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Manchester Intermittent Diet in Gestational Diabetes Acceptability Study (MIDDAS-GDM): A Randomised Feasibility Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity

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(MIDDAS-GDM): A Randomised Feasibility Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity

Authors: Dapre, E., Issa, B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington, A., Vyas, A., Yates, J., Mackie, S., Evans, B., Mubita, W., Lombardelli, C.

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Abstract (word count 298)

Introduction: The prevalence of gestational diabetes mellitus (GDM) is rising in the UK and is associated with maternal and neonatal complications. National Institute for Health and Care Excellence (NICE) guidance advises first line management with healthy eating and physical activity which is only moderately effective for achieving glycaemic targets. Approximately 30% of women require medication with metformin and/or insulin. There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM. Intermittent low-energy diets (ILEDs) are associated with improved glycaemic control and reduced insulin resistance in type 2 diabetes (T2DM) and could be a viable option in the management of GDM. This study aims to test the safety and feasibility of an ILED intervention amongst women with GDM compared to best NHS care.

Method and analysis: We aim to recruit 48 women with GDM diagnosed between 24-28 weeks gestation from antenatal clinics at Wythenshawe and St Mary's hospitals, Manchester Foundation Trust (MFT) over 13 months starting in November 2022. Participants will be randomised (1:1) to ILED (2 low-energy diet days/week of 1000kcal and 5 days/week of the best NHS care healthy diet and physical activity advice) or best NHS care 7 days/week until delivery of their baby. Primary outcomes include uptake and retention of participants to the trial, and adherence to both dietary interventions. Safety outcomes will include birthweight, gestational age at delivery, neonatal hypoglycaemic episodes requiring intervention, neonatal hyperbilirubinaemia, admission to special care baby unit or neonatal intensive care unit, stillbirths, the percentage of women with hypoglycaemic episodes requiring third-party assistance, and significant maternal ketonaemia (defined as ≥1.0mmol/L) Secondary outcomes will assess the fidelity of delivery of the interventions, and

 qualitative analysis of participant and healthcare professionals' experiences of the diet. Exploratory outcomes include the number of women requiring metformin and/or insulin.

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Ethics and dissemination: Ethical approval has been granted by the Cambridge East Research Ethics Committee (22/EE/0119). Findings will be disseminated via publication in peer-reviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists.

Trial Registration Number: NCT05344066

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Strengths and limitations of this study

- This trial will inform the feasibility of recruiting and retaining women with GDM by testing an intermittent low-energy diet, and assessing its acceptability and safety in relation to foetal and maternal complications.
- The outcomes of the trial will inform the design of a future definitive trial.
- Limitations include a limited sample size.
- Women joining this study are likely to be highly motivated and adherence may not reflect that seen in the wider general population.

INTRODUCTION (word count: 3539)

Background

In the UK up to 16% of pregnant women develop gestational diabetes (GDM) and the incidence is rising, in part due to increasing rates of obesity and maternal age(1,2). GDM is associated with maternal and neonatal complications (the risk increases with poor glycaemic control), including macrosomia, shoulder dystocia, caesarean-sections, neonatal hypoglycaemia and/or hyperbilirubinaemia, preterm delivery, preeclampsia, and stillbirth(2). Women who have had GDM have an estimated seven to ten-fold risk of developing type 2 diabetes (T2DM) later in life, and their children have a higher risk of developing adult obesity and T2DM(2–4).

Excessive weight gain in pregnancy is a particular problem for women with GDM(5). Harper *et al* demonstrated that, in women with GDM, every additional 1lb/week gained following diagnosis of GDM resulted in a 36-83% increased risk of preeclampsia, caesarean-section, macrosomia, and large for gestational age babies(5). Such studies highlight the importance of adequate weight control throughout pregnancy in women with GDM in order to reduce both maternal and neonatal complications.

First-line therapy for GDM is diet and physical activity. NICE guidance encourages a healthy diet with increased fruit and vegetables, low-glycaemic index (GI) foods, reduced refined sugars, regular mealtimes and regular physical activity(6,7). These dietary measures fail to achieve glycaemic targets in ~30% of women who require medication with metformin and/or insulin(8). A range of dietary approaches have been studied including daily diets promoting low-GI diets (limiting refined and

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promoting complex carbohydrates), continuous modest energy-restriction (1800 Kcal/day), and low carbohydrate diets(9). There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM.

Intermittent Low-Energy Diets (ILED)

The pathogenesis of GDM is strongly linked to obesity and chronic insulin resistance with many clinicians viewing GDM as a form of evolving T2DM. ILEDs typically include several days of a food based or meal replacement (e.g. drinks/bars) lowenergy diet (650-1000kcal) diet, with normal eating on the remaining days of the week. These diets are associated with significant reductions in weight, insulin resistance and hyperglycaemia in patients with prediabetes (HbA1c between 42-47mmol/mol, impaired glucose tolerance, or impaired fasting glycaemia), those with T2DM, and otherwise healthy subjects with overweight/obesity(10–17). These changes are equivalent to, or greater than, those achieved with standard daily energy restriction. A popular intermittent diet involves 2 consecutive or nonconsecutive days/week of a low-energy diet (650-1000kcal) and 5 days of normal eating/week, known as the 5:2 diet. The Manchester Intermittent vs. Daily Diabetes App Study (MIDDAS), a study comparing an ILED and a continuous low-energy diet in T2D conducted in our unit, has shown the feasibility and safety of an ILED (800kcal for 2 days/week) in patients with T2DM and obesity, including those using insulin(18). At the end of the study approximately 70% of participants in the ILED group completed the study and achieved a 6% reduction of their baseline body weight. Forty two percent achieved an HbA1c of <48 mmol/mol(18). Given the strong overlap between GDM and T2DM, an ILED may be a promising dietary intervention for those with GDM.

A successful dietary approach to glycaemic control could empower women to take charge of the management of their GDM. Women with GDM are motivated to modify their diet driven by a desire to improve foetal outcomes(19–21).

Our Patient and Public Involvement and Engagement (PPIE) work indicates that women find the current National Institute for Health and Care Excellence (NICE) healthy eating guidance(6,7) confusing and vague. Women are keen to try alternative dietary approaches, particularly if alternative diets are more effective in preventing the need to progress to medications such as metformin and insulin.

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Aim

The aim of this trial is to test the feasibility of being able to recruit and retain participants for a future randomised controlled trial (RCT) of an ILED in GDM, assess and ensure the safety of the intervention, and assess the ability of participants to adhere to the diet. An exploratory outcome will be the difference in progression to, and the magnitude of, antidiabetic medication in women with GDM following the ILED and best NHS care. This will inform the primary outcomes for a future largescale RCT.

METHODS

Trial Design

The study is a 28-week feasibility two-arm RCT in one NHS trust performed in patients with GDM and BMI \geq 27.5 kg/m², or \geq 25 kg/m² in high-risk minority ethnic groups (i.e. South Asian, Black African, African Caribbean). There will be an embedded qualitative sub-study for participants and healthcare professionals. Due to the nature of the intervention, it will not be possible to blind the participants, clinicians, or study team to the treatment allocation after randomisation (the statistician and laboratory technicians will remain blinded).

Trial Setting and Recruitment

Participants will be recruited from antenatal clinics at Wythenshawe and St Mary's Hospitals, MFT. Assessments will be carried out at MFT, or remotely if required by COVID-19 restrictions. The qualitative sub-study will be carried out at MFT, remotely, or at a location of the participant's choosing. We aim to recruit eligible participants over a period of 13 months. Potential participants will be given written information about the study and the opportunity to ask questions about the study prior to providing written consent (figure 1).

Eligibility Criteria

<IMAGE ONE; figure1 inclusion exclusion jpg>

Participant Flow

Participants who fulfil the broad eligibility criteria will be notified about the trial by the GDM nurse/midwife at the time of their diagnosis. Those who are interested will be provided with a comprehensive patient information sheet (see appendix) and more detailed eligibility screening questions. They will be asked to attend their first appointment having fasted for at least 6 hours and complete a four-day food diary (in line with our departments usual care). On attending their first routine clinic appointment, interested participants will receive further information from the research team. They will have the opportunity to ask questions, have their eligibility confirmed, and will be asked for their written consent to take part. Baseline assessments will be taken and participants will be randomised to their allocated treatment group using an online randomisation platform. Participant flow through the study is demonstrated in figure 2.

Sample Size

We plan to recruit 24 participants per study arm (n=48) which, when considering an estimated attrition rate of 15%, will provide complete outcome data on 40 participants(22–24). It has been estimated that 24 participants per group will be sufficient to determine study outcomes, in line with sample size recommendations for feasibility studies(25–27). This number will allow us to evaluate the other objectives of the trial, to assess the impact of the intervention on each of the outcome measures, to estimate parameters necessary to design a main trial, and will enable estimation of recruitment/retention parameters with sufficient precision.

Randomisation

The randomisation schedule will be independently set up and known only by the trial statistician. The trial statistician will be blinded to the participant's identity using "sealed envelope" software (https://www.sealedenvelope.com/). Randomisation will be carried out by generating an online pseudo-random list with random permuted

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blocks of varying size, known only to the statistician, and will be stratified for two variables:

- Age (18-35, >35 years)
- BMI (27.5-34.99kg/m² and >35kg/m2, >25-32.49kg/m² and >32.5kg/m² for high-risk minority ethnic groups (i.e. South Asian, Black African, African Caribbean)

Treatment to intervention and control groups will be allocated in a 1:1 ratio. A member of the research team (who will be unaware of the randomisation algorithm) will trigger the randomisation procedure onsite; participants and clinicians will then be informed of the allocated treatment group. Clinicians will not be blinded due to the need to remain astute to safety, adherence, and side effects, requiring open and honest discussions with patients at each appointment. The statistician will remain blinded to treatment allocation until all outcome measures for all subjects have been collected.

Interventions

Study Arm 1: Best NHS Care Diet

All dietetic advice will be face to face or via video calls or the telephone. Participants will receive one to one personalised written and verbal advice from a dietitian to follow NICE diet and physical activity recommendations(6,7). Dietitians and midwives will receive training to ensure standardised delivery of information in clinic, and standardised patient information leaflets will be supplied to include information about increased fruit/vegetable intake, low-glycaemic index foods, and a reduction in free sugars. Information will include advice about the importance of regular meals; dietary advice aims to ensure that participants include at least 70g protein/28g fibre, and predominantly mono- and polyunsaturated fats as per American Diabetes Association recommendations(28). Participants will be advised to be physically active, for example walking for 30 minutes after a meal. Participants will receive ongoing dietetic education and support every 2 weeks until delivery. They will receive suggested menus and recipes to follow the NICE recommended healthy diet for GDM. Participants will be asked to measure their capillary glucose four times each day and their ketones on two random (recorded) days of the week of their choosing (see appendix).

