventions to reduce multi-
80 morbidity. However, although a number of interventions have been shown to be effective in
81 intensive research studies, this success has not always been replicated in routine settings. For

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3 82 example, there was no significant reduction in weight when a weight loss programme adapted from
4 83 the DPP was delivered by primary care teams⁸. Our recent review of interventions suitable for use in
5 84 routine care⁹ and a second review, using slightly different inclusion criteria, of interventions
6 85 specifically delivered in primary care¹⁰ both concluded that behavioural weight management
7 86 interventions led by primary care practitioners were ineffective. This may relate in part to the
8 87 complexity of advice needed for successful dietary change and the need for frequent contact to
9 88 provide support which exceeds the capacity of routine primary care systems. However, although a
10 89 number of interventions have been shown to be effective in intensive research studies, this success
11 90 has not always been replicated in routine settings. GP referral to a commercial provider offering
12 91 group-based support is an effective option for weight management in primary care, and our meta-
13 92 analysis showed a mean reduction in weight of 2.3 kg over no intervention at one year⁹. However,
14 93 greater weight losses would be expected to bring greater health gains.
15 94 Very low energy diets (VLEDs) have been used for weight loss over many years in specialist settings.
16 95 A VLED is defined as a diet providing ≤ 800 kcal a day, based on the use of specially formulated
17 96 products designed as the sole source of nutrition during periods of total diet replacement. When
18 97 used as directed, these formula products meet 100% of the dietary reference values for vitamins,
19 98 minerals and trace elements for healthy, weight-stable people and are enriched with high biological-
20 99 value protein. Although most contain some dietary fibre, a fibre supplement may also be
21 100 recommended. A recent systematic review and meta-analysis of the available randomised controlled
22 101 trials showed that behavioural weight management interventions incorporating a VLED led to 3.9 kg
23 102 greater weight loss at one year compared with intensive specialist-delivered behavioural
24 103 programmes¹¹. However, most of the trials included in this review were small, typically including
25 104 only 50-100 participants that were treated by obesity specialists and many trials had methodological
26 105 limitations.
27 106 UK guidance from the National Institute for Health and Care Excellence (NICE) recommends that
28 107 VLEDs may only be used for a maximum of 12 weeks in people who have a clinical need to lose
29 108 weight rapidly, such as prior to a knee replacement surgery or those seeking fertility services, but
30 109 recommends against their routine use to manage obesity¹². Clinical guidance in the USA does not
31 110 recommend the routine use of VLEDs, but rather suggests that their use “*may* be reasonable in
32 111 limited circumstances, but only when provided by trained practitioners in a medical care setting
33 112 where medical monitoring and high intensity lifestyle intervention can be provided”¹³.
34 113 Nevertheless, there has been growing interest in the potential for routine use of weight loss
35 114 programmes similar to traditional VLEDs, in so far as they incorporate a period of total diet
36 115 replacement using specially formulated products as the sole source of nutrition, but where the

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3 116 energy content is more than 800kcal/day but less than 1200 kcal/day. The NICE guidelines suggest
4 117 that this type of low-energy diet could be considered for weight management, providing care is
5 118 taken to ensure they are nutritionally complete¹². There is one observational report (n = 91) on the
6 119 use of these low-energy total diet replacement programmes in primary care which found that 64%
7 120 of participants completed the 810kcal/day dietary programme, defined as either 12 weeks or
8 121 reaching 20kg weight loss, with a mean weight loss of 16.9 kg (standard deviation (SD) = 6.0 kg). One
9 122 third of participants starting the programme maintained a weight loss of ≥ 15 kg at 12 months¹⁴. A
10 123 large randomised controlled trial, the DiRECT study, is currently underway to investigate whether
11 124 this type of low-energy total diet replacement programme can be used to treat type 2 diabetes
12 125 among people who are also overweight¹⁵. It will compare the health effects of the current best-
13 126 available type 2 diabetes care with those achieved through weight management based on a low-
14 127 energy total diet replacement programme. While this will provide important mechanistic evidence
15 128 on the links between weight loss and diabetes risk, it will be delivered by NHS staff whereas the
16 129 present study will test the effectiveness of referral outside the NHS to a commercial provider.
17 130 To fill this evidence gap we will conduct a randomised controlled trial to specifically test the
18 131 effectiveness of a GP referral to a community-based low energy total diet replacement programme
19 132 for patients who are obese and likely to benefit from weight loss. It will assess the clinical
20 133 effectiveness of a weight loss intervention by measuring weight loss and the change in biomarkers of
21 134 cardiovascular risk at 12 months relative to weight loss advice provided by practice nurses. This
22 135 comparator is intended to represent 'usual care', though in practice most patients who are obese
23 136 are not offered support to lose weight.
24 137 The context for this trial follows the established model for GP referral to community group-based
25 138 weight loss programmes¹⁶. This uses the generic authority and credibility of health professionals to
26 139 motivate patients to consider weight management and the specialist knowledge of the commercial
27 140 provider to guide the intervention and offer frequent contact and behavioural support to the
28 141 patient. If successful, it will provide another option for weight management that can be offered to
29 142 patients in primary care, and GPs will be able to guide patients towards the treatment which best fits
30 143 their circumstances and preferences. This trial will specifically test whether a partnership between
31 144 GPs and providers will allow for the safe provision of low energy total diet replacement programmes
32 145 even for patients with multi-morbidity who may gain the greatest benefits from such interventions
33 146 but who may also need clinical oversight and adjustments to some of their medications as they lose
34 147 weight. It will provide the opportunity for qualitative research to investigate the perspectives of
35 148 patients and health care practitioners on this type of treatment.
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3 150 **OBJECTIVE:**

4 151 The aim of the DROPLET trial is to determine the clinical effectiveness, feasibility and acceptability of
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6 152 referral to a low-energy total diet replacement programme compared with usual weight
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8 153 management interventions in primary care.
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For peer review only

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3 154 **METHODS:**

4 155 **Design and Setting**

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6 156 The study will take place in general practices in England. Designed as an individually randomised,
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8 157 two arm and parallel group superiority trial with the primary endpoint as objectively measured
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10 158 changes in body weight from baseline to 12 months. Due to the nature of the intervention it will not
11
12 159 be possible to blind participants, clinicians or some of the study team to the treatment allocation
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14 160 after randomisation.
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16 162 **Recruitment**

17 163 Around 10 general practices will be identified to take part through the clinical research networks.
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19 164 Recruited practices will be asked to conduct a search of their electronic health records in order to
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21 165 identify suitable patients for the DROPLET study. As a result of this search, eligible patients will be
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23 166 sent an invitation letter from their GP as part of a staggered mail out. Patients will be encouraged to
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25 167 call the research team if they are interested in taking part.
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27 168 GPs may also identify eligible patients during routine consultations. The GP will provide the patient
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29 169 with an invitation letter and suggest that the patient ring the study team. The study team will
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31 170 provide the potential participants with information on what taking part in the study will entail, and
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33 171 an initial assessment of suitability to take part. Those who make contact and self-report meeting the
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35 172 eligibility criteria will be scheduled for a baseline/enrolment appointment.

36 173 **Inclusion Criteria:**

- 37 174
- 38 175 • Participant is willing and able to give informed consent for participation in the study.
 - 39 176 • Aged 18 years or above.
 - 40 177 • Body Mass Index ≥ 30 kg/m².
 - 41 178 • Likely to benefit from weight loss in the GP's opinion.

42 179 **Exclusion criteria:**

- 43 180 • Unable to understand English
 - 44 181 • Currently or recently (within 3 months of study entry) attended a weight management
45 182 programme or currently participating in another weight loss study.
 - 46 183 • Had bariatric surgery, or scheduled bariatric surgery.
 - 47 184 • Pregnant, breastfeeding, or planning to become pregnant during the course of the study.
 - 48 185 • Receiving insulin therapy
 - 49 186 • Heart attack or stroke within the last 3 months,
 - 50 187 • Heart failure of grade II New York Heart Association and more severe
 - 51 188 • Angina, arrhythmia, including atrial fibrillation or prolonged QT syndrome
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- 188 • Taking MAOI medication
- 189 • Taking anticoagulant medication (e.g. warfarin)
- 190 • Taking varenicline (smoking cessation medication)
- 191 • Chronic renal failure of stage 4 or 5
- 192 • Active liver disease (except NAFLD) a past history of hepatoma or within 6 months of onset
- 193 of acute hepatitis.
- 194 • People having active treatment for cancer other than skin cancer treated with curative intent by
- 195 local treatment only or people taking hormonal or other long-term secondary prevention
- 196 treatment after initial cancer treatment.
- 197 • Active treatment or investigation for possible or confirmed gastric or duodenal ulcer.
- 198 Maintenance treatment with acid-suppression is not a contra-indication.
- 199 • Porphyria
- 200 • Scheduled for surgery within 12 months
- 201 • A member of household is already enrolled in the study
- 202 • Unwilling to provide blood samples
- 203 • Patients that the GP judges not able to meet the demands of either treatment programme
- 204 or measurement schedule. This may include severe medical problems not listed above or
- 205 severe psychiatric problems including substance misuse that make following the treatment
- 206 programme or adhering to the protocol unlikely.