Study Arm 2: Intermittent Low-Energy Diet (ILED)

Participants will receive advice on adopting an ILED which involves 2 nonconsecutive low-energy diet days/week (1000kcal to include 100g low-GI carbohydrate and 70g of protein) and 5 days/week of the NICE healthy eating low-GI diet and physical activity recommended for the best NHS care group. The lowenergy days involve women selecting a set number of portions of protein, carbohydrate, fat, fruit, vegetables, and dairy/dairy alternatives as described in previous studies(29). Each low-energy day includes ~210g of lean protein foods, 3-4 portions of wholegrain carbohydrates, 1x7g portion of fat, 5 portions of vegetables, 2 of fruit, and 3 of dairy/dairy alternatives. Food and drink will be self-selected and not provided by the study team. Participants will be provided with comprehensive food lists, advice on portion sizes for the low-energy days and suggested menus and recipes to follow for both the low-energy and NICE recommended healthy diet days. Both diets can be successfully adapted for people of different ethnicities and those following omnivorous, vegetarian and vegan diets. Participants will be asked to measure their capillary glucose four times each day and their ketones on (and the ئد بts jpg> morning after) the two low-energy days (see appendix).

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<IMAGE 2: figure 2 flow jpg>

<IMAGE 3: figure 3 sched assessments jpg>

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Outcomes

Primary outcomes

- Uptake rate measured as a percentage of eligible participants who consent to take part, including the proportion of women who were screened who did not meet the eligibility criteria, and the number of women who did not give consent to take part
- Recruitment rate measured as the number of eligible participants who consent to take part per month
- Retention rate measured as the number of randomised participants who complete the trial (those who attend the final visit) and the percentage of participants who attend all 8 visits
- Adherence to the dietary interventions assessed from self-reported adherence to the potential low calorie days between randomisation and delivery
- Completion of self-assessed glucose and ketone readings assessed as a percentage of the required readings
- Safety outcomes:
 - Percentage of women following ILED/best NHS care with hypoglycaemia (episodes of blood glucose of <3.0mmol/mol) and hypoglycaemia requiring third-party assistance
 - Percentage of women who develop significant ketonaemia in both groups (defined as ≥1.0mmol/L)
 - Percentage of neonatal hypoglycaemic episodes requiring intervention (blood glucose checked 2- hours post-delivery and 2-hours thereafter for 12 hours according to local protocol), neonatal birth weight, gestational age at delivery, hyperbilirubinaemia/jaundice, and/or admission to Special Care Baby Unit or neonatal intensive care, and stillbirths
 - The incidence and rate of other adverse effects (e.g. headaches, lethargy, and constipation between the start of the trial intervention and delivery – mild, moderate and severe, as defined by Common Terminology Criteria for Adverse Events version 5 (CTCAEv5)(30). Hospital admission for routine labour and delivery will not be classified as an adverse event.

Secondary outcomes

- Completeness of collection of trial endpoints including the percentage of completed weight measurements, 4-day food diaries, and International Physical Activity Questionnaire (IPAQ) scores
- Fidelity of delivery of the interventions will be measured through the number and modality of completed planned patient contacts with the dietitian
- Qualitative analysis of the acceptability and implementation of the interventions will be explored amongst a subset of participants (~10 in each group) and healthcare professionals through in-depth interviews
- Dietary changes in both groups will be assessed using the UK Diabetes and Diet Questionnaire (UKDDQ), analysis of completed food diaries, and any other dietary modifications self-reported at the two weekly dietitian reviews

Exploratory outcomes

- 1. Maternal outcomes:
 - The percentage of women requiring metformin and/or insulin
 - Four-point capillary glucose profiles during third trimester (four times daily until delivery)
 - Change in fasting blood test results between baseline measurements, 36-37 weeks' gestation, and 12 weeks post-delivery (including oral glucose tolerance tests (OGTT)
 - Mode of delivery, development of preeclampsia, polyhydramnios (maximum liquor volume pool depth ≥8 cm)
 - Quality of life and health status questionnaires (WHOQoL-BREF and SF-36 questionnaires)(31,32)

2. Foetal outcomes:

- Foetal weight
- Gestational age at delivery
- Cord-blood glucose, insulin and C-peptide, where collection is possible.

Measurements

The full schedule of assessments can be found in figure 3.

Physical measurements

Height, weight and blood pressure will be measured using standardised calibrated equipment in antenatal clinic.

Blood samples

Fasting venous blood samples will be collected to assess maternal HbA1c, fasting glucose, insulin, beta-hydroxybutyrate, liver function tests, free fatty acids, thyroid function tests, and full blood count. A cord blood sample will be collected at the time of delivery to measure neonatal glucose, and insulin and C-peptide where collection is possible. At the end of the study all samples will be disposed of in accordance with the Human Tissue Act (2004).

Questionnaires

Participants will be asked to complete four questionnaires at four time points throughout the trial. Quality of life and health status will be assessed using the World Health Organisation Quality of Life Questionnaire (brief version) and the 36-Item Short Form Survey respectively(31,32). Physical activity will be measured using the International Physical Activity Questionnaire – Short Form, and diet quality will be assessed using the UK Diabetes and Diet Questionnaire(33,34).

Food Diaries

4-day dietary records will be completed using Libro (Nutritics Mobile Application) or paper food diaries, which will be entered into Nutritics software (Nutritics, Dublin, Ireland)(35). Diaries will provide the research team with information about the intake of energy, carbohydrate, fat, protein, fibre, glycaemic index, and the timing of meals for participants in both groups. Participants will be asked what other dietary modifications, if any, they have made at their fortnightly dietitian reviews to establish the adoption of any alternative dietary practices in the cohort.

Adverse Events

Participants in both groups will be asked about any adverse effects that they have experienced at each visit. These will include, but are not limited to, the potential effects of a low-energy diet, e.g. headache, lethargy, dizziness, constipation, indigestion, poor concentration, and hunger. Adverse events will be graded as per CTAEv5(30). Participants will be issued with a participation/emergency card with emergency contact details for the research team to be carried at all times and to be shown to the attending physician in case of emergency admission to hospital. All participants will be issued with clear instructions as to how to manage a hypoglycaemic and/or ketonaemic event (see appendix).

Data management

Participant data will be anonymised and will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act (2018) and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations (2006) as defined in the MFT Clinical Trials Office Archiving SOP (11; Retention of Data, Off-Site Archiving, and Destroying Documents). Deidentified data will be stored in a study-specific Research Electronic Data Capture (REDCap) database. The sponsor will periodically audit the site study file, a sample of the case report form, consent forms, and source data, and check accuracy of the study database to ensure satisfactory completion. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Statistical methods

A statistical analysis plan specifying the full details of the primary and secondary outcomes, other variables, and methods, will be produced prior to trial analysis. The main analysis will be conducted via intention-to-treat population and will not undertake any significance tests. Descriptive, graphical (summary), and basic statistics (e.g. i. number, frequencies and percentages, ii. mean and standard deviation, or iii. median and quartiles as appropriate) will be presented as appropriate for each group respectively, for group difference jointly, and for each stratum. Per-protocol analysis will be considered as a secondary analysis. Levels of missing data will be investigated and used to inform future studies. No imputation will be used. The end of study questionnaire will be analysed using appropriate descriptive statistics for closed questions and key themes will be extracted without formal analysis from open questions to inform future research.

Progression Criterion

The success of the feasibility trial will be defined by the progression criteria as outlined in table 1.

	Feasible (green)	Feasible with modification of the protocol (amber)	Not feasible (red)	
Recruitment	≥4 patients/month	>2 patients/month	≤2 patients/month	
Uptake to the feasibility study	≥15%	10-15%	<10%	
Retention to the feasibility study	>70%	70% 50-70%		
Adherence to the	>50% of the low-	>50% of the low- 30-50% of the low-		
ILED intervention	energy days	gy days energy days		
	completed (2/week	completed (2/week	completed (2/week	
	between weeks 24-	between weeks 24-	between weeks 24-	
	28 and delivery)	28 and delivery)	28 and delivery)	

 Table 1: Trial progression criterion

Qualitative sub-study

Participants will be invited to take part in an optional qualitative sub-study at 11-13 weeks post-partum. Healthcare professionals delivering the interventions will also be invited to take part in this study.

We will undertake 110-120 semi-structured interviews with a subset of women from each group (ILED n=10 and best NHS Care n=10) at around 12 weeks post-delivery. The final sample size will be contingent on obtaining data saturation. We will also interview a sample of healthcare professionals (HCPs) involved in the delivery of care to study participants, including dieticians, obstetricians and midwives. Sampling will be purposive, aiming to obtain women from a range of ethnic groups, ages, socioeconomic backgrounds, and self-reported engagement with the intervention. Participants and HCPs will be asked about their experiences and thoughts regarding

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the intervention, including motivating factors, and facilitators/barriers to engagement. Interviews will be conducted by a researcher from the University of Manchester/MFT who is independent from the research staff involved in the delivery and assessment of the programmes. Analysis will be conducted by two independent researchers at the University of Manchester/MFT using Braun and Clarke's thematic analysis approach to identify key issues around the acceptability, usefulness of the programmes, and feasibility of a subsequent trial(36). Analysis will be inductive: open-ended, exploratory, and driven by the data.

All participants will also be asked to complete an optional and anonymous end of study questionnaire developed by the study team at their post-partum visit (see appendix). This will give participants the opportunity to feedback on their experience and will enable the study team to identify improvements to the design of a possible follow-up study.

Trial Steering Committee (TSC)

The trial steering committee will include an independent consultant endocrinologist, obstetrician, dietitian, and the patient representative. The committee will oversee the trial to ensure that it is carried out to the expected standards. The TSC will liaise with the CI to develop a schedule of meetings, proposed to occur every four months, with meetings to occur no less than annually. Minutes will be taken at TSC meetings and copies of the minutes will be filed in the Trial Master File; they will be shared with relevant stakeholders as appropriate.

Patient and public involvement

Patient and public involvement was actively sought throughout the planning and design of this trial and continues to form a key part of the trial as it progresses. The patient and public involvement and engagement (PPIE) group assisted in the development of all participant materials and provided valuable insight into the wording of participant information and acceptability of the proposed intervention. The PPIE group will be updated as the trial progresses and a further focus group will be held to advise on the interview schedule and wording for the qualitative sub-study. The group will also be invited to aid in the development of summarising key findings for dissemination to relevant patient groups.

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Ethics and dissemination

This study has been approved by the Cambridge East Research Ethics Committee and is sponsored by MFT. Findings will be disseminated via publication in peerreviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists. Anonymised data will be available upon formal request once the principal results of the study have been published. Planned modifications to the protocol will be approved by the research ethics committee before they are adopted into the study. An audit trail of ethical amendments and documentation will allow monitoring by the research team and external regulatory bodies.