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208 **Participant Flow**

209 The baseline/eligibility assessment will be scheduled with a practice nurse or health care assistant at
210 their own GP practice, where informed consent for participation in the study will be obtained before
211 eligibility will be formally assessed. After demographic information and all baseline measurements
212 have been collected the participant will be randomised to the allocated treatment group using the
213 online randomisation system. The patients' own GP will be notified by letter of the enrolment and
214 randomisation of their patient, so that it may be documented on their medical record. Participants
215 allocated to the low-energy total diet replacement programme and taking medications for type 2
216 diabetes, hypertension or high cholesterol will have their medications reviewed by a prescribing
217 member of the clinical care team, usually the GP or trained nurse prescriber. During this medication
218 review the clinician will decide what changes to medications are required at the time the participant
219 commences the low energy total diet replacement programme, with guidance provided by the study
220 team (Supplementary Figure 1). In addition, participants randomised to the low-energy total diet
221 replacement group and who take anti-hypertensive medications will be provided with a home blood
222 pressure monitor and asked to record blood pressure once daily during the weight loss phase (weeks

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3 223 1-12). These readings can be used to guide clinicians with any further changes in hypertension
4 224 medications.
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6 225 All participants will be invited to attend a 4 week follow-up appointment with the practice nurse.
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8 226 The main purpose of the visit is a clinical review of medication, including any adjustments required.
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10 227 Any changes in medication will be recorded on the concomitant medication log. Participants will be
11 228 invited to attend further follow-up visits with a member of the trial team at the GP practice at 12
12 229 weeks, 6 months and 12 month following randomisation. Participant flow through the study is
13 230 outlined in **Figure 1**.
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232 **Sample size**

19 233 The total number of participants to be recruited for this study is 270. This is based on a sample size
20 234 calculation for the primary outcome using equal variance independent samples t-test assuming a
21 235 difference between groups at 12 months of 4kg with a standard deviation in both groups of 9kg;
22 236 obtained from a meta-analysis of published studies¹¹. The sample size has been inflated by 20%, to
23 237 account for attrition, and assumes 90% power and two-sided alpha of 5%.
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239 **Randomisation**

30 240 All eligible, consenting participants will be randomised with an allocation ratio of 1:1 to low-energy
31 241 total diet replacement or usual care programmes using an online program which reveals group
32 242 allocation as per a computer-generated randomisation list. The randomisation criteria will be
33 243 validated by an independent statistician. Allocation will be stratified by GP Practice and baseline BMI
34 244 ($\leq 35\text{kg}/\text{m}^2$ or $> 35\text{kg}/\text{m}^2$) using stratified block randomisation with randomly varying block sizes of
35 245 size 2, 4, and 6. The randomisation software ensures full allocation concealment, with the allocation
36 246 group only revealed to the person performing the randomisation once a study identifier and
37 247 required stratification details have been entered.
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3 248 **Interventions**

4 249 **Low-energy total diet replacement**

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6 250 The programme offered to participants randomised to the active intervention will be provided by
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8 251 Cambridge Weight Plan Ltd.™ Northants., United Kingdom.

9
10 252 Following randomisation participants allocated to this group will be referred to a local Cambridge
11 253 Weight Plan Counsellor who will invite the participant to attend regular appointments for 24 weeks.

12 254 These appointments consist of motivational support, encouragement, reassurance and problem-
13 255 solving. All counsellors attend a 1-day in-person training course covering screening for suitability,

14 256 nutrition, behavioural approaches, and medical monitoring. They must pass and accreditation

15 257 examination before they are allowed to deliver the programme in the community. Thereafter, they

16 258 have a yearly training updates, a nominated sponsor (experienced counsellor) and access to an

17 259 online chat forum for sharing queries. Cambridge Weight Plan has a healthcare professional

18 260 available for the counsellors to consult for advice on specific medical and nutritional queries.

19 261 Counsellors delivering the intervention for the purposes of this trial received short trial specific

20 262 training before being allocated study participants.

21 263 During the first 12 weeks the participant will meet with their counsellor weekly. Patients will be

22 264 asked to follow a programme based on using formula meal replacement products (soups, shakes and

23 265 bars) and milk comprising 810kcal/day (3389kJ/d). For the first eight weeks patients will be advised

24 266 to replace *all* their usual foods and drinks with four of the formula products daily, 750ml of skimmed

25 267 milk, 2.25L of water or other non-calorific drinks and a fibre supplement (total diet replacement

26 268 stage). During the first two weeks, the formula products will be limited to liquid products (soups and

27 269 shakes), but from week 3 onwards participants will have the option to include meal replacement

28 270 bars as part of the formula product allowance. After eight weeks there will be a four week stepwise

29 271 reduction in the use of formula meal replacement products and a gradual re-introduction of food-

30 272 based meals. The weight maintenance phase from week 12 to 24 participants attend monthly

31 273 appointments at 16, 20 and 24 weeks, during this phase participants will consume only one formula

32 274 product a day, with the remainder of diet provided by food. This weight maintenance phase will

33 275 include a recommendation to return to the total diet replacement stage for periods of up to 4 weeks

34 276 if a participant regains 1kg or more than their weight measured at 12 weeks.

35 277 All consultations with counsellors and formula products will be provided to participants by their

36 278 nominated counsellor and will be free of charge for the first 24 weeks, after which the intervention

37 279 will end. Participants in both groups will be free to choose whether or not to continue with the

38 280 programme, but at their own cost.
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4 282 **Comparator**
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6 283 The comparator intervention will consist of the usual weight management programme provided by a
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8 284 member of the practice nurse team who has been trained to offer a weight loss programme. The
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10 285 trial will take place only in practices where this is routine care. Participants allocated to the usual
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12 286 care group will not be prevented from attending other weight management groups if they choose to
13
14 287 do so, but no NHS referrals to these schemes will be offered during the trial. The practice nurse will
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16 288 give participants a copy of the booklet "So you want to lose weight ... for good"¹⁷. This 47 page
17
18 289 booklet provides advice akin to a behavioural weight management programme. The aim is to
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20 290 produce a weight loss goal of 0.5 to 1kg/week. It includes goal setting, advice on portion control and
21
22 291 physical activity, other behavioural strategies, and monitoring and feedback on progress. Nurses will
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24 292 be asked to offer a programme for 12 weeks, at a frequency that is usually used in the practice (e.g.
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26 293 weekly or bi-weekly).

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295 **Physical activity**

296 We recognise the importance of the role of aerobic and resistance exercise in facilitating weight loss
297 and maintaining lean body mass to facilitate weight loss maintenance.

298 Participants randomised to the low-energy total diet replacement arm are given appropriate advice
299 based on their previous exercise history, current ability and what is appropriate for their stage
300 weight loss programme. Clinical guidelines in the UK emphasise the importance of advice to
301 increase physical activity and we would expect this to be incorporated into the control 'usual care'
302 intervention.

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304 **Outcomes:**

305 **Primary outcome**

- 306 • Change in body weight from baseline to 12 months

307 **Secondary outcomes**

- 308 • Change in body weight from baseline at 3 and 6 months
- 309 • Proportion of participants achieving 5% and 10% weight loss at 12 months
- 310 • Change in fat mass between baseline and 12 months
- 311 • Change in LDL cholesterol concentrations between baseline and 12 months
- 312 • Change in HbA1c between baseline and 12 months
- 313 • Change in systolic and diastolic blood pressure between baseline and 12 months

314 **Exploratory outcomes**

- 315 • Change in fat mass from baseline to 12 weeks and from baseline to 6 months.
- 316 • Change in waist circumference from baseline to 3, 6, and 12 months.
- 317 • Change in triglyceride and HDL cholesterol concentrations between baseline and 12 months.
- 318 • Change in fasting glucose and insulin concentrations and change in HOMA-IR, HOMA-%S and
- 319 HOMA-%B between baseline and 12 months.
- 320 • Change in systolic and diastolic blood pressure between baseline and 3 months and between
- 321 baseline and 6 months.
- 322 • Change in QRISK between baseline and 12 months.
- 323 • Change in the EQ-5D scale between baseline and 12 months
- 324 • Change in obesity related quality of life measured with the OWLQOL between baseline, 3, 6, and
- 325 12 months.
- 326 • Proportion of people continuing their weight loss attempt and following the prescribed
- 327 programme at 4, 8, and 12 weeks.
- 328 • The number of weight control behaviours that participants are using assessed using the OxFAB
- 329 questionnaire¹⁸ at 3 and 6 months.
- 330 • Qualitative interviews with a sub-sample of participants at 6 and 12 months
- 331 • Adverse Event reports up to 12 weeks, the end of the weight loss intervention or 6 months for
- 332 AE's known or presumed to be related to gallstones.

333 **Measurements**

334 Figure 2 provides a summary of the measurements collected.

335 *Socio-demographic characteristics*; Participants' will be asked to self-report age, sex, ethnicity
336 *Medical History*; Relevant medical history and all concomitant medication will be recorded and
337 checked against the participants' medical record. Participants will also be asked to self-report items
338 required to determine cardiovascular risk score using QRISK2¹⁹.

339 *Physical measurements*; Height will be measured to the nearest 1cm using stadiometers available in
340 the practice. Weight will be recorded to the nearest 0.1kg using an electronic scale (SC240 MA,
341 Tanita Japan) which will also record the proportion of body fat using bioelectrical impedance. Waist
342 circumference will be measured in the horizontal plane at the upper border of the iliac crest at the
343 end of expiration²⁰ using a fibreglass non-stretch tape measure fitted with a tensioning device (Gulik
344 II Tape Measure, Fitness Mart USA). Seated blood pressure will be measured in triplicate with 1 min
345 between each measure. All physical measures are performed by assessors trained according to the
346 study manual of procedures.

347 *Fasting blood sample*; A fasting venous blood sample will be collected (to be analysed for glucose,
348 insulin, HbA1c, HDL and LDL cholesterol, triglycerides). When baseline/enrolment appointments are

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3 349 scheduled at times when it may be inappropriate to fast, participants will be asked to arrange for a
4 350 fasting blood sample to be collected at an alternative appointment within 7 days of the enrolment
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6 351 visit and before the participant commences the allocated weight loss programme.
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8 352 *Questionnaires*; Participants will be provided with a questionnaire booklet which they will be asked
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10 353 to complete and return to the trial team in a postage paid envelope provided. The questionnaire
11 354 booklet contains the following measures:
12 355 *Obesity specific quality of life (OWLQOL)*; a weight-specific instrument intended to be used to assess
13 356 obesity specific symptoms and quality of life, general functional status and well-being, and person-
14 357 specific preference measurement ²¹.
15
16 358 *Quality of Life*; EQ-5D will be used as a standardised validated instrument used for measuring
17 359 general health status ²².
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19 360 *Programme adherence*; Self-reported adherence to the allocated programme and methods
20 361 participants are using to attempt to lose weight will be recorded by questionnaire.
21 362 *Programme feedback*; will be assessed using several 5-point Likert scales, including whether there is
22 363 an aim to continue with the programme.
23 364 *Oxford Food and Activity Behaviours (OxFAB)*: a questionnaire to assess personal strategies used by
24 365 individuals for the purposes of weight loss¹⁸.
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3 366 **Retention and withdrawal**

4 367 We will seek to follow up all participants except those who expressly withdraw from the study.

5 368 Participants who decide to withdraw from or discontinue the intervention allocated as part of the
6 369 study will be asked to return for follow-up visits to collect outcome measures. To promote
7 370 participant retention and complete follow-up participants will be offered a £10 gift card for
8 371 attending each of the 6 month and 12 month follow-up visits.

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10 373 **Adverse Events**

11 374 Adverse events are of relevance in this trial because many practitioners feel these programmes are
12 375 poorly tolerated and unsuitable for routine use in primary care. We will record AEs following Good
13 376 Clinical Practice (GCP). All serious and non-serious AE's that occur during the first 12 weeks of the
14 377 study or until the termination of the weight loss programme will be recorded in participants who
15 378 initiate one of the weight loss interventions. We will also record all AEs that are presumed to be or
16 379 known to be related to gallstones up to 6 months.

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18 381 **Data management**

19 382 Data will be recorded in a web-based data capture system (OpenClinica), which is hosted by the
20 383 Primary Care Clinical Trials Unit of the University Oxford. This system is customised and has an audit
21 384 trail facility. Ranges and programmed validation checks are implemented in the system in order to
22 385 aid reliable data entry.

23 386

24 387 **Statistical Analysis**

25 388 The primary and secondary outcomes will be assessed using an intention-to-treat (ITT) analysis by an
26 389 independent statistician. Each continuous outcome will be assumed to follow the normal
27 390 distribution and be analysed by means of a linear mixed effects model, adjusted for outcome at
28 391 baseline. The model will include fixed effects terms for randomised group, visit, interaction between
29 392 randomised group and visit, and baseline BMI (for non-weight outcomes only), and random effects
30 393 to account for repeated measures on the same participant at 3, 6 and 12 months. No adjustment will
31 394 be made for baseline BMI in the analysis of the weight outcomes due to its strong collinearity with
32 395 baseline weight. A random effect will also be included for individual practice. An unstructured
33 396 variance covariance matrix will be specified between repeated measurements on the same
34 397 individual and the random effects for patient and practice will be assumed to be independent. The
35 398 adjusted treatment effect together with the 95% confidence interval and p-value will be reported.
36 399 The analysis will be performed using PROC MIXED in a current version of SAS. The proportion of

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3 400 participants who lose 5% and 10% of their initial weight at 12 months respectively will be presented
4 401 and the adjusted difference between two arms and 95% confidence interval will be reported. The
5 402 binary outcome will be analysed by means of a logistic mixed effects model, adjusting for baseline
6 403 BMI (fixed effect) and practice (random effect). The number needed to treat (NNT) to achieve 5 or
7 404 10% weight loss, defined as the inverse of the absolute difference in proportions, will be reported if
8 405 the differences between the treatment and control groups are statistically significant. A full
9 406 statistical analysis plan will be prepared prior to any data analysis.

14 407 **Qualitative sub-study**

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17 408 The purpose of this study is to examine participants' views of the programmes. In particular, we aim
18 409 to examine the features that helped or hindered adherence to the programme and participants'
19 410 views of the behavioural support provided in the respective programmes. We will therefore
20 411 purposively sample participants based on their responses to the satisfaction questionnaire,
21 412 reflecting positive, neutral and negative evaluations. Where possible, we will select participants to
22 413 reflect both genders, socioeconomic status, and ethnic group differences. We anticipate
23 414 interviewing around 20 participants in the intervention group and 10 in the control group but
24 415 sampling will continue until saturation is reached, evidenced by no new themes occurring.
25 416 We will develop a semi-structured topic guide for the interviews. The interviewer will encourage
26 417 respondents to discuss their perceptions and experiences freely and in depth. The interview will set
27 418 the context by asking about previous experience of weight management. Thereafter, we will ask for
28 419 participants' views on which component parts of their treatment they felt were effective and which
29 420 they felt were not effective; thoughts about ability to continue to manage their weight when
30 421 treatment has ended; and their views on medication adjustments where these occurred. The
31 422 acceptability of the weight management treatment programmes and any preference they initially
32 423 had for the total diet replacement programme or the usual care programme will be explored.
33 424 Data from participants will be collected in a confidential, telephone interview which will be audio
34 425 recorded. All interviews will be transcribed. To examine saturation, analysis will proceed
35 426 concurrently with interviewing.

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50 428 **Trial Steering Committee**

51 429 An independent Trial Steering Committee (TSC) will provide oversight of all matters relating to
52 430 participant safety and data quality and value to the public. Due to the low risk nature of the
53 431 DROPLET trial and that it is an open label trial, the TSC also has the role of the Data Monitoring
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3 432 Committee in addition to their role as the TSC. However, there are no early stopping rules and all
4 433 AEs are evaluated un-blinded to allocation by the trial management group as well as the TSC.
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6 434 The TSC includes an independent clinician, dietitian, statistician and two patient representatives.
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8 435 The TSC has reviewed the trial protocol, statistical analysis plan and the suitability of the proposed
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10 436 safety data to be collected. No interim analysis is planned for this trial due to the short recruitment
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12 437 period and low risk nature of the two dietary approaches¹¹. The trial may be subject to inspection
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14 438 and audit by University of Oxford, under their remit as sponsor, the trial coordinating centre as the
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16 439 Sponsor's delegate and other regulatory bodies.
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441 **Ethics and dissemination**

19 442 The study protocol (Version: 4.0 Date: 5th October 2016) was reviewed and approved by the South
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21 443 Central Oxford B REC Committee (Ref: 157/SC/0337). Any protocol modifications will be sent for
22
23 444 review by the research ethics committee and will be amended at the trial registry.
24
25 445 It is planned that results will be disseminated to academic and health professional audiences via
26
27 446 presentations at conferences and publication in peer-reviewed journals. Participants will be sent a
28
29 447 summary of the trial findings at the time when the main article is published. If the trial shows this
30
31 448 intervention is effective, results will be communicated to policymakers and commissioners of weight
32
33 449 management services through briefing papers summarising the main findings. We will also provide
34
35 450 the results to all participants coincident with publication and disseminate the results to the public
36
37 451 through a press release, regardless of what the results show.
38
39 452

453 **Acknowledgements**

40 454 The low-energy total diet replacement programme including the formula meal replacement
41
42 455 products will be provided by Cambridge Weight Plan Ltd, Northants, UK.
43
44 456

457 **Funding and Sponsorship**

45 458 This research is funded by research grants from Cambridge Weight Plan Ltd and NIHR Collaboration
46
47 459 for Leadership in Applied Health Research and Care (CLAHRC) Oxford at Oxford Health NHS
48
49 460 Foundation to the University of Oxford. The sponsor of the trial is the University of Oxford.
50
51 461

52 **Contributions**

53 463 The protocol was initiated and designed by the investigators who have no personal financial
54
55 464 relationships with the Cambridge Weight Plan Ltd. Although Cambridge Weight Plan were consulted
56
57 465 and commented on the protocol, the final decisions lay with the investigators. There are no
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3 466 restrictions on publication of results arising from this study and the contract between the funder and
4 467 the University ensures that the funding body will have no input into the decisions regarding
5 468 publication.

6
7 469 SAJ and PA designed the study and secured the funding. NA and ST helped to develop the protocol.
8 470 NA is the trial manger and AN is the trial statistician.

9
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11 471

12 472 **Competing interests**

13
14 473 SAJ and PA have led publicly funded trials in which the weight management intervention was
15 474 provided free of charge by other commercial companies. They receive no personal financial benefits
16 475 from these trials or from the companies. NMA, ST, and AN have no competing interests.

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19 476

20 477 **Footnotes**

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22 478 As sponsor, the University of Oxford has a specialist insurance policy in place that would operate in
23 479 the event of any participant suffering harm as a result of their involvement in the research.

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26 480

27 481 **Provenance and peer review**

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29 482 Not commissioned; external peer review for ethical approval prior to submission.