This is the first study to assess the feasibility and safety of an ILED in GDM as compared to best NHS care. Given the increasing incidence of GDM and associated health risks this research is both pertinent and important. The study is not powered to show differences between ILED and best NHS care, however the planned quantitative and qualitative assessments will inform the feasibility of the programme and a future definitive trial.

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Authors' contributions

Michelle Harvie, Basil G. Issa, Elizabeth Dapre, Brian McMillan, Ting-Li Su, Fahmy Hanna, Andrea Pilkington and Avni Vyas designed the study, wrote the protocol, and secured the funding. Elizabeth Dapre drafted the manuscript for publication, with input from Michelle Harvie, Basil G. Issa, Brian McMillan, and Ting-Li Su. All other authors have proofed and checked the manuscript.

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Competing interests statement.

Michelle Harvie has co-authored three self-help books for the public to follow intermittent diets. All author proceeds are paid directly to the charity Prevent Breast Cancer (registered charity number 1109839) to fund breast cancer research.

Appendix

1.0 Patient Information Sheet (supplementary document 1)

2.0 Consent Form (supplementary document 2)

3.0 Self-monitoring schedule for capillary glucose and ketone monitoring

ILE	Ð	Best NI	HS Care
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)
the morning after each of		on 2 non-consecutive	
the low-energy days		days / week	
1 hour post evening meal	1hr post breakfast	1 hour post evening	1hr post breakfast
on each of the low-energy		meal on 2 non-	
days		consecutive days / week	
	1hr post lunch		1hr post lunch
	1hr post dinner		1hr post dinner

4.0 Medical Management Protocols

Hypoglycaemia

Participants will be advised to take 15-20g of rapid acting carbohydrate in the event of hypoglycaemia, (defined as blood glucose <4 mmol/L) which is anticipated to raise blood glucose by 3 mmol/L. Examples of rapid acting carbohydrate include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). Participants will be advised to repeat the treatment every 15 minutes until blood glucose is ≥4 mmol/l. The following table highlights when participants should consider taking additional follow-up slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g
More than 2 hours before the next meal	15-20g

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Ketonaemia

Ketone levels \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If ketone level has improved (<1.0mmol/L), no further action required.
- If ketone level has increased or remains the same, repeat ketone level after 2 hours.
- If ketone level is persistently increased, consume 40g carbohydrates and repeat in 2 hours.
- Continue to do this until ketone levels <1.0mmol/L.

If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed.

Guidance for the introduction of diabetes medication (week 24-delivery)

Diabetes medication will be introduced according to the following protocol:

- If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated.
- If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l,
- and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence prandial fast acting insulin analogue (Humalog or Novorapid)
 2-4 units with the relevant meal. Uptitrate the dose by 2 units every 3 days aiming for a 1 hour postprandial glucose of ≤7 mmol/l.
- Medication adjustment will be made in accordance with the above guidance.

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59 60 5.0 Intermittent Low Energy Diet Day Example (supplementary document 3)

6.0 End of Study Questionnaire (supplementary document 4)

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- usic Schedule of <image 1>: Figure 1: Inclusion and exclusion criteria _
- <image 2>: Figure 2: Participant flow through trial -
- <image 3>: Figure 3: Schedule of assessments -

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Inclusion Criteria

\triangleright	Pregnant	women	≥18	year
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- BMI of ≥27.5kg/m2 or a BMI ≥25 kg/m² in high risk minority ethnic group (i.e. South Asian, Black African, African Caribbean) and <50 kg/m2 at booking appointment (8-12 weeks' gestation)</p>
- ➢ Newly diagnosed GDM according to local diagnostic criteria (fasting glucose ≥5.3mmol/l and/or 2-hour postprandial glucose ≥8.5mmol/l in a 75g OGTT) scheduled to receive first line diet and physical activity (best NHS care)
- > 24-30 weeks' pregnant at screening appointment

Exclusion Criteria

- Pregestational type 1 or type 2 diabetes.
- Fasting glucose of ≥7 or 2-hour postprandial of ≥11 on OGTT (immediate intervention with medication would be required in this group of women)
- Current multiple pregnancy
- Maturity Onset Diabetes of the Young (MODY)
- Significant comorbid disease that in PI's opinion would preclude participation in the study e.g. chronic kidney disease, significant cardiac disease, significant history of disordered eating or severe psychological problems.
- > Current participation in a GDM medication treatment trial
- People who are not capable of providing informed consent or adhering to the monitoring and safety protocols
- People who have previously had bariatric surgery for weight loss including gastric bypass and sleeve gastrectomy, and/or those prescribed weight loss medications (e.g. orlistat).
- Medications at the time of the OGTT that may interfere with results (e.g. high dose oral steroids, immunosuppressants)
- Previous history of intrauterine growth restriction
- Women who have lost more than 5% of their weight from booking appointment to screening appointment.

Figure 1: Inclusion and exclusion criteria

159x144mm (220 x 220 DPI)



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	2 			Study	Visit			
	1	2	3	4	5	6	7	8
Gestation (weeks)	~24-30	~24-30	-30-34	~32-36	~34-38	~36-40	delivery	11-13 post- partum
Eligibility confirmed	x							
Informed consent	x							
Randomisation	x							
Tailored dietitian review (face to face or remote)	x	×	x	x	×	×		x
Height	х							
Weight*	x	x	×	x	x	x	×	x
Blood Pressure ^A	x	x	x	x	x	x	x	x
Fasting blood sample*	x				x			x
Questionnaires#	x		x		x			x
4-day food diary			×		x			x
Foetal growth scan	x		x		x			
Review of glucose and ketone measurements		×	x	x	x	×		
Neonatal measurements≢							x	
Oral glucose tolerance test								x
Exit interview / end of study questionnaires								x
Invitation to optional qualitative sub-study ⁵								x
*Frequency of assessm COVID-19 restrictions *Fasting bloods: urea a hydroxybutyrate, free f #Questionnaires: Worl Physical Activity Questi #Neonatal measureme ⁶ Sub-study involves sen	ent will be 2 nd electrolyt atty acids, fu d Health Org onnaire (sho nts include g ni-structured	-4 weekly de tes, liver func ill blood cour anisation Qu rt form), UK estational ag d interviews o	pending on ction tests, b nt, fasting gl ality of Life (Diabetes an te at delivery exploring par	whether app one profile, l ucose, insulir brief version d Diet Quest r, mode of de ticipants' th	ointment is ! ipids, thyroid i), 36-Item SI ionnaire slivery, neon oughts and e	face-to-face d function to hort Form Si atal weight, experiences	or virtual du ests, HbA1c, I urvey, Intern cord blood g of the trial	e to seta ational lucose
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for Health Research

NHS Foundation Trust Consultant Endocrinologist – Dr. Basil Issa **Research Dietitian – Dr. Michelle Harvie** Email: mft.middas.gdm@nhs.net Tel: 07815987910

Manchester University

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MIDDAS-GDM

Manchester Intermittent Diet in Gestational Diabetes Acceptability Study

Participant information sheet

We would like to invite you to take part in a research study that is testing two different diet programmes which aim to help people with gestational diabetes control their blood sugars.

If you decide to take part:

- You will be assigned to one of two diet programmes for the duration of your pregnancy. One involves following the standard NHS healthy diet recommendations for pregnancy, and the other follows the standard NHS healthy diet for 5 days/week plus two nonconsecutive calorie restricted days of 1,000 kcal per week (both groups will be encouraged to be physically active).
- You will be asked to attend your routine appointments at Wythenshawe or St Marys Hospital and will have fortnightly appointments until delivery of your baby (some appointments may be virtual depending on COVID-19 restrictions). You will be asked to attend the hospital for a blood test 12 weeks after having your baby.
- You will be supported by a diabetes specialist dietitian, midwife, consultant • endocrinologist, and your obstetric team throughout the study to help manage your pregnancy and blood glucose safely.
- Throughout the study you will be asked to monitor your food intake via a . smartphone/tablet app, or on paper if you prefer, and you will receive feedback on this during your dietary reviews. Comprehensive dietary advice and recipes will be provided.
- Throughout the study you will be asked to monitor your blood sugar using a blood sugar meter four times a day, and you will also be asked to monitor your ketone levels three times on two days of the week (ketones indicate how well your body is using sugar or fat as an energy source). You will be taught how to check your blood sugar and ketone levels.
- If you would like to take part, or you have any questions, then please contact mft.middas.gdm@nhs.net

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This study is being carried out by a team of trained dietitians, doctors, nurses, midwives and researchers under the supervision of Dr. Basil Issa and Dr. Michelle Harvie at Wythenshawe and St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what taking part would involve for you. Please take your time to read the following information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.

Please ring the research team at the number at the top of the first page, or e-mail mft.middas.gdm@nhs.net if there is anything that is not clear, or if you would like more information. You can attend an information session about the diets and the study before agreeing to take part if you would like to.

Your participation in the study is entirely voluntary; you do not have to take part if you do not want to and you can opt out of the study at any time without giving a reason. Thank you for reading this information. We hope this research will be of interest to you.

Why are we doing this research?

Around 1 in 8 pregnant women can develop gestational diabetes. This condition causes risks to mother and baby from high blood sugar, high blood pressure, induced labours, caesareansections, and larger babies. Women often need medication to control blood sugar despite following recommended NHS healthy eating plans for pregnancy. Intermittent low-calorie diets (two non-consecutive days over the course of the week) improve blood sugar control and reduce the need for medication in patients with type 2 diabetes. We want to find out whether intermittent low-calorie diets might also improve blood sugar control in gestational diabetes and reduce the need for medication as it is a similar condition to type 2 diabetes.

What is the purpose of this research?

This study aims to assess the acceptability (to you) and safety of an intermittent low-calorie diet compared to the usual recommended NHS healthy eating and lifestyle plan for gestational diabetes. A computer system will randomly allocate you to one of the two diets. We want to find out which diet is most acceptable to women, whether there is any difference in the two diets' effect on blood sugar control, and any side effects experienced by women. The findings of this study will inform a larger study which will be designed to more closely compare the effect of the two diets on blood sugar control in women with gestational diabetes.

Why have I been asked to take part?

You have been invited to take part in this study because you have been diagnosed with gestational diabetes. We hope to recruit around 48 people to take part in this study.



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What happens if you agree to take part?

If you agree to take part you will be randomly allocated via a computer system to one of two diet and lifestyle programmes for the remaining weeks of your pregnancy.