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32 484 **Data sharing**

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34 485 For access to the data set, a formal request should be sent to the DROPLET study group. The request
35 486 will only be considered when the principal results of the study have been published.

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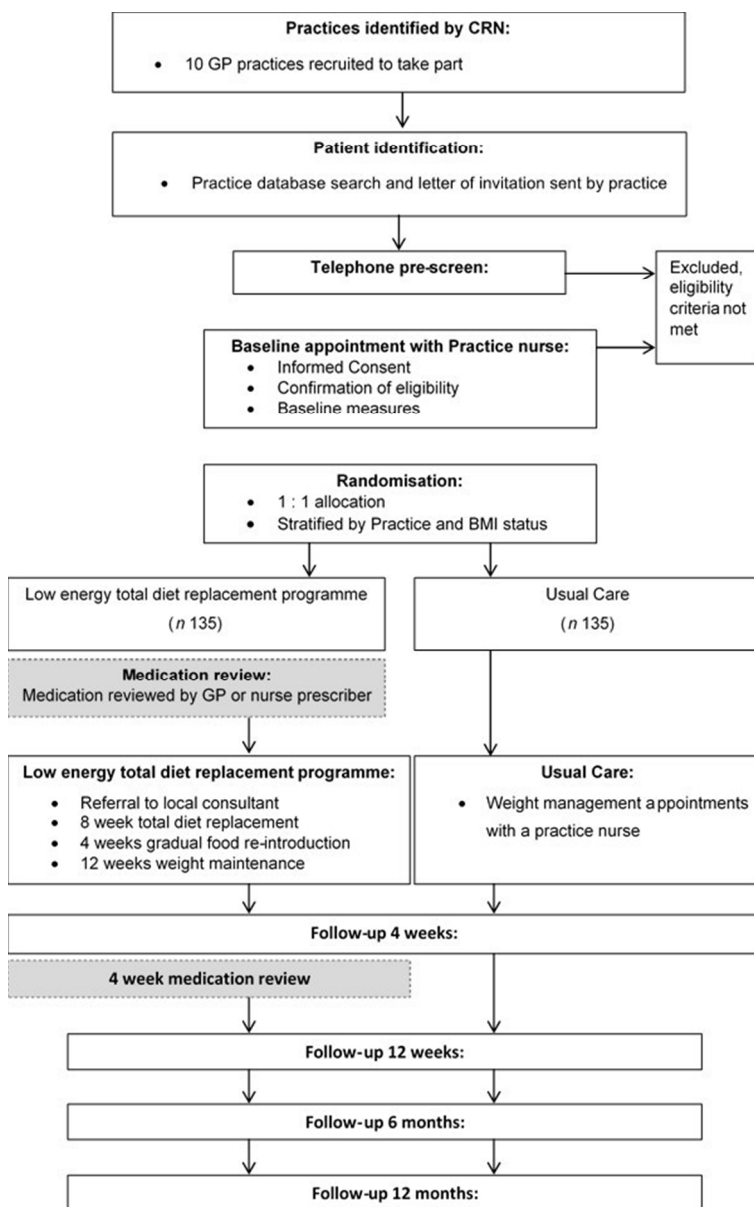
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3 **Figure 1** : Participant flow through the study
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7 **Figure 2:** Schedule of measurements
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- 9 1. Hartmann-Boyce J, Aveyard P, Koshiaris C, et al. Development of tools to study personal weight
10 control strategies: OxFAB taxonomy. Obesity (Silver Spring) 2016;**24**(2):314-20 doi:
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Participant flow through the study

159x252mm (96 x 96 DPI)

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VISIT					
	Enrolment	Follow-up visits			
TIMEPOINT	Baseline	4 weeks	12 weeks	6 months	12 months
ENROLMENT:					
Informed consent	X				
Eligibility screen	X				
Randomisation	X				
INTERVENTIONS:					
Low energy total diet replacement programme		→			
Usual Care		→			
ASSESSMENTS:					
Demographic	X				
Medical History	X				
Concomitant Medication	X	X	X	X	X
Height	X				
Weight	X	X	X	X	X
Body composition	X	X	X	X	X
Waist circumference	X	X	X	X	X
Blood Pressure	X	X	X	X	X
Fasting blood sample	X				X
Medication review	X	X			
QUALITATIVE INTERVIEWS			X		X
QUESTIONNAIRES:					
Quality of life: (EQ-5D and OWLQOL)	X		X	X	X
Programme adherence		X	X	X	X
Programme feedback		X	X	X	
OXFAB ¹			X	X	

Schedule of measurements

190x275mm (96 x 96 DPI)

Medication changes



Guidance on making adjustments to your patients' medications

This guidance aims to help you make these medication adjustments, but if in doubt please use your clinical judgement or contact the GP lead for this study.

The adjustments detailed below should be made when commencing the low-energy total diet replacement programme.

TYPE 2 DIABETES		
Patient currently takes:		Recommendation
Metformin		HALF daily dose
Sulphonylurea		STOP
Glitazone		STOP
Glinide		STOP
DPP IV inhibitor		STOP
Acarbose		STOP
At the end of the weight loss phase, re-assess patients requirements for oral diabetic therapies using HbA1c measurements or a finger prick blood glucose measurement.		
HYPERTENSION		
Patient currently takes:	Current dose	Recommendation
Loop Diuretic:		
<i>Furosemide</i>	≤ 40 mg daily	STOP
	80 – 120 mg daily	REDUCE by 40 mg daily
	≥ 120 mg daily	REDUCE by 40 mg daily
<i>Bumetamide</i>		
	≤ 1 mg daily	STOP
	2-3 mg daily	REDUCE to 1mg daily
	≥ 3 mg daily	REDUCE by 1mg daily
Thiazide Diuretic		
β Blocker	Used for hypertension	STOP
	Other uses	CONTINUE
α Blocker		
		HALF daily dose
Ca channel blocker		
		HALF daily dose
ACE inhibitors or ARBs		
	Used for hypertension	STOP
	Used for heart failure	HALF daily dose
LIPID DRUGS		
Patient currently takes:		Recommendation
Fibrates		STOP
Statins		CONTINUE
Ezetimibe		CONTINUE

209x297mm (150 x 150 DPI)



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P15
Funding	4	Sources and types of financial, material, and other support	P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	P1
	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	P15

	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)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4-6
	6b	Explanation for choice of comparators	P10-11
Objectives	7	Specific objectives or hypotheses	P6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
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	P9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P12
	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	P13
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	P13
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	P13/14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/14
	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)	P13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P15

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P15
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)	P15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P8
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	_P16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15
	31b	Authorship eligibility guidelines and any intended use of professional writers	P15-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P16
Appendices			

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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<hr/>
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	<hr/>

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

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BMJ Open

Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using total diet replacement products: a protocol for a randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016709.R2
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Complete List of Authors:	Jebb, Susan; University of Oxford, Nuffield Department of Primary Care Health Sciences Astbury, Nerys; University of Oxford, Nuffield Department of Primary Care Health Sciences Tearne, Sarah; University of Oxford, Nuffield Department of Primary Care Health Sciences Nickless, Alecia; University of Oxford, Nuffield Department of Primary Care Health Sciences Aveyard, Paul; University of Oxford, Nuffield Department of Primary Care Health Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Obesity, Diet, Weight loss, PRIMARY CARE

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Manuscripts

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1 **Doctor referral of overweight people to a low-energy treatment (DROPLET) in primary care using**
2 **total diet replacement products: a protocol for a randomised controlled trial**^a

4 Susan A Jebb¹

5 Nerys M Astbury¹

6 Sarah Tearne¹

7 Alecia Nickless¹

8 Paul Aveyard¹

10 *Corresponding Author: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary
11 Care Building, Woodstock Road, Oxford, OX2 6GG, email: nerys.astbury@phc.ox.ac.uk,
12 tel: 01865 617871

14 ¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford UK

16 ^a This trial is sponsored by the University of Oxford, Clinical Trials and Research Governance, Joint
17 Research Office, Block 60, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, UK.

19 Keywords: Obesity, diet, weight loss, primary care

1
2
3 20 **ABSTRACT**

4
5 21 **Introduction**

6 22 The global prevalence of obesity has risen significantly in recent decades. There is a pressing need to
7
8 23 identify effective interventions to treat established obesity that can be delivered at scale. The aim of
9
10 24 the DROPLET study is to determine the clinical effectiveness, feasibility and acceptability of referral
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12 25 to a low-energy total diet replacement programme compared with usual weight management
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14 26 interventions in primary care.

15 27 **Methods and Analysis**

16 28 The DROPLET trial is a randomised controlled trial comparing a low-energy total diet replacement
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18 29 programme with usual weight management interventions delivered in primary care. Eligible patients
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20 30 will be recruited through primary care registers and randomised to receive a behavioural support
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22 31 programme delivered by their practice nurse or a referral to a commercial provider offering an initial
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24 32 810 kcal/d low-energy total diet replacement programme for 8 weeks, followed by gradual food
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26 33 reintroduction, along with weekly behavioural support for 24 weeks. The primary outcome is weight
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28 34 change at 12 months. The secondary outcomes are weight change at 3 and 6 months, the
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30 35 proportion of participants achieving 5% and 10% weight loss at 12 months and change in fat mass,
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32 36 HbA1c, LDL cholesterol and systolic and diastolic blood pressure at 12 months. Data will be analysed
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34 37 on the basis of intention to treat. Qualitative interviews on a sub-sample of patients and healthcare
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36 38 providers will assess their experiences of the weight loss programmes and identify factors affecting
37
38 39 acceptability and adherence.

39 40 **Ethics and dissemination**

40 41 This study has been reviewed and approved by NHS/HRA Research Ethics Committee (Ref:
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42 42 SC/15/0337). The trial findings will be disseminated to academic and health professionals through
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44 43 presentations at meetings and peer reviewed journals and to the public through the media. If the
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46 44 intervention is effective, the results will be communicated to policymakers and commissioners of
47
48 45 weight management services.

49 46 **Trial registration number**

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48 STRENGTHS & LIMITATIONS

- 49 • This study is the largest randomised controlled trial to date of a low-energy total diet
50 replacement programme for weight management in routine primary care
- 51 • This intervention is based on a model of care where GPs refer patients to a programme
52 delivered in the community by a commercial provider using non-NHS staff, which, if
53 successful, could be readily adopted into practice without the need for specialist training for
54 the primary care workforce
- 55 • The primary outcome is weight at one year. Although this is 9 months after the low-energy
56 total diet replacement, epidemiological evidence suggests that any weight lost will continue
57 to be regained beyond one year.
- 58 • The intention of obesity treatment programmes is to improve long-term health but this
59 study does not include morbidity or mortality outcomes.
- 60 • Longer term follow-up data would be helpful to better estimate the longer health impact
61 and cost effectiveness of the intervention.

62 INTRODUCTION

63 The prevalence obesity worldwide has more than doubled since 1980¹. According to the latest
64 estimates from the World Health Organization (WHO) more than 1.9 billion adults were overweight,
65 of whom 600 million were obese, representing 39% and 13% of the world's adult population,
66 respectively². Obesity is associated with premature mortality³ but also substantial morbidity,
67 including significantly increased risks of diabetes, cardiovascular disease and most non-smoking
68 related cancers, as well as physical impairments linked to excess weight such as breathlessness, joint
69 problems and back pain⁴. Collectively this creates a burden of ill-health and reduced quality of life
70 for individuals, additional treatment costs to the NHS and reductions in economic productivity⁵.
71 While high priority must be given to prevent future cases of obesity, in the short term there is a
72 pressing need to identify effective interventions to treat established obesity. Research has shown
73 that even modest reductions in weight can bring significantly reduced risks of disease. For example,
74 in the US Diabetes Prevention Program (DPP) individuals randomised to an intensive lifestyle
75 intervention lost 7kg by the end of the first year. Although some of this weight was regained, the
76 intensive lifestyle group remained 4 kg lighter than the usual care group at four years and this
77 reduced the incidence of diabetes by 58% relative to usual care⁶ with benefits persisting to at least
78 15 year follow-up despite weight regain⁷.

79 Primary care is an important setting for weight management interventions to reduce multi-
80 morbidity. However, although a number of interventions have been shown to be effective in
81 intensive research studies, this success has not always been replicated in routine settings. For

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3 82 example, there was no significant reduction in weight when a weight loss programme adapted from
4 83 the DPP was delivered by primary care teams⁸. Our recent review of interventions suitable for use in
5 84 routine care⁹ and a second review, using slightly different inclusion criteria, of interventions
6 85 specifically delivered in primary care¹⁰ both concluded that behavioural weight management
7 86 interventions led by primary care practitioners were ineffective. This may relate in part to the
8 87 complexity of advice needed for successful dietary change and the need for frequent contact to
9 88 provide support which exceeds the capacity of routine primary care systems. However, although a
10 89 number of interventions have been shown to be effective in intensive research studies, this success
11 90 has not always been replicated in routine settings. GP referral to a commercial provider offering
12 91 group-based support is an effective option for weight management in primary care, and our meta-
13 92 analysis showed a mean reduction in weight of 2.3 kg over no intervention at one year⁹. However,
14 93 greater weight losses would be expected to bring greater health gains.
15 94 Very low energy diets (VLEDs) have been used for weight loss over many years in specialist settings.
16 95 A VLED is defined as a diet providing ≤ 800 kcal a day, based on the use of specially formulated
17 96 products designed as the sole source of nutrition during periods of total diet replacement. When
18 97 used as directed, these formula products meet 100% of the dietary reference values for vitamins,
19 98 minerals and trace elements for healthy, weight-stable people and are enriched with high biological-
20 99 value protein. Although most contain some dietary fibre, a fibre supplement may also be
21 100 recommended. A recent systematic review and meta-analysis of the available randomised controlled
22 101 trials showed that behavioural weight management interventions incorporating a VLED led to 3.9 kg
23 102 greater weight loss at one year compared with intensive specialist-delivered behavioural
24 103 programmes¹¹. However, most of the trials included in this review were small, typically including
25 104 only 50-100 participants that were treated by obesity specialists and many trials had methodological
26 105 limitations.
27 106 UK guidance from the National Institute for Health and Care Excellence (NICE) recommends that
28 107 VLEDs may only be used for a maximum of 12 weeks in people who have a clinical need to lose
29 108 weight rapidly, such as prior to a knee replacement surgery or those seeking fertility services, but
30 109 recommends against their routine use to manage obesity¹². Clinical guidance in the USA does not
31 110 recommend the routine use of VLEDs, but rather suggests that their use “*may* be reasonable in
32 111 limited circumstances, but only when provided by trained practitioners in a medical care setting
33 112 where medical monitoring and high intensity lifestyle intervention can be provided”¹³.
34 113 Nevertheless, there has been growing interest in the potential for routine use of weight loss
35 114 programmes similar to traditional VLEDs, in so far as they incorporate a period of total diet
36 115 replacement using specially formulated products as the sole source of nutrition, but where the

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3 116 energy content is more than 800kcal/day but less than 1200 kcal/day. The NICE guidelines suggest
4 117 that this type of low-energy diet could be considered for weight management, providing care is
5 118 taken to ensure they are nutritionally complete¹². There is one observational report (n = 91) on the
6 119 use of these low-energy total diet replacement programmes in primary care which found that 64%
7 120 of participants completed the 810kcal/day dietary programme, defined as either 12 weeks or
8 121 reaching 20kg weight loss, with a mean weight loss of 16.9 kg (standard deviation (SD) = 6.0 kg). One
9 122 third of participants starting the programme maintained a weight loss of ≥ 15 kg at 12 months¹⁴. A
10 123 large randomised controlled trial, the DiRECT study, is currently underway to investigate whether
11 124 this type of low-energy total diet replacement programme can be used to treat type 2 diabetes
12 125 among people who are also overweight¹⁵. It will compare the health effects of the current best-
13 126 available type 2 diabetes care with those achieved through weight management based on a low-
14 127 energy total diet replacement programme. While this will provide important mechanistic evidence
15 128 on the links between weight loss and diabetes risk, it will be delivered by NHS staff whereas the
16 129 present study will test the effectiveness of referral outside the NHS to a commercial provider.
17 130 To fill this evidence gap we will conduct a randomised controlled trial to specifically test the
18 131 effectiveness of a GP referral to a community-based low energy total diet replacement programme
19 132 for patients who are obese and likely to benefit from weight loss. It will assess the clinical
20 133 effectiveness of a weight loss intervention by measuring weight loss and the change in biomarkers of
21 134 cardiovascular risk at 12 months relative to weight loss advice provided by practice nurses. This
22 135 comparator is intended to represent 'usual care', though in practice most patients who are obese
23 136 are not offered support to lose weight.
24 137 The context for this trial follows the established model for GP referral to community group-based
25 138 weight loss programmes¹⁶. This uses the generic authority and credibility of health professionals to
26 139 motivate patients to consider weight management and the specialist knowledge of the commercial
27 140 provider to guide the intervention and offer frequent contact and behavioural support to the
28 141 patient. If successful, it will provide another option for weight management that can be offered to
29 142 patients in primary care, and GPs will be able to guide patients towards the treatment which best fits
30 143 their circumstances and preferences. This trial will specifically test whether a partnership between
31 144 GPs and providers will allow for the safe provision of low energy total diet replacement programmes
32 145 even for patients with multi-morbidity who may gain the greatest benefits from such interventions
33 146 but who may also need clinical oversight and adjustments to some of their medications as they lose
34 147 weight. It will provide the opportunity for qualitative research to investigate the perspectives of
35 148 patients and health care practitioners on this type of treatment.
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3 150 **OBJECTIVE:**

4 151 The aim of the DROPLET trial is to determine the clinical effectiveness, feasibility and acceptability of
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6 152 referral to a low-energy total diet replacement programme compared with usual weight
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8 153 management interventions in primary care.
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For peer review only

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3 154 **METHODS:**

4 155 **Design and Setting**

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6 156 The study will take place in general practices in England. Designed as an individually randomised,
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8 157 two arm and parallel group superiority trial with the primary endpoint as objectively measured
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10 158 changes in body weight from baseline to 12 months. Due to the nature of the intervention it will not
11
12 159 be possible to blind participants, clinicians or some of the study team to the treatment allocation
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14 160 after randomisation.
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16 162 **Recruitment**

17 163 Around 10 general practices will be identified to take part through the clinical research networks.
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19 164 Recruited practices will be asked to conduct a search of their electronic health records in order to
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21 165 identify suitable patients for the DROPLET study. As a result of this search, eligible patients will be
22
23 166 sent an invitation letter from their GP as part of a staggered mail out. Patients will be encouraged to
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25 167 call the research team if they are interested in taking part.
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27 168 GPs may also identify eligible patients during routine consultations. The GP will provide the patient
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29 169 with an invitation letter and suggest that the patient ring the study team. The study team will
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31 170 provide the potential participants with information on what taking part in the study will entail, and
32
33 171 an initial assessment of suitability to take part. Those who make contact and self-report meeting the
34
35 172 eligibility criteria will be scheduled for a baseline/enrolment appointment.