Best NHS Care Healthy Diet programme

You will receive personalised advice from a specialist dietician. Recommendations will include increased fruit/vegetable intake, low glycaemic index starchy foods (i.e starchy foods which are slowly absorbed and take a while to raise your blood sugar level), reducing refined sugar, and having regular mealtimes. You will be advised how to design your diet to include the right amount of protein, fats, carbohydrates, and fibre, and will be given meal plans and recipes. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Intermittent Low-Calorie Diet programme

If you are allocated to this group you will receive personalised advice to follow a low-calorie diet of 1,000 kcal on two non-consecutive days of the week and the NHS healthy diet on the other five days of the week. The 1,000 kcal days include a set number of portions of protein, carbohydrates and fat foods, fruits, vegetables and dairy/dairy alternatives typically including ~210g (7 oz) of lean protein foods and 3-4 portions of wholegrain carbohydrates, 5 portions of vegetables, 2 of fruit, and 3 of dairy or dairy alternatives and a small amount of healthy fat. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Monitoring

You will have all of your usual routine antenatal appointments including checks on your weight, blood pressure, blood tests and ultrasound scans. Extra blood tests will be done as part of the study and these will be added on to samples taken during your routine blood tests.

You will be asked to monitor your blood sugar at home four times a day until your baby is born, and your ketone levels on two days of the week (you will be taught how to do this using a finger prick machine). The results will be recorded when you attend clinic.

We would like to collect a sample of blood from the umbilical cord at delivery to check blood sugar and insulin levels, and your baby's birthweight will be documented. Guidelines currently recommend that wherever possible the umbilical cord is clamped after 1-2 minutes; this is referred to as 'delayed cord clamping' and means that babies receive as much blood as possible from the placenta. This is normal practice. The cord blood sample will not affect your ability to have delayed cord clamping and will not cause any harm to your baby. It will not be possible, however, to delay clamping of the cord for so long that all blood has left the cord (the sample needs to be taken whilst there is still some blood left in the cord).

When babies are born to mothers with gestational diabetes it is normal that their birth weight is recorded and that their blood sugar is monitored for 12 hours following delivery; these results will be recorded by the research team.

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You will be asked to attend an additional glucose tolerance test at the hospital 12 weeks after delivery to assess whether you have any residual diabetes (95% of women do not) and also to assess how sensitive your body is to insulin (an important risk factor for the development of diabetes in the future). You will be asked to attend at 9:00am having fasted (no food or drink apart from water) from midnight. A blood sample (around 10 mL/2 teaspoons) will be taken for glucose and insulin and you will be asked to drink a sugary drink with 75 grams of glucose. A further blood sample will be taken after 2 hours for glucose and insulin. You will need to remain in hospital during this time. The reason for this is to help us to understand whether there could be any difference in the body's ability to process sugar between the two diet groups, and also to find out whether any women still have signs of diabetes after pregnancy.

Any blood samples taken as part of the study will be identifiable only using your study identification number and will have none of your personal details. Part of the sample will be sent for immediate analysis and any remaining will be stored securely, accessible only by the research team. At the end of the study any left over samples will be disposed of in accordance with the Human Tissue Act (2004).

You will be asked to record your food intake via the Libro smartphone/tablet app or in a paper diary for four days during four weeks throughout the study. You will also be asked to complete three questionnaires to assess your wellbeing and level of physical activity in these weeks, and a final end of study questionnaire at the final appointment.

Ongoing support from a specialist team of healthcare professionals

Your specialist team includes a Consultant Endocrinologist, Consultant Obstetrician, diabetes specialist dietitian, midwives, and a GP trainee with a special interest in women's health. The specialist team work closely with the usual obstetric teams involved in your care. Reviews with the team will be either face to face when you attend clinic or remotely using video calls.

Mobile Applications and Glucose Meters

The study will use a smartphone application called 'Libro' to help you record information. Libro is a smartphone application which allows you to record your dietary intake during the study. We will ask you to record 4 days of food and drink intake during 4 weeks across the study. Your diaries will be viewed by your allocated dietitian who will provide personalised dietary feedback via the app. You are also free to record more days of your diet should you wish, which some people find helpful. If you do not want to use the mobile app you can use paper instead. You will be supported to set up and use the Nutritics Libro App at your appointments. You do not have to use the application to be part of the study.

Your blood sugar will be monitored using a glucose monitoring device which checks your blood sugar using a 'fingerprick' blood test. You will be shown how to do this yourself. With your permission the research team will make a note of your glucose readings at every visit, either by checking your glucose monitoring device, or by uploading your glucose meter readings onto the computer if you are using a mobile application.

The self-monitoring schedule is as follows:

MIDDAS-GDM | IRAS 302762 | Participant Information Sheet | Version 3.0 | 02/03/2023 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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NIHR National Institute for Health Research

Intermittent low-ene	ergy diet monitoring	Best NHS car	re monitoring
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)
the morning after each		on 2 non-consecutive	
of the low calorie days		days / week	
1 hour post evening	1hr post breakfast	1 hour post evening	1hr post breakfast
meal on each of the low		meal on 2 non	
calorie days		consecutive days / week	
	1hr post lunch		1hr post lunch
	1hr post dinner		1hr post dinner

What should I do if my blood glucose or ketones are out of range?

Low Blood Sugar

You are advised to take 15-20g of 'rapid acting' carbohydrate if your blood glucose is <4 mmol/L). Examples include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). You will need to repeat the treatment every 15 minutes until your blood glucose is ≥4 mmol/l.

The following table highlights when you need to consider an additional slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g (eg half of one of the items below)
More than 2 hours before the next meal	15-20g (eg slice of toast, piece of fruit, small
	bowl of cereal, glass of milk)

Raised Ketones

If your ketone levels are \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If your ketone level has improved (<1.0mmol/L), no further action is required.
- If your ketone level has increased or remains the same, repeat your ketone level after 2 hours.
- If your ketone level is persistently increased, consume 40g carbohydrates (eg one bagel, bowl of cereal and a banana, small jacket potato), and repeat in 2 hours.
- Continue to do this until your ketone levels are <1.0mmol/L.

Make Immediate Contact with the research team if:

Blood glucose	• Your blood glucose is <3.0 mmol/l or you have symptoms requiring medical	
	attention which are thought to be due to low blood glucose,	

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	 Your fasting blood glucose is >5.2 mmol/L on more than a quarter of your measurements on two days in a row, Your 1 hour post-meal blood glucose is >7.7 mmol/L on more than a quarter of your measurements on two days in a row
Ketones	Your blood ketones are >1.0 mmol/L

Will I need medications?

If your blood sugars are found to be high despite following the recommended diet and lifestyle programmes you may be advised to start medication to help control your blood sugar. You will be advised on changes to your medications by a diabetes specialist nurse/diabetes midwife and also a Consultant Endocrinologist if required. This is usual practice regardless of whether you are taking part in the study.

What care will I receive after the study has stopped?

At the end of the study, you will be provided appropriate ongoing dietary advice from the study dietitian following your final glucose tolerance test to follow the NHS healthy eating and lifestyle plan. You will receive routine postnatal care from your GP, hospital team, and dietitian if required. You will be advised to see your GP for an annual blood test to check your blood sugar levels (this is routine care for women with gestational diabetes). Approximately 5% of women with gestational diabetes have residual diabetes after delivery. This will be identified from your glucose tolerance test/HbA1c; if this is the case you and your GP will be informed. Your GP will take over the management of your diabetes as per routine care outside the study.

Interview sub study

Women in this study may be invited to take part in an interview at the end of the study . You will be asked about your views and experiences on trying to follow your allocated diet programme. This interview can be arranged at a time that suits you, either at Wythenshawe or St Marys Hospital, at your home, or over the telephone. There is no obligation to take part in this interview study.

Frequently asked questions

Do I have to take part?

No, you do not have to take part if you do not wish to and your decision will not affect any standard of care you receive at Wythenshawe or St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

What happens if I change my mind?

It is OK if you agree to take part in the study but later change your mind. You do not need to give a reason and it will not affect the standard of care you receive. The study team may also choose to withdraw you if it is necessary for your health or safety due to unexpected findings during the study. If you decide to withdraw from the study, or the study is stopped for any reason, you will be asked whether or not you are happy for us to keep the data that may have already been collected. If you do withdraw from the study you will continue to be cared for by your usual specialist diabetes and obstetric teams for the duration of your pregnancy. You will

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still have the option of completing the end of study questionnaire and/or interview to provide feedback; this is very useful for the research team to help us understand potential reasons you may have chosen to withdraw from the study.

You will also have the option that if you withdraw, researchers may still collect relevant information about your pregnancy and/or gestational diabetes from your medical records within the 18-month study duration. This will be an option on the consent form.

Are there any benefits from taking part?

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You will receive frequent personalised advice and support to follow two diet and lifestyle programmes which may help to control your blood sugar levels throughout your pregnancy. The information gained from this study will also help inform the future NHS care of patients with gestational diabetes.

Are there any risks from taking part?

Research has found that diets consisting of two low-calorie days a week are very low risk. Pregnant women will develop slightly higher levels of ketones when following low calorie diets than women who are not pregnant. Ketones are produced naturally by the body when the body uses fat stores for energy (i.e. when we follow a low calorie diet or haven't eaten enough because we are ill).

Some research suggests that very high levels of ketones throughout pregnancy may cause a higher risk of babies being slightly smaller than average. It is very unlikely that you will develop high levels of ketones by following this diet. You will be provided with a ketone meter and you will be asked to check your ketone levels before your lunch and evening meal on your low-calorie days, and the following morning, to make sure that your ketone levels are normal.

On your low-calorie days you may feel slightly more hungry, or you may experience other effects such as increased nausea, light headedness, or tiredness. It is important that you eat regularly throughout the day to reduce the risk of this happening. You will be asked to report any side effects of following the diet to the team at each appointment.

What happens if my baby or I become unwell during the study?

The safety of you and your baby are of utmost importance and remain our priority. In the instance that either of you become unwell your case will be reviewed by our specialist team and your suitability for continuing in the trial will be decided. Although it remains exceptionally rare, were you to experience the unexpected loss of your baby you will be withdrawn from the trial and supported by the dedicated specialist bereavement team at the hospital. Any information which has been collected as part of the trial will be stored securely and once we have finished the study we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What will happen to blood samples which are taken?

Some blood samples taken as part of the study will be sent to the laboratory immediately for analysis and any remaining will be stored securely for the duration of the study. Only your 'study ID' will be used – the samples will have none of your personal details on them. At the end of

MIDDAS-GDM | IRAS 302762 | Participant Information Sheet | Version 3.0 | 02/03/2023 Page 7 of 11 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml **BMJ** Open

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the study any remaining samples will be disposed of in accordance with the Human Tissue Act (2004).

What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (Dr. Basil Issa or Dr. Michelle Harvie – via the study office – via michelle.harvie@manchester.ac.uk or telephone 0161 **291** 4410). If you remain unhappy and wish to complain formally, you can do so through the NHS complaints procedure. Details can be obtained from the NHS Patient and Liaison Service (PALS) on **Tel:** 0161 276 8686 or contact the team by email pals@mft.nhs.uk.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme. If something did go wrong and you were harmed or suffered deterioration in your health as a result of taking part in this study then you may have grounds for legal action or compensation.

Additional information about the study

Will my lifestyle be affected if I take part?

An essential aspect of this study is a change to your diet and physical activity patterns with support from a specialist team of healthcare professionals.

Payments

We are able to offer free parking at Wythenshawe/St Marys Hospitals for study visits and offer reimbursement for reasonable travel expenses (car, bus or tram) linked to visits for this study. There are no other payments for taking part.

Will my details be kept confidential?

Yes. The study team and any associated regulatory authorities follow strict ethical and legal guidance regarding participant confidentiality. Any information we have about you will be handled in confidence and will only be used for the purposes of this study. All data recorded will be coded and your name will remain anonymous.

During the study we will inform your GP via letter of your participation in the study and your ongoing results, including your weight, blood tests, any abnormal findings and any recommendations for treatment.

If you join the study, some relevant parts of your medical records may be looked at by authorised personnel at Wythenshawe or St Marys hospitals prior to starting the study. These records may also be looked at by an independent auditing body and regulatory authorities to check that the study is being carried out correctly. We will only access parts of your medical records that are relevant to this research and all information accessed will be kept strictly confidential.

How will we use information about you?

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NHS Foundation Trust We will need to use information from you and from your medical records for this research

This information will include the following:

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- Initials
- NHS number .
- Name .

project.

- Contact details
 - Medical History including test results

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Other researchers from outside the Trust may ask to see this data for the purposes of furthering their research. We will only share this upon written request to the Trust. The external researchers will be asked to sign a Confidentiality Agreement before any data is shared.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health during pregnancy from your hospital records. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
- by sending an email to mft.middas.gdm@nhs.net or
- by ringing us on 07815987910

How will my details be used to access the Mobile Applications?

50 None of your personal details (other than the telephone number from which an application is 51 52 downloaded) will be needed to access the mobile applications. Once you have given your 53 consent to take part in the study you will be issued with a 'dummy' e-mail and password under 54 a pseudonym (fake name). Only the research team will know the dummy e-mail address you 55 have been assigned to, in order to be able to review your data. The application will not contain 56 your identifiable data. If you choose to use a mobile application to monitor your blood sugar 57

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levels the relevant terms of service for the app and the app developers privacy policy will apply. It will be your responsibility to read and understand these prior to download.

Will my insurance be affected if I take part in this study?

It is unlikely that your insurance premiums will be affected by participation in this study as the study has the potential to improve your diabetic control and reduce your risk of ill health. However, if you are at all concerned, then we advise that you contact your insurers and seek expert advice before agreeing to participate.

Who has reviewed this study?

Research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is made up of experts, non-experts and members of the general public. Together they review research applications to ensure your safety, rights, wellbeing and dignity are protected at all times. This study has been reviewed and given favourable opinion by REC.

What will happen to the study results?

It is intended that the results of this study will be presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. To do this our study information is double-checked by other professionals in research and healthcare. There is a possibility that the study and its results may be publicised for example on radio, television, magazines, books and websites. You will not be identified in any publicity, reports or publication arising from this study. If you would like a general summary of the results of the study you can select this on the consent form or please contact the research team.

Who is organising and funding the research?

Researchers from Wythenshawe hospital, have designed this study and will be carrying out this research. This study has been funded by the National Institute of Health and Research.

Further information and contact details

For further information about this study, please contact mft.middas.gdm@nhs.net or

Thank you for taking the time to read this information sheet. We hope it has been of interest to you.



Example of 1 day meal plan for Diet Day

The diet days aim to limit the calories to 1000 calories per day. You are aiming to include 2 (not consecutive) diet days each week. The other 5 days, follow the Mediterranean diet as described earlier. To keep the calories to 1000, the diet day will look like this:

Mixed diet		Vegetarian/ vegan diet
4	Carbohydrate portions	3
6	Protein portions	7
5	Vegetable portions	5
2	Fruit portions	2
3	Dairy portions	3
1	Fat portions	1

Below are some examples of meals that can be used to help you follow a 1000 calorie diet.. There are options for a mixed diet or vegan or vegetarian options, if you feel you wanted to try meat free days. Filling up on vegetables will make you feel less hungry

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Mixed diet options

Breakfast	Portion	Dairy	Protein	Carb	Veg	Fruit	Fat
Grilled lean bacon	1 rasher	0	1	0	0	0	0
Grilled tomatoes	7 cherry tomatoes	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Diet or natural yogurt	1 small carton	1	0	0	0	0	0
Lunch							
Wholegrain bread	2 medium slices	0	0	2	0	0	0
Tuna	⅓ of a 120g can	0	1	0	0	0	0
Green salad	Cereal bowl full / 80 g with oil-free dressing	0	0	0	1	0	0
Satsumas	2	0	0	0	0	1	0
Mid afternoon							
Low fat cheese	30g / match box size	1	0	0	0	0	0
Apple slices	I medium apple (80g)	0	0	0	0	1	0
Tea/ coffee		0	0	0	0	0	0
Evening							
Vegetable rice	4 tablespoons cooked rice 160g of mix vegetables	0	0	2	2	0	0
Chicken curry	90g /average chicken breast (no skin) & ½ can tomatoes, 1 desertspoon oil	0	3	0	1	0	1
Bedtime							
Low fat houmous	1 level tablespoon	0	1	0	0	0	0
Pepper sticks	1/2 red pepper	0	0	0	1	0	0
Milk	1 small glass	1	0	0	0	0	0
Total portions	a day	3	6	4	5	2	1
	-	portions	portions	portions	portions	portions	portion

Vegetarian option

Breakfast		Dairy	Protein	Carb	Veg	Fruit	Fat
Egg	2 poached	0	2	0	0	0	0
Mushrooms	2 cupped handfuls / 80g	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Cheddar cheese	1 match box size / 30g	1	0	0	0	0	0
Cucumber	Sliced handful	0	0	0	1	0	0
Lunch							
Baked beans	2 tablespoons	0	1	0	0	0	0
Seeded bread toasted	1 medium sliced	0	0	1	0	0	0
Blueberries	1 handful	0	0	0	0	1	0
Mid afternoon							
Meat free ham	2 slice small	0	1	0	0	0	0
Pepper	1/2 sliced	0	0	0	1	0	0
Avocado	1/4	0	0	0	0	0	1
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Vegetarian sausage casserole Jacket potato (100g)	1 grilled sausage 2 cereal bowls vegetables 1 ½ egg sized (100 g)	0	2	1	2	0	0
Bedtime							
Pear	1 medium	0	0	0	0	1	0
Low fat cream cheese	1 tablespoon	1	0	0	0	0	0
Whole wheat cracker	2 biscuits	0	0	1	0	0	0
Milk	1 small glass	1	1	0	0	0	0
Total portion	s a day	3	7	3	5	2	1
		portions	portions	portions	portions	portions	portions

Vegan options

Breakfast		Dairy equivalent	Protein	Carb	Veg	Fruit	Fat
Branflakes	3 tablespoons	0	0	1	0	0	0
Milk- soya	200 ml	1	0	0	0	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Soya yogurt	3 tablespoons	1	0	0	0	0	0
Lunch							
Kidney bean & Vegetable chilli Wholemeal	3 tablespoons of beans 60g with 1 cereal bowl mixed vegetables & 1/2 can chopped tomatoes ½ pitta	0	2	1	2	0	0
pitta	4 P		0				0
Banana	1 medium	0	0	0	0	1	0
afternoon							
Low fat hummus	2 level tablespoon	0	2	0	0	0	0
1 carrot	I medium carrot (80g)	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Quinoa	2 tablespoon cooked	0	0	21	0	0	0
Tofu	4 matchbox	0	2	0	0	0	0
Mixed salad with edamame beans	2 x Cereal bowl full with oil free dressing & 1 tablespoons of edamame	0	1	0	2	0	0
Bedtime							
Peanut butter	1 heaped teaspoon	0	0	0	0	0	1
Apple	1 medium sliced	0	0	0	0	1	0
Milk	1 small glass	1	0	0	0	0	0
Total portion	s a day	3 portions	7	2	5	2	1
-	-	-					

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To help with estimation of portions the following tables outline weight and measures of the different food groups. Where possible household measures are given to make things a little easier. Use these to help you plan your 2 days in the week of 1000 calories.

Carbohydrate 4 portions - mixed diet 3 portions - vegan/vegetarian	Equal to
Wholewheat or oat breakfast cereal, e.g. wholewheat biscuit, malted wholewheat squares, Grapenuts, bran flakes, fruit & fibre	24g or 3 tablespoons or 1 whole wheat biscuit
Porridge oats or no-added sugar muesli	20g or 1 heaped tablespoon
Wholegrain, wholemeal, rye, granary bread	36g or medium slice of bread (other than rye), 1½ slices of rye, or ½ roll
Wholemeal or multigrain pitta bread or tortilla wrap, chapatti made without fat	60g or 1x 8" tortilla or 1 standard pitta or small thin chapatti
Rye crispbread, crackers, oak cakes	22g or 2 crispbreads/ 2 oatcakes
Wholegrain rice cake	16g or 2 rice cakes
Wholewheat pasta or rice - cooked amount Cous cous, Bulgar wheat, Quinoa, Pearl barley	1 tablespoon uncooked 2 tablespoons cooked
	30g- raw weight or 60g cooked
Lasagne (wholemeal if possible)	20g raw weight or 1 large sheet or 1½ smaller sheets
Noodles (wholemeal if possible)	25g raw weight or ½ block/nest
Baked or boiled potato (in skin), cassava, sweet potato	1½ egg sized potatoes or 100g raw weight
Wholemeal pizza base (topping is from other food groups)	35g or $^{1}/_{6}$ of thin 10" pizza base
Unsweetened popcorn	20g or 2 handfuls