36 173 **Inclusion Criteria:**

- 37 174
- 38 175 • Participant is willing and able to give informed consent for participation in the study.
 - 39 176 • Aged 18 years or above.
 - 40 177 • Body Mass Index ≥ 30 kg/m².
 - 41 178 • Likely to benefit from weight loss in the GP's opinion.

42 179 **Exclusion criteria:**

- 43 180 • Unable to understand English
 - 44 181 • Currently or recently (within 3 months of study entry) attended a weight management
45 182 programme or currently participating in another weight loss study.
 - 46 183 • Had bariatric surgery, or scheduled bariatric surgery.
 - 47 184 • Pregnant, breastfeeding, or planning to become pregnant during the course of the study.
 - 48 185 • Receiving insulin therapy
 - 49 186 • Heart attack or stroke within the last 3 months,
 - 50 187 • Heart failure of grade II New York Heart Association and more severe
 - 51 188 • Angina, arrhythmia, including atrial fibrillation or prolonged QT syndrome
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3 188 • Taking MAOI medication
4 189 • Taking anticoagulant medication (e.g. warfarin)
5 190 • Taking varenicline (smoking cessation medication)
6 191 • Chronic renal failure of stage 4 or 5
7 192 • Active liver disease (except NAFLD) a past history of hepatoma or within 6 months of onset
8 193 of acute hepatitis.
9 194 • People having active treatment for cancer other than skin cancer treated with curative intent by
10 195 local treatment only or people taking hormonal or other long-term secondary prevention
11 196 treatment after initial cancer treatment.
12 197 • Active treatment or investigation for possible or confirmed gastric or duodenal ulcer.
13 198 Maintenance treatment with acid-suppression is not a contra-indication.
14 199 • Porphyria
15 200 • Scheduled for surgery within 12 months
16 201 • A member of household is already enrolled in the study
17 202 • Unwilling to provide blood samples
18 203 • Patients that the GP judges not able to meet the demands of either treatment programme
19 204 or measurement schedule. This may include severe medical problems not listed above or
20 205 severe psychiatric problems including substance misuse that make following the treatment
21 206 programme or adhering to the protocol unlikely.
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208 **Participant Flow**

209 The baseline/eligibility assessment will be scheduled with a practice nurse or health care assistant at
210 their own GP practice, where informed consent for participation in the study will be obtained before
211 eligibility will be formally assessed. After demographic information and all baseline measurements
212 have been collected the participant will be randomised to the allocated treatment group using the
213 online randomisation system. The patients' own GP will be notified by letter of the enrolment and
214 randomisation of their patient, so that it may be documented on their medical record. Participants
215 allocated to the low-energy total diet replacement programme and taking medications for type 2
216 diabetes, hypertension or high cholesterol will have their medications reviewed by a prescribing
217 member of the clinical care team, usually the GP or trained nurse prescriber. During this medication
218 review the clinician will decide what changes to medications are required at the time the participant
219 commences the low energy total diet replacement programme, with guidance provided by the study
220 team (Supplementary Figure 1). In addition, participants randomised to the low-energy total diet
221 replacement group and who take anti-hypertensive medications will be provided with a home blood
222 pressure monitor and asked to record blood pressure once daily during the weight loss phase (weeks

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3 223 1-12). These readings can be used to guide clinicians with any further changes in hypertension
4 224 medications.
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6 225 All participants will be invited to attend a 4 week follow-up appointment with the practice nurse.
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8 226 The main purpose of the visit is a clinical review of medication, including any adjustments required.
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10 227 Any changes in medication will be recorded on the concomitant medication log. Participants will be
11 228 invited to attend further follow-up visits with a member of the trial team at the GP practice at 12
12 229 weeks, 6 months and 12 month following randomisation. Participant flow through the study is
13 230 outlined in **Figure 1**.
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232 **Sample size**

19 233 The total number of participants to be recruited for this study is 270. This is based on a sample size
20 234 calculation for the primary outcome using equal variance independent samples t-test assuming a
21 235 difference between groups at 12 months of 4kg with a standard deviation in both groups of 9kg;
22 236 obtained from a meta-analysis of published studies¹¹. The sample size has been inflated by 20%, to
23 237 account for attrition, and assumes 90% power and two-sided alpha of 5%.
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239 **Randomisation**

30 240 All eligible, consenting participants will be randomised with an allocation ratio of 1:1 to low-energy
31 241 total diet replacement or usual care programmes using an online program which reveals group
32 242 allocation as per a computer-generated randomisation list. The randomisation criteria will be
33 243 validated by an independent statistician. Allocation will be stratified by GP Practice and baseline BMI
34 244 ($\leq 35\text{kg/m}^2$ or $> 35\text{kg/m}^2$) using stratified block randomisation with randomly varying block sizes of
35 245 size 2, 4, and 6. The randomisation software ensures full allocation concealment, with the allocation
36 246 group only revealed to the person performing the randomisation once a study identifier and
37 247 required stratification details have been entered.
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3 248 **Interventions**

4 249 **Low-energy total diet replacement**

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6 250 The programme offered to participants randomised to the active intervention will be provided by
7
8 251 Cambridge Weight Plan Ltd.™ Northants., United Kingdom.

9
10 252 Following randomisation participants allocated to this group will be referred to a local Cambridge
11 253 Weight Plan Counsellor who will invite the participant to attend regular appointments for 24 weeks.

12 254 These appointments consist of motivational support, encouragement, reassurance and problem-
13 255 solving. All counsellors attend a 1-day in-person training course covering screening for suitability,

14 256 nutrition, behavioural approaches, and medical monitoring. They must pass and accreditation

15 257 examination before they are allowed to deliver the programme in the community. Thereafter, they

16 258 have a yearly training updates, a nominated sponsor (experienced counsellor) and access to an

17 259 online chat forum for sharing queries. Cambridge Weight Plan has a healthcare professional

18 260 available for the counsellors to consult for advice on specific medical and nutritional queries.

19 261 Counsellors delivering the intervention for the purposes of this trial received short trial specific

20 262 training before being allocated study participants.

21 263 During the first 12 weeks the participant will meet with their counsellor weekly. Patients will be

22 264 asked to follow a programme based on using formula meal replacement products (soups, shakes and

23 265 bars) and milk comprising 810kcal/day (3389kJ/d). For the first eight weeks patients will be advised

24 266 to replace *all* their usual foods and drinks with four of the formula products daily, 750ml of skimmed

25 267 milk, 2.25L of water or other non-calorific drinks and a fibre supplement (total diet replacement

26 268 stage). During the first two weeks, the formula products will be limited to liquid products (soups and

27 269 shakes), but from week 3 onwards participants will have the option to include meal replacement

28 270 bars as part of the formula product allowance. After eight weeks there will be a four week stepwise

29 271 reduction in the use of formula meal replacement products and a gradual re-introduction of food-

30 272 based meals. The weight maintenance phase from week 12 to 24 participants attend monthly

31 273 appointments at 16, 20 and 24 weeks, during this phase participants will consume only one formula

32 274 product a day, with the remainder of diet provided by food. This weight maintenance phase will

33 275 include a recommendation to return to the total diet replacement stage for periods of up to 4 weeks

34 276 if a participant regains 1kg or more than their weight measured at 12 weeks.

35 277 All consultations with counsellors and formula products will be provided to participants by their

36 278 nominated counsellor and will be free of charge for the first 24 weeks, after which the intervention

37 279 will end. Participants in both groups will be free to choose whether or not to continue with the

38 280 programme, but at their own cost.
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4 282 **Comparator**
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6 283 The comparator intervention will consist of the usual weight management programme provided by a
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8 284 member of the practice nurse team who has been trained to offer a weight loss programme. The
9
10 285 trial will take place only in practices where this is routine care. Participants allocated to the usual
11
12 286 care group will not be prevented from attending other weight management groups if they choose to
13
14 287 do so, but no NHS referrals to these schemes will be offered during the trial. The practice nurse will
15
16 288 give participants a copy of the booklet "So you want to lose weight ... for good"¹⁷. This 47 page
17
18 289 booklet provides advice akin to a behavioural weight management programme. The aim is to
19
20 290 produce a weight loss goal of 0.5 to 1kg/week. It includes goal setting, advice on portion control and
21
22 291 physical activity, other behavioural strategies, and monitoring and feedback on progress. Nurses will
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24 292 be asked to offer a programme for 12 weeks, at a frequency that is usually used in the practice (e.g.
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26 293 weekly or bi-weekly).

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295 **Physical activity**

296 We recognise the importance of the role of aerobic and resistance exercise in facilitating weight loss
297 and maintaining lean body mass to facilitate weight loss maintenance.

298 Participants randomised to the low-energy total diet replacement arm are given appropriate advice
299 based on their previous exercise history, current ability and what is appropriate for their stage
300 weight loss programme. Clinical guidelines in the UK emphasise the importance of advice to
301 increase physical activity and we would expect this to be incorporated into the control 'usual care'
302 intervention.