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Protein 6 portions – mixed diet 7 portions – vegan/vegetarian	Equal to
Fresh or smoked white fish (e.g. haddock or cod)	60g or 2oz 2 fish finger size
Seafood, e.g. prawns, mussels, crab	45g or 1½oz
Canned tuna or salmon in brine or spring water	45g or 1½oz ⅓ standard tin (120g)
Oily fish (fresh or tinned in tomato sauce or olive oil - drained), e.g. mackerel, sardines, salmon, fresh tuna, kippers, smoked salmon or trout	30g or 1oz or ¼ standard tin (120g) or ¼ fillet of salmon
Chicken, turkey, duck, pheasant (cooked without skin) Lean beef, pork, lamb, rabbit, venison, offal (fat removed) Quorn fillets, steak, mince or pieces Vegetarian mince frozen	30g or 1oz or 1 slice size of playing card
Lean grilled bacon Quorn ham	25g or ¾oz or 1 rasher
Lean ham Quorn bacon rashers (not slices)	30g or 1oz or 1 medium, 2 small or 4 wafer thin slices
Eggs	60 g or 2 oz or 1 egg
Tofu	50g or 1 ² / ₃ oz or Size of 2 match boxes
Tempeh	25 g or 1 oz or Size of 1 match box
Baked beans (reduced sugar)	60 g or 2 oz or 2 tablespoons
Lentils, chickpeas and kidney beans, mung beans, black eye beans, puy lentils, toor dahl, urad dahl, Raw weight	20g or ⅔ oz or 1 tablespoon raw
Cooked or tinned weight	65g or 2oz or 1½ tablespoons cooked /tinned or 1 cupped handful
Soya beans (frozen or cooked) or edamame beans	30g or 1oz or 1 tablespoon
Vegetarian sausage	25g or ¾ oz or ½ sausage
Textured vegetable protein (TVP)	10g or ⅓ oz uncooked or 1 heaped tablespoon uncooked
Low fat hummus	30g or 1oz or 1 level tablespoon

Vegetables – min 5 portions 1 portion = 80g or 2 ² / ₃ oz	1 portion is equal to
Asparagus, Aubergines, Broccoli, Brussel sprouts, Carrots, Cabbage, Cauliflower, Chinese leaves, Courgettes, Cucumber, Curly kale, Green beans, Lettuce (mixed leaves), Mange tout, Methi, Mushrooms, Okra, Pak choi, Peas, Sugar snap, Spinach, Spring greens cooked, Sweetcorn, Tomatoes, Watercress fresh	80g or 2 ² / ₃ oz or 2 spears of broccoli, 8 cauliflower florets. 3 heaped tablespoons of vegetables or large cereal bowl of salad.
Fruit - 2 portions. 1 portion = 80g or 2 ² / ₃ oz (30g or 1oz dried fruits)	1 portion is equal to
Berries (e.g. blackberries, blueberries, redcurrants, raspberries, strawberries) Cherries or grapes	80g or 2⅔oz 1 handful
Grapefruit, guava and mango	80g or 2⅔oz or ½ a whole fruit
Large fruit (e.g. melon, pineapple, papaya)	80g or 2⅔oz or 1 medium slice
Medium fruits (e.g. apple, pear, nectarine, orange, peach, banana, pomegranate)	80g or 2⅔oz 1 fruit
Small fruit (e.g. fresh apricots, kiwi, clementine, passion fruit, plums)	80g or 2⅔oz or 2 fruits
Any stewed fruit—unsweetened or with calorie-free sweetener e.g. apple, rhubarb	80g or 2⅔oz or 3 tablespoons
Kumquats, lychees, physalis	5 fruits
Dried fruits (raisins, currants, apricots)	30g or 1oz or 1 tablespoon

Milk and dairy foods - 3 portions	Equal to
Milk (semi-skimmed or skimmed)	¹ ⁄₃ pint or 200ml or
Alternative 'milks' with added calcium, e.g. soya **	1 small glass
Diet yoghurts, Low fat/fat-free Greek or Greek Style or	120-150g or 4-5oz or
natural yoghurts, fromage frais or plain soya yoghurt, high	1 small pot or
protein yogurt	3 tablespoons
Whole milk natural vogurt	80g or 1 ⅔ oz or
	2 tablespoons
Cottage cheese	75g or 1½oz or
	1/4 pot, 2 tablespoons
Cream cheese (light or extra light)	30g or 1oz or
	1 tablespoon
Lower fat hard cheeses e.g.:	30g or 1oz or Matchbox size
Reduced fat cheddar, Edam,	No more than 180g or 6oz a
Bavarian smoked, feta, ricotta, mozzarella, reduced fat	week
halloumi, paneer made from semi-skimmed milk	

** we recommend soya milk as coconut, oat and almond milks are lower in protein and calcium

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Equal to
8g or 1 teaspoon 1 dessertspoon of oil
7g or 1 dessertspoon
7g or 1 dessertspoon 3 walnut halves, 3 Brazil, 4 almonds, 8 peanuts, 10 cashews or pistachios
50g or 10 olives
15g or ½ oz or 1 tablespoon
11g or ⅓ oz or 1 heaped teaspoon
12 g or ⅓ oz or 2 heaped teaspoons
40g or 1⅓ oz or 1/4 of an average pear
40g or 1 ¹ / ₃ oz or 2 tablespoons

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MIDDAS-GDM End of Study Questionnaire

Thank you for taking part in the MIDDAS-GDM Study.

 This is one of the first studies of its kind. We hope to learn as much as possible from this study, in particular the views of people who have taken part. We are inviting you to provide your views on different aspects of the study and following the diet, and how we can improve our programmes and research studies in future.

Please complete the following questions and return this questionnaire to the MIDDAS-GDM study team in the envelope provided. If there is anything else you would like to say about your experiences of the study, please use the section at the end. Your answers to the questions below will remain anonymous.

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Additional support from			Face to face / phone	
the doctors in the clinic				
More contact with other			Face to face / phone	
women in the study				
following the diets				
-				
Other, please specify:				
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16. Did you receive any s	uppor	t outs	ide of the study team help	ο to keep you on track as yoι
progressed through the second s	ne stu	dy?		
□ No				
□ Yes				
f yes, what support did you	ı recei	ve?		
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			Record keeping	
17. How did you find the	finge	r pric	k testing requirements on	the study? (tick all those the
apply)				
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	allenging at all				
□ I felt it	was <u>necessary</u> to te	st this often to en	sure my safety		
□ I felt it	was <u>unnecessary</u> to	test this often to	ensure my safety		
Comments:.					
19. How did	you find using Dia	send software?			
Straig	ntforward				
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□ Challe	nging and <u>not achiev</u>	able			
□ I felt u	ncomfortable using o	omputer software	to keep track of m	y medical details	
□ I felt c	omfortable using con	nputer software to	keep track of my r	nedical details	
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NHS Foundation	Trust
\Box Challenging but on the whole achievable	рріу)
□ Challenging and not achievable	
□ Not challenging at all	
Comments:	
<u>Libro® app</u>	
23. Did you use the Librow app?	
\Box No (please move to question 25)	
24. Did you find the App helpful?	
1 2 3 4 5 6 7 8 9 10 Not at all Slightly Moderately Very Extrem	ely
Comments	
25. What did you like about the App?	
26. What did you dislike about the App and could be improved?	
27. If you didn't use the ann what were the reasons for this 2 (tick all that apply)	



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🗆 Don	't like usi	ng apps in gene	ral	□ Not use	r frienc	dly			
🗆 Labo	our inten	sive / time consu	uming	Prefer to	o use p	oen ar	nd pape	er	
Find	I mobile (devices challeng	ing						
□ Lacl	k of regul	ar internet acces	SS						
□ Othe	er (provic	le details below)	1						
28. Did you fi	ind the C	Diasend softwar	<u>Diase</u> e helpfu	end Softwa	are				
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Wythenshawe Hospital, Manchester, M23 9LT	MIDDAS-GDM Study Team, Nightingale Centre,	
	Wythenshawe Hospital, Manchester, M23 9LT	

1 2 3 4		MeSH Descriptors
5 6	Infant, newborn	
7	Pregnancy	
8	Glucose Intolerance	
9 10	Diabetes. Gestational	
11	Insulin	
12 12	Hyperglycaemia	
13	Prediabetic state	
15	Metformin	
16 17	Glycated Hemoglobin	
17	Overweight	
19	Obesity	
20 21	Diabetes Mellitus, Type 2 🖉	
22	Diet, Healthy	
23	Feasibility Studies	
24 25	Mobile Applications	
26	Body Weight	
27	Hypoglycaemic agents	
28 29	Fasting	
30	Intermittent Fasting	
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SPIRIT CHECKLIST

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	2b	
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Funding	4	
Roles and responsibilities	5a	
	5b	
	5c 5d	
Introduction		
Background and rationale	6a	CL.
	6b	
Objectives	7	
Trial Design	8	31
Methods: Participants, interventions, and	loutcomes	
Study setting	9	
Eligibility criteria	10	
Interventions	11a	
	1	J



11b

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	11c	
	11d	
Outcomes	12	
Participant Timeline	13	
Sample Size	14	
Recruitment	15	0
Methods: Assignment of interventions (fo	or controlled tri	4
Allocation		
Sequence generation	16a	
Allocation concealment mechanism	16b	
Implementation	16c	



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Methods: Data collection, management, a	and analysis	
Data collection methods	18a	
	18b	
Data management	19	
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	21b	
Harms	22	
Auditing	23	
Ethics and dissemination		
Research ethics approval	24	
Protocol amendments	25	
Consent or assent	26a	
	26b	R
Confidentiality	27	.2
Declaration of interests	28	24
Access to data	29	
Ancillary and post-trial care	30	
Dissemination policy	31a	

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	31b
	31c
Appendices	
nformed consent materials	32
Biological specimens	33

Description	Location
Descriptive title identifying the study design, population,	1
nterventions, and, if applicable, trial acronym	L
Trial identifier and registry name. If not yet registered, name	2
of intended registry	5
All items from the World Health Organization Trial	throughout
Registration Data Set	
Date and version identifier	n/a
Sources and types of financial, material, and other support	23
Names, affiliations, and roles of protocol contributors	1
Name and contact information for the trial sponsor	name only, 23
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	23
oublication including whether they will have ultimate	
authority over any of these activities	
Composition roles and responsibilities of the coordinating	
centre steering committee endpoint adjudication committee	
data management team, and other individuals or groups	10
overseeing the trial if applicable (see Item 21a for data	10
monitoring committee)	
Departmention of response question and justification for	
undertaking the trial including summary of relevant studios	
(nublished and unpublished) examining benefits and harms	4-5
for each intervention	
Explanation for choice of comparators	4-5
Specific objectives or hypotheses	13-14
Description of trial design including type of trial (eq. parallel	13 14
proup crossover factorial single group) allocation ratio and	
framework (eq. superiority, equivalence, poninferiority	6
exploratory)	
Description of study settings (eg, community clinic, academic	_
nospital) and list of countries where data will be collected.	6
Reference to where list of study sites can be obtained	
Inclusion and exclusion criteria for participants. If applicable,	
eligibility criteria for study centres and individuals who will	7
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perform the interventions (eg, surgeons, psychotherapists)	
perform the interventions (eg, surgeons, psychotherapists)	
perform the interventions (eg, surgeons, psychotherapists)	9

Criteria for discontinuing or modifying allocated interventions or a given trial participant (eg, drug dose change in response	
o harms, participant request, or improving/worsening disease)	n/a
Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	13-14
Fime schedule of enrolment, interventions (including any run- ns and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Strategies for achieving adequate participant enrolment to reach target sample size	n/a
ls)	
Vethod 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	8
Vechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence	8
until interventions are assigned	

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
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	9-15
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	supplementary PIS
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	16
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	16
Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
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	18

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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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 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) Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Iten 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	n/a 13, 16 16 n/a 19
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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 Financial and other competing interests for principal	n/a
Financial and other competing interests for principal	16
investigators for the overall trial and each study site	23
Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	supplementary PIS
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	

Authorship eligibility guidelines and any intended use of professional writers	n/a
Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	19
Model consent form and other related documentation given to participants and authorised surrogates	supplementary materials
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	15

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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TD	DieR	The TIDieR (Template for Intervention Description and Replice	tign) Checklist*	:
emplate f	or Intervention and Replication	Information to include when describing an intervention and the location	of the information	
ltem	Item	din ng	Where	located **
number		for uses relation	Primary paper	Other † (details)
1.	BRIEF NAME Provide the name	e or a phrase that describes the intervention.	24. Downloa	
	WHY	d dat	ieur (
2.	Describe any ratio	onale, theory, or goal of the elements essential to the intervention.	ABES).	
	WHAT		://bm	
3.	Materials: Descrit	be any physical or informational materials used in the intervention, including those	8 12, 15	_appendix
	provided to partic	ipants or used in intervention delivery or in training of intervention providers.	n.bm	
	Provide information	on on where the materials can be accessed (e.g. online appendix, URL).	ij.com/ o	
4.	Procedures: Desc	cribe each of the procedures, activities, and/or processes used in the intervention, $\frac{3}{6}$	5 <u>5</u> 6-12	
	including any ena	abling or support activities.	ne 12, 20;	
	WHO PROVIDED		25 at	
5.	For each categor	y of intervention provider (e.g. psychologist, nursing assistant), describe their	& 1, 7-12, 17-18	
	expertise, backgr	ound and any specific training given.	ıce Bibliogra	
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6.	<u>ع</u> Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or	20 26-18	
	telephone) of the intervention and whether it was provided individually or in a group.	78264 (
	WHERE to the test of t	on 10 l	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary	j ^e 6-18	
	infrastructure or relevant features.	uary 2	
	WHEN and HOW MUCH	024. D	
8.	Describe the number of times the intervention was delivered and over what period of time including	§ 6-18	
	the number of sessions, their schedule, and their duration, intensity or dose.	loaded	
		from	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why,	25 2 6-18	
	when, and how.	//bmjop	
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10. [‡]	If the intervention was modified during the course of the study, describe the changes (what, why,	an/A	
	when, and how).	u on Ju	
	HOW WELL	ne 12	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any $\frac{\sigma}{\sigma}$.	2013-14	
	» strategies were used to maintain or improve fidelity, describe them.	5 at Aç	
12. [‡]	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	lencer/A	
	intervention was delivered as planned.	Sibli	

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** Authors - use N/A if an item is not applicable for the intervention being described. Reviewers -	use '?' if informatign about the element is not reported/not
sufficiently reported.	t, in 1782

- + If the information is not provided in the primary paper, give details of where this information is available. This may ingeluge locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL). + If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains a second and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study ether elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist $\mathbf{\hat{P}}_{\mathbf{\hat{k}}}$ a randomised trial is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of the CONSORT 2010 Statement. When a clinical trial protocol is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement a statement Statement (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropria study design (see (ABES ata mini www.equator-network.org). cer review on

TIDieR checklist

Manchester Intermittent Diet in Gestational Diabetes Acceptability Study (MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater Manchester

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-078264.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Nov-2023
Complete List of Authors:	Dapre, Elizabeth; Wythenshawe Hospital Issa, Basil; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Harvie, Michelle; University Hospital of South Manchester NHS Foundation Trust, Genesis prevention centre Su, Ting-Li; University of Manchester, Dentistry McMillan, Brian; The University of Manchester, Centre for Primary Care and Health Services Research Pilkington, A.; Wythenshawe Hospital Hanna, F.; University Hospitals of North Midlands NHS Trust Vyas, Avni; Manchester Metropolitan University Faculty of Health Psychology and Social Care, Health Professionals Mackie, S.; Wythenshawe Hospital Yates, James; Manchester University NHS Foundation Trust Evans, Benjamin; Manchester University NHS Foundation Trust Mubita, Womba; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Lombardelli, Cheryl; Manchester University NHS Foundation Trust
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Obstetrics and gynaecology, Reproductive medicine
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, DIABETES & ENDOCRINOLOGY, Obesity, NUTRITION & DIETETICS, Feasibility Studies, Maternal medicine < OBSTETRICS



1	<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>				
2	(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent				
3	Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater				
4		Manchester			
5					
6	Authors: Dapre, E., Issa,	B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,			
7	A., Vyas, A., Yates, J., M	ackie, S., Evans, B., Mubita, W., Lombardelli, C.			
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1 2	18	
3	19	<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>
4 5	20	(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent
6 7	21	Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater
8 9	22	Manchester
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11	24	Authors: Dapre, E., Issa, B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,
13 14	25	A., Vyas, A., Yates, J., Mackie, S., Evans, B., Mubita, W., Lombardelli, C.
15 16	26	
17	27	Corresponding Author: elizabeth.dapre@nhs.net
18 19	28	
20 21	29	Abstract (word count 298)
22 23	30	Introduction: The prevalence of gestational diabetes mellitus (GDM) is rising in the
24	31	UK and is associated with maternal and neonatal complications. National Institute for
25 26	32	Health and Care Excellence (NICE) guidance advises first line management with
27 28	33	healthy eating and physical activity which is only moderately effective for achieving
29 30	34	glycaemic targets. Approximately 30% of women require medication with metformin
31	35	and/or insulin. There is currently no strong evidence base for any particular dietary
32 33	36	regimen to improve outcomes in GDM. Intermittent low-energy diets (ILEDs) are
34 35	37	associated with improved glycaemic control and reduced insulin resistance in type 2
36 37 38 20	38	diabetes (T2DM) and could be a viable option in the management of GDM. This
	39	study aims to test the safety, feasibility and acceptability of an ILED intervention
39 40	40	amongst women with GDM compared to best National Health Service (NHS) care.
41 42	41	
43	42	Method and analysis: We aim to recruit 48 women with GDM diagnosed between 24-
44 45	43	28 weeks gestation from antenatal clinics at Wythenshawe and St Mary's hospitals,
46 47	44	Manchester Foundation Trust, over 13 months starting in November 2022.
48 49	45	Participants will be randomised (1:1) to ILED (2 low-energy diet days/week of
50	46	1000kcal and 5 days/week of the best NHS care healthy diet and physical activity
51 52	47	advice) or best NHS care 7 days/week until delivery of their baby. Primary outcomes
53 54	48	include uptake and retention of participants to the trial, and adherence to both dietary
55 56	49	interventions. Safety outcomes will include birthweight, gestational age at delivery,
57	50	neonatal hypoglycaemic episodes requiring intervention, neonatal
58 59	51	hyperbilirubinaemia, admission to special care baby unit or neonatal intensive care
60	52	unit, stillbirths, the percentage of women with hypoglycaemic episodes requiring

1 2	53	third-party assistance, and significant maternal ketonaemia (defined as ≥1.0mmol/L)
3	54	Secondary outcomes will assess the fidelity of delivery of the interventions, and
4 5	55	qualitative analysis of participant and healthcare professionals' experiences of the
6 7	56	diet. Exploratory outcomes include the number of women requiring metformin and/or
8 9	57	insulin.
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49 50	81	Ethics and dissemination: Ethical approval has been granted by the Cambridge
51 52	82	East Research Ethics Committee (22/EE/0119). Findings will be disseminated via
53 54	83 84	diabetes charitable bodies and organisations in the UK. such as Diabetes UK and
55	85	the Association of British Clinical Diabetologists.
50 57	86	
58 59	87	
60	88	Trial Registration Number: NCT05344066

3 Strengths and limitations of this study 5 Strengths 6 To the best of our knowledge this is the first study to look at intermittent women with gestational diabetes 9 This study adds to the limited literature of safety of low-calorie diets and women with gestational diabetes 10 This study adds to the limited literature of safety of low-calorie diets and women with gestational diabetes 12 This study has been informed by an experienced patient and public involves and engagement group 17 Limitations 19 This study involves a small sample size and is not powered to show effect the intervention 20 Women joining this study are likely to be highly motivated and adherence	
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 ⁸ women with gestational diabetes ¹⁰ This study adds to the limited literature of safety of low-calorie diets among women with gestational diabetes ¹³ This study has been informed by an experienced patient and public involves and engagement group ¹⁷ Limitations ¹⁸ This study involves a small sample size and is not powered to show efficient the intervention ¹⁰ Women joining this study are likely to be highly motivated and adherence 	diets in
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Women joining this study are likely to be highly motivated and adherence	
	e may
not reflect that seen in the wider general population	
26 90	
28 91 INTRODUCTION (word count: 3539)	
²⁹ ₃₀ 92 Background	
$\frac{31}{32}$ 93 In the UK up to 16% of pregnant women develop gestational diabetes (GDM	1) and
³³ 94 the incidence is rising, in part due to increasing rates of obesity and materna	al
$_{35}^{34}$ 95 age(1,2). GDM is associated with maternal and neonatal complications (the	risk
$\frac{36}{37}$ 96 increases with poor glycaemic control), including macrosomia, shoulder dys	tocia,
³⁸ 97 caesarean-sections, neonatal hypoglycaemia and/or hyperbilirubinaemia, pr	eterm
98 delivery, preeclampsia, and stillbirth(2). Women who have had GDM have a	n
$\frac{41}{42}$ 99 estimated seven to ten-fold risk of developing type 2 diabetes (T2DM) later i	n life,
$^{43}_{44}$ 100 and their children have a higher risk of developing adult obesity and T2DM(2	<u>2</u> —4).
45 101	
⁴⁰ 102 Excessive weight gain in pregnancy is a particular problem for women with (GDM(5).
⁴⁸ ₄₉ 103 Harper <i>et al</i> demonstrated that, in women with GDM, every additional 1lb/we	ek
⁵⁰ 104 gained following diagnosis of GDM resulted in a 36-83% increased risk of pr	e-
⁵² 105 eclampsia, caesarean-section, macrosomia, and large for gestational age b	abies(5).
$_{54}^{53}$ 106 Such studies highlight the importance of adequate weight control throughou	t
⁵⁵ ₅₆ 107 pregnancy in women with GDM in order to reduce both maternal and neona	tal
⁵⁷ 108 complications.	
59 109 60	

First-line therapy for GDM is diet and physical activity. National Institute for Health and Care Excellence (NICE) guidance encourages a healthy diet with increased fruit and vegetables, low-glycaemic index (GI) foods, reduced refined sugars, regular mealtimes and regular physical activity(6,7). These dietary measures fail to achieve glycaemic targets in ~30% of women who require medication with metformin and/or insulin(8). A range of dietary approaches have been studied including daily diets promoting low-GI diets (limiting refined and promoting complex carbohydrates), continuous modest energy-restriction (1800 Kcal/day), and low carbohydrate diets(9). There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM.