303
304 **Outcomes:**

305 **Primary outcome**

- 306 • Change in body weight from baseline to 12 months

307 **Secondary outcomes**

- 308 • Change in body weight from baseline at 3 and 6 months
- 309 • Proportion of participants achieving 5% and 10% weight loss at 12 months
- 310 • Change in fat mass between baseline and 12 months
- 311 • Change in LDL cholesterol concentrations between baseline and 12 months
- 312 • Change in HbA1c between baseline and 12 months
- 313 • Change in systolic and diastolic blood pressure between baseline and 12 months

314 **Exploratory outcomes**

- 315 • Change in fat mass from baseline to 12 weeks and from baseline to 6 months.
- 316 • Change in waist circumference from baseline to 3, 6, and 12 months.
- 317 • Change in triglyceride and HDL cholesterol concentrations between baseline and 12 months.
- 318 • Change in fasting glucose and insulin concentrations and change in HOMA-IR, HOMA-%S and
- 319 HOMA-%B between baseline and 12 months.
- 320 • Change in systolic and diastolic blood pressure between baseline and 3 months and between
- 321 baseline and 6 months.
- 322 • Change in QRISK between baseline and 12 months.
- 323 • Change in the EQ-5D scale between baseline and 12 months
- 324 • Change in obesity related quality of life measured with the OWLQOL between baseline, 3, 6, and
- 325 12 months.
- 326 • Proportion of people continuing their weight loss attempt and following the prescribed
- 327 programme at 4, 8, and 12 weeks.
- 328 • The number of weight control behaviours that participants are using assessed using the OxFAB
- 329 questionnaire¹⁸ at 3 and 6 months.
- 330 • Qualitative interviews with a sub-sample of participants at 6 and 12 months
- 331 • Adverse Event reports up to 12 weeks, the end of the weight loss intervention or 6 months for
- 332 AE's known or presumed to be related to gallstones.

333 **Measurements**

334 Figure 2 provides a summary of the measurements collected.

335 *Socio-demographic characteristics*; Participants' will be asked to self-report age, sex, ethnicity
336 *Medical History*; Relevant medical history and all concomitant medication will be recorded and
337 checked against the participants' medical record. Participants will also be asked to self-report items
338 required to determine cardiovascular risk score using QRISK2¹⁹.

339 *Physical measurements*; Height will be measured to the nearest 1cm using stadiometers available in
340 the practice. Weight will be recorded to the nearest 0.1kg using an electronic scale (SC240 MA,
341 Tanita Japan) which will also record the proportion of body fat using bioelectrical impedance. Waist
342 circumference will be measured in the horizontal plane at the upper border of the iliac crest at the
343 end of expiration²⁰ using a fibreglass non-stretch tape measure fitted with a tensioning device (Gulik
344 II Tape Measure, Fitness Mart USA). Seated blood pressure will be measured in triplicate with 1 min
345 between each measure. All physical measures are performed by assessors trained according to the
346 study manual of procedures.

347 *Fasting blood sample*; A fasting venous blood sample will be collected (to be analysed for glucose,
348 insulin, HbA1c, HDL and LDL cholesterol, triglycerides). When baseline/enrolment appointments are

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3 349 scheduled at times when it may be inappropriate to fast, participants will be asked to arrange for a
4 350 fasting blood sample to be collected at an alternative appointment within 7 days of the enrolment
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6 351 visit and before the participant commences the allocated weight loss programme.
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8 352 *Questionnaires*; Participants will be provided with a questionnaire booklet which they will be asked
9
10 353 to complete and return to the trial team in a postage paid envelope provided. The questionnaire
11 354 booklet contains the following measures:
12 355 *Obesity specific quality of life (OWLQOL)*; a weight-specific instrument intended to be used to assess
13 356 obesity specific symptoms and quality of life, general functional status and well-being, and person-
14 357 specific preference measurement ²¹.
15
16 358 *Quality of Life*; EQ-5D will be used as a standardised validated instrument used for measuring
17 359 general health status ²².
18
19 360 *Programme adherence*; Self-reported adherence to the allocated programme and methods
20 361 participants are using to attempt to lose weight will be recorded by questionnaire.
21 362 *Programme feedback*; will be assessed using several 5-point Likert scales, including whether there is
22 363 an aim to continue with the programme.
23 364 *Oxford Food and Activity Behaviours (OxFAB)*: a questionnaire to assess personal strategies used by
24 365 individuals for the purposes of weight loss¹⁸.
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3 366 **Retention and withdrawal**

4 367 We will seek to follow up all participants except those who expressly withdraw from the study.

5 368 Participants who decide to withdraw from or discontinue the intervention allocated as part of the
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7 369 study will be asked to return for follow-up visits to collect outcome measures. To promote
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9 370 participant retention and complete follow-up participants will be offered a £10 gift card for
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11 371 attending each of the 6 month and 12 month follow-up visits.

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14 373 **Adverse Events**

15 374 Adverse events are of relevance in this trial because many practitioners feel these programmes are
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17 375 poorly tolerated and unsuitable for routine use in primary care. We will record AEs following Good
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19 376 Clinical Practice (GCP). All serious and non-serious AE's that occur during the first 12 weeks of the
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21 377 study or until the termination of the weight loss programme will be recorded in participants who
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23 378 initiate one of the weight loss interventions. We will also record all AEs that are presumed to be or
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25 379 known to be related to gallstones up to 6 months.

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27 381 **Data management**

28 382 Data will be recorded in a web-based data capture system (OpenClinica), which is hosted by the
29
30 383 Primary Care Clinical Trials Unit of the University Oxford. This system is customised and has an audit
31
32 384 trail facility. Ranges and programmed validation checks are implemented in the system in order to
33
34 385 aid reliable data entry.

35 386

36 387 **Statistical Analysis**

37 388 The primary and secondary outcomes will be assessed using an intention-to-treat (ITT) analysis by an
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39 389 independent statistician. Each continuous outcome will be assumed to follow the normal
40
41 390 distribution and be analysed by means of a linear mixed effects model, adjusted for outcome at
42
43 391 baseline. The model will include fixed effects terms for randomised group, visit, interaction between
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45 392 randomised group and visit, and baseline BMI (for non-weight outcomes only), and random effects
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47 393 to account for repeated measures on the same participant at 3, 6 and 12 months. No adjustment will
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49 394 be made for baseline BMI in the analysis of the weight outcomes due to its strong collinearity with
50
51 395 baseline weight. A random effect will also be included for individual practice. An unstructured
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53 396 variance covariance matrix will be specified between repeated measurements on the same
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55 397 individual and the random effects for patient and practice will be assumed to be independent. The
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57 398 adjusted treatment effect together with the 95% confidence interval and p-value will be reported.
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59 399 The analysis will be performed using PROC MIXED in a current version of SAS. The proportion of
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3 400 participants who lose 5% and 10% of their initial weight at 12 months respectively will be presented
4 401 and the adjusted difference between two arms and 95% confidence interval will be reported. The
5 402 binary outcome will be analysed by means of a logistic mixed effects model, adjusting for baseline
6 403 BMI (fixed effect) and practice (random effect). The number needed to treat (NNT) to achieve 5 or
7 404 10% weight loss, defined as the inverse of the absolute difference in proportions, will be reported if
8 405 the differences between the treatment and control groups are statistically significant. A full
9 406 statistical analysis plan will be prepared prior to any data analysis.

14 407 **Qualitative sub-study**

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17 408 The purpose of this study is to examine participants' views of the programmes. In particular, we aim
18 409 to examine the features that helped or hindered adherence to the programme and participants'
19 410 views of the behavioural support provided in the respective programmes. We will therefore
20 411 purposively sample participants based on their responses to the satisfaction questionnaire,
21 412 reflecting positive, neutral and negative evaluations. Where possible, we will select participants to
22 413 reflect both genders, socioeconomic status, and ethnic group differences. We anticipate
23 414 interviewing around 20 participants in the intervention group and 10 in the control group but
24 415 sampling will continue until saturation is reached, evidenced by no new themes occurring.
25 416 We will develop a semi-structured topic guide for the interviews. The interviewer will encourage
26 417 respondents to discuss their perceptions and experiences freely and in depth. The interview will set
27 418 the context by asking about previous experience of weight management. Thereafter, we will ask for
28 419 participants' views on which component parts of their treatment they felt were effective and which
29 420 they felt were not effective; thoughts about ability to continue to manage their weight when
30 421 treatment has ended; and their views on medication adjustments where these occurred. The
31 422 acceptability of the weight management treatment programmes and any preference they initially
32 423 had for the total diet replacement programme or the usual care programme will be explored.
33 424 Data from participants will be collected in a confidential, telephone interview which will be audio
34 425 recorded. All interviews will be transcribed. To examine saturation, analysis will proceed
35 426 concurrently with interviewing.