21 121 Intermittent Low-Energy Diets (ILED)

The pathogenesis of GDM is strongly linked to obesity and chronic insulin resistance with many clinicians viewing GDM as a form of evolving T2DM. ILEDs typically include several days of a food based or meal replacement (e.g. drinks/bars) low-energy diet (650-1000kcal) diet, with a standard healthy (non-restrictive) diet recommended on the remaining days of the week. These diets are associated with significant reductions in weight, insulin resistance and hyperglycaemia in patients with prediabetes (HbA1c between 42-47mmol/mol, impaired glucose tolerance, or impaired fasting glycaemia), those with T2DM, and otherwise healthy subjects with overweight/obesity(10–17). These changes are equivalent to, or greater than, those achieved with standard daily energy restriction. A popular intermittent diet involves 2 consecutive or non-consecutive days/week of a low-energy diet (650-1000kcal) and 5 days of normal eating/week, known as the 5:2 diet. The Manchester Intermittent vs. Daily Diabetes App Study (MIDDAS), a study comparing an ILED and a continuous low-energy diet in T2D conducted in our unit, has shown the feasibility and safety of an ILED (800kcal for 2 days/week) in patients with T2DM and obesity. including those using insulin(18). At the end of the study approximately 70% of participants in the ILED group completed the study and achieved a 6% reduction of their baseline body weight. Forty two percent achieved an HbA1c of <48 mmol/mol(18). Given the strong overlap between GDM and T2DM, an ILED may be a promising dietary intervention for those with GDM.

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A successful dietary approach to glycaemic control could empower women to take charge of the management of their GDM. Women with GDM are motivated to modify their diet driven by a desire to improve foetal outcomes(19–21).

7 146

Our Patient and Public Involvement and Engagement (PPIE) work indicates that women find the current National Institute for Health and Care Excellence (NICE) healthy eating guidance(6,7) confusing and vague. Our PPIE work has indicated that women are keen to try alternative dietary approaches, particularly if alternative diets are more effective in preventing the need to progress to medications such as metformin and insulin.

19 153

Aim

The aim of this trial is to test the safety, feasibility, and acceptability of an ILED in
 GDM to inform a future large-scale RCT.

26 157

²⁷ 28 158 **METHODS**

159 Trial Design

The study is a 28-week feasibility two-arm RCT in one NHS trust performed in patients with GDM and BMI ≥27.5 kg/m², or ≥25 kg/m² in high-risk minority ethnic groups (i.e. South Asian, Black African, African Caribbean) in Greater Manchester, between December 2022 and July 2024(22,23). There will be an embedded qualitative sub-study for participants and healthcare professionals. Due to the nature of the intervention, it will not be possible to blind the participants, clinicians, or study team to the treatment allocation after randomisation (the statistician and laboratory technicians will remain blinded).

45 168

169 Trial Setting and Recruitment

Participants will be recruited from antenatal clinics at Wythenshawe and St Mary's Hospitals, Manchester Foundation Trust (MFT) between November 2022 and December 2023. This is an urban area within Greater Manchester, and MFT serves patients from a wide range of minority ethnic and socio-demographic backgrounds. Women may self-refer to the antenatal clinic or be referred by their primary care team. Assessments will be carried out at MFT, or remotely if required by COVID-19 restrictions. The qualitative sub-study will be carried out at MFT, remotely, or at a location of the participant's choosing. We aim to recruit eligible participants over a

1 2	178	period of 13 months. Potential participants will be given written information about the
- 3 4 5	179	study and the opportunity to ask questions about the study prior to providing written
	180	consent (figure 1).
6 7	181	
8 9	182	Eligibility Criteria
10 11	183	
12	184	<image exclusion="" figure1="" inclusion="" jpg="" one;=""/>
13 14	185	
15 16	186	
17	187	Participant Flow
18 19	188	Participants who fulfil the broad eligibility criteria will be notified about the trial by the
20 21	189	GDM nurse/midwife at the time of their diagnosis. Those who are interested will be
22 23	190	provided with a comprehensive patient information sheet (see appendix) and more
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	191	detailed eligibility screening questions. They will be asked to attend their first
	192	appointment having fasted for at least 6 hours and complete a four-day food diary (in
	193	line with our departments usual care). On attending their first routine clinic
	194	appointment, interested participants will receive further information from the research
	195	team. They will have the opportunity to ask questions, have their eligibility confirmed,
	196	and will be asked for their written consent to take part. Baseline assessments will be
	197	taken and participants will be randomised to their allocated treatment group using an
	198	online randomisation platform. Participant flow through the study is demonstrated in
	199	figure 2.
	200	
	201	Sample Size
43	202	We plan to recruit 24 participants per study arm (n=48) which, when considering an
44 45	203	estimated attrition rate of 15%, will provide complete outcome data on 40
46 47	204	participants(24–26). It has been estimated that 24 participants per group will be
48 40	205	sufficient to determine study outcomes, in line with sample size recommendations for
49 50	206	feasibility studies(27–29).
51 52	207	
53 54	208	This number will allow us to enable estimation of recruitment/retention parameters
55	209	with sufficient precision. For example, based on 40 completed participants, it will
56 57	210	enable recruitment rates in the region of 25% to be estimated with an error of +/-
58 59	211	13.42% at most; retention of 85% will be estimated with error of +/-11.07% at most. It
60	212	is also sufficient for estimation of variability (e.g. standard deviation) in gestational

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1 2	213	weight gain and capillary glucose concentrations (proposed outcomes for the future
3	214	definitive trial) with negligible bias (30).
4 5	215	
6 7	216	
8 0	217	Randomisation
10	218	The randomisation schedule will be independently set up and known only by the trial
11 12	219	statistician. The trial statistician will be blinded to the participant's identity using
13 14	220	"sealed envelope" software (https://www.sealedenvelope.com/). Randomisation will
15 16	221	be carried out by generating an online pseudo-random list with random permuted
17	222	blocks of varying size, known only to the statistician, and will be stratified for two
18 19	223	variables:
20 21	224	- Age (18-35, >35 years)
22 23	225	 BMI (27.5-34.99kg/m² and >35kg/m2, >25-32.49kg/m² and >32.5kg/m² for
24	226	high-risk minority ethnic groups (i.e. South Asian, Black African, African
25 26	227	Caribbean)
27 28	228	These stratification variables have been chosen to reduce potential bias as we
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	229	expect varying severity of GDM with increasing age and BMI, and possible
	230	differences in diet adherence(31).
	231	
	232	Treatment to intervention and control groups will be allocated in a 1:1 ratio. A
	233	member of the research team who will be unaware of the randomisation algorithm
	234	(principal investigator, clinical research nurse, clinical research fellow or project
	235	manager) will trigger the randomisation procedure onsite; participants and clinicians
	236	will then be informed of the allocated treatment group. Clinicians will not be blinded
	237	due to the need to remain astute to safety, adherence, and side effects, requiring
	238	open and honest discussions with patients at each appointment. The statistician will
	239	remain blinded to treatment allocation until all outcome measures for all subjects
	240	have been collected.
	241	
	242	Interventions
53 54	243	Study Arm 1: Best NHS Care Diet
55	244	All dietetic advice will be face to face or via video calls or the telephone. Participants
56 57	245	will receive one to one personalised written and verbal advice from a dietitian to
58 59	246	follow NICE diet and physical activity recommendations(6,7). Dietitians and midwives
60	247	will receive training to ensure standardised delivery of information in clinic, and

standardised patient information leaflets will be supplied to include information about increased fruit/vegetable intake, low-glycaemic index foods, and a reduction in free sugars. Information will include advice about the importance of regular meals; dietary advice aims to ensure that participants include at least 70g protein/28g fibre, and predominantly mono- and polyunsaturated fats as per American Diabetes Association recommendations(32). Participants will be advised to be physically active, for example walking for 30 minutes after a meal. Participants will receive ongoing dietetic education and support every 2 weeks until delivery. This level of support is higher than typically provided in NHS GDM antenatal clinics due to limited resources but has been utilised to reflect best NHS care. They will receive suggested menus and recipes to follow the NICE recommended healthy diet for GDM. Participants will be asked to measure their capillary glucose four times each day and their ketones on two random (recorded) days of the week of their choosing (see appendix). Study Arm 2: Intermittent Low-Energy Diet (ILED)

Participants will receive the same level of dietetic support as the best NHS care group. They will be given advice on adopting an ILED which involves 2 non-consecutive low-energy diet days/week (1000kcal to include 100g low-GI carbohydrate and 70g of protein) and 5 days/week of the NICE healthy eating low-GI diet and physical activity recommended for the best NHS care group. The low-energy days involve women selecting a set number of portions of protein, carbohydrate, fat, fruit, vegetables, and dairy/dairy alternatives as described in previous studies(33). Each low-energy day includes ~210g of lean protein foods, 3-4 portions of wholegrain carbohydrates, 1x7g portion of fat, 5 portions of vegetables, 2 of fruit, and 3 of dairy/dairy alternatives. Food and drink will be self-selected and not provided by the study team. Participants will be provided with comprehensive food lists, advice on portion sizes for the low-energy days and suggested menus and recipes to follow for both the low-energy and NICE recommended healthy diet days. Both diets can be successfully adapted for people of different ethnicities and those following omnivorous, vegetarian and vegan diets. Participants will be asked to measure their capillary glucose four times each day and their ketones on (and the morning after) the two low-energy days (see appendix).

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7 8 9 10	287	
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11 12	289	
13	290	Outcomes
14	291	Primary outcomes
16 17	292	 Uptake rate measured as a percentage of eligible participants who consent to
18 19	293	take part, including the proportion of women who were screened who did not
20	294	meet the eligibility criteria, and the number of women who did not give
21	295	consent to take part
23 24 25	296	Recruitment rate measured as the number of eligible participants who consent
25 26	297	to take part per month 🚫
27	298	 Retention rate measured as the number of randomised participants who
20 29 30 31 32 33 34 35 36 37 38 39 40 41	299	complete the trial (those who attend the final visit) and the percentage of
	300	participants who attend all 8 visits
	301	 Adherence to the dietary interventions assessed from self-reported adherence
	302	to the potential low-calorie days between randomisation and delivery
	303	 Completion of self-assessed glucose and ketone readings assessed as a
	304	percentage of the required readings
	305	
	306	Safety outcomes:
42 43	307	 Percentage of women following ILED/best NHS care with
44 45	308	hypoglycaemia (episodes of blood glucose of <3.0mmol/mol) and
46 47	309	hypoglycaemia requiring third-party assistance as measured by
48	310	participants