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50 428 **Trial Steering Committee**

51 429 An independent Trial Steering Committee (TSC) will provide oversight of all matters relating to
52 430 participant safety and data quality and value to the public. Due to the low risk nature of the
53 431 DROPLET trial and that it is an open label trial, the TSC also has the role of the Data Monitoring
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3 432 Committee in addition to their role as the TSC. However, there are no early stopping rules and all
4 433 AEs are evaluated un-blinded to allocation by the trial management group as well as the TSC.
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6 434 The TSC includes an independent clinician, dietitian, statistician and two patient representatives.
7
8 435 The TSC has reviewed the trial protocol, statistical analysis plan and the suitability of the proposed
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10 436 safety data to be collected. No interim analysis is planned for this trial due to the short recruitment
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12 437 period and low risk nature of the two dietary approaches¹¹. The trial may be subject to inspection
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14 438 and audit by University of Oxford, under their remit as sponsor, the trial coordinating centre as the
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16 439 Sponsor's delegate and other regulatory bodies.
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441 **Ethics and dissemination**

19 442 The study protocol (Version: 4.0 Date: 5th October 2016) was reviewed and approved by the South
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21 443 Central Oxford B REC Committee (Ref: 157/SC/0337). Any protocol modifications will be sent for
22
23 444 review by the research ethics committee and will be amended at the trial registry.
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25 445 It is planned that results will be disseminated to academic and health professional audiences via
26
27 446 presentations at conferences and publication in peer-reviewed journals. Participants will be sent a
28
29 447 summary of the trial findings at the time when the main article is published. If the trial shows this
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31 448 intervention is effective, results will be communicated to policymakers and commissioners of weight
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33 449 management services through briefing papers summarising the main findings. We will also provide
34
35 450 the results to all participants coincident with publication and disseminate the results to the public
36
37 451 through a press release, regardless of what the results show.
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39 452

453 **Acknowledgements**

40 454 The low-energy total diet replacement programme including the formula meal replacement
41
42 455 products will be provided by Cambridge Weight Plan Ltd, Northants, UK.
43
44 456

457 **Funding and Sponsorship**

45 458 This research is funded by research grants from Cambridge Weight Plan Ltd and NIHR Collaboration
46
47 459 for Leadership in Applied Health Research and Care (CLAHRC) Oxford at Oxford Health NHS
48
49 460 Foundation to the University of Oxford. The sponsor of the trial is the University of Oxford.
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51 461

52 462 **Contributions**

53 463 The protocol was initiated and designed by the investigators who have no personal financial
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55 464 relationships with the Cambridge Weight Plan Ltd. Although Cambridge Weight Plan were consulted
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57 465 and commented on the protocol, the final decisions lay with the investigators. There are no
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3 466 restrictions on publication of results arising from this study and the contract between the funder and
4 467 the University ensures that the funding body will have no input into the decisions regarding
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6 468 publication.

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8 469 SAJ and PA designed the study and secured the funding. NA and ST helped to develop the protocol.
9
10 470 NA is the trial manger and AN is the trial statistician.

11 471

12 472 **Competing interests**

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14 473 SAJ and PA have led publicly funded trials in which the weight management intervention was
15
16 474 provided free of charge by other commercial companies. They receive no personal financial benefits
17
18 475 from these trials or from the companies. NMA, ST, and AN have no competing interests. Cambridge
19
20 476 Weight Plan Ltd, as the funder of this trial is also the manufacturer of the nutritional products used
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22 477 in the trial, and provided the products used in the trial free of charge to the participants.

23 478

24 479 **Footnotes**

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26 480 As sponsor, the University of Oxford has a specialist insurance policy in place that would operate in
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28 481 the event of any participant suffering harm as a result of their involvement in the research.

29 482

30 483 **Provenance and peer review**

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32 484 Not commissioned; external peer review for ethical approval prior to submission.

33 485

34 486 **Data sharing**

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37 487 For access to the data set, a formal request should be sent to the DROPLET study group. The request
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39 488 will only be considered when the principal results of the study have been published.

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3 **Figure 1** : Participant flow through the study
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7 **Figure 2:** Schedule of measurements

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9 1. Hartmann-Boyce J, Aveyard P, Koshiaris C, et al. Development of tools to study personal weight
10 control strategies: OxFAB taxonomy. Obesity (Silver Spring) 2016;**24**(2):314-20 doi:
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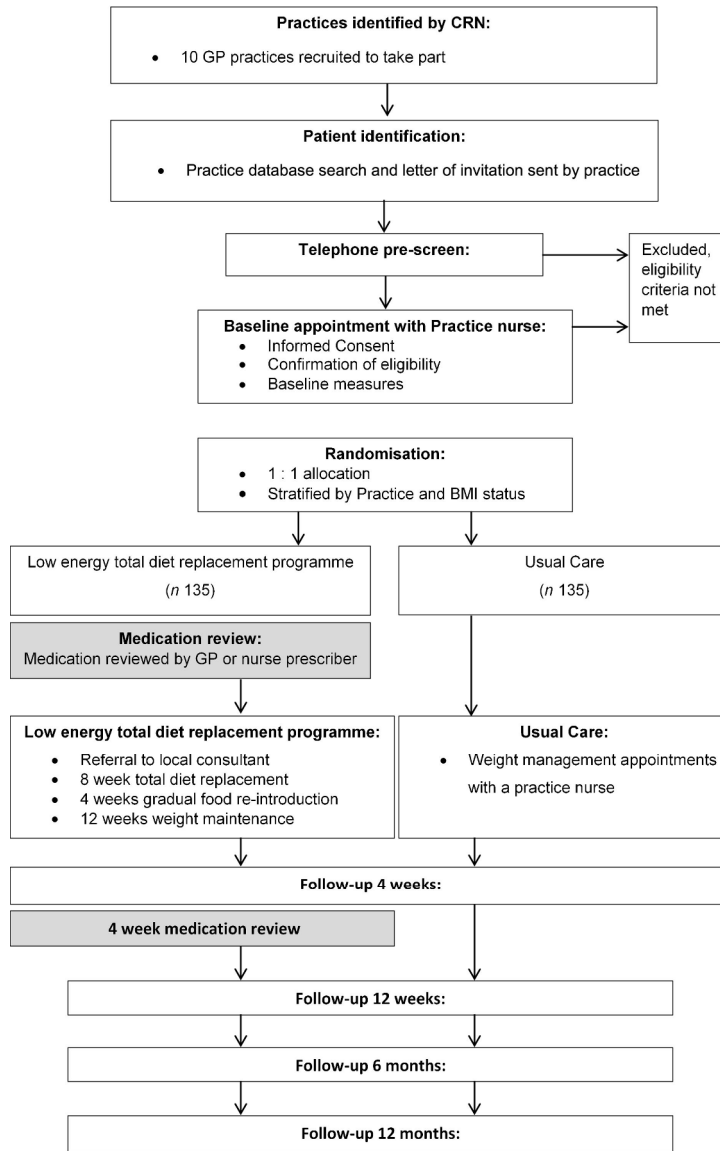


Figure 1: Participant flow through the study

159x265mm (300 x 300 DPI)

TIMEPOINT	VISIT				
	Enrolment	Follow-up visits			
	Baseline	4 weeks	12 weeks	6 months	12 months
ENROLMENT:					
Informed consent	X				
Eligibility screen	X				
Randomisation	X				
INTERVENTIONS:					
<i>Low energy total diet replacement programme</i>					
<i>Usual Care</i>					
ASSESSMENTS:					
<i>Demographic</i>	X				
<i>Medical History</i>	X				
<i>Concomitant Medication</i>	X	X	X	X	X
<i>Height</i>	X				
<i>Weight</i>	X	X	X	X	X
<i>Body composition</i>	X	X	X	X	X
<i>Waist circumference</i>	X	X	X	X	X
<i>Blood Pressure</i>	X	X	X	X	X
<i>Fasting blood sample</i>	X				X
<i>Medication review</i>	X	X			
QUALITATIVE INTERVIEWS			X		X
QUESTIONNAIRES:					
<i>Quality of life: (EQ-5D and OWLQOL)</i>	X		X	X	X
<i>Programme adherence</i>		X	X	X	X
<i>Programme feedback</i>		X	X	X	
OXFAB¹			X	X	

Figure 2: Schedule of measurements

176x215mm (300 x 300 DPI)

Medication changes



Guidance on making adjustments to your patients' medications

This guidance aims to help you make these medication adjustments, but please use your clinical judgement or contact the GP lead for this study.

TYPE 2 DIABETES		
Patient currently takes:		Recommendation
Metformin		HALF daily dose
Sulphonylurea		STOP
Glitazone		STOP
Glinide		STOP
DPP IV inhibitor		STOP
Acarbose		STOP
At the end of the weight loss phase, re-assess patients requirements for oral diabetic therapies using		
HYPERTENSION		
Patient currently takes:	Current dose	Recommendation
Loop Diuretic:		
<i>Furosemide</i>	≤ 40 mg daily	STOP
	80 – 120 mg daily	REDUCE by 40 mg daily
	≥ 120 mg daily	REDUCE by 40 mg daily
<i>Bumetamide</i>	≤ 1 mg daily	STOP
	2–3 mg daily	REDUCE to 1mg daily
	≥ 3 mg daily	REDUCE by 1 mg daily
Thiazide Diuretic		STOP
β Blocker	Used for hypertension	STOP
	Other uses	CONTINUE
β Blocker		HALF daily dose
Ca channel blocker		HALF daily dose
ACE inhibitors or ARBs	Used for hypertension	STOP
	Used for heart failure	HALF daily dose
LIPID DRUGS		
Patient currently takes:		Recommendation
Fibrates		STOP
Statins		CONTINUE
Ezetimibe		CONTINUE

209x297mm (300 x 300 DPI)



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P15
Funding	4	Sources and types of financial, material, and other support	P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	P1
	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	P15

	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)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4-6
	6b	Explanation for choice of comparators	P10-11
Objectives	7	Specific objectives or hypotheses	P6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
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	P9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P12
	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	P13
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	P13
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	P13/14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/14
	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)	P13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P15

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P15
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)	P15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P8
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	_P16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15
	31b	Authorship eligibility guidelines and any intended use of professional writers	P15-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P16
Appendices			

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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<hr/>
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	<hr/>

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

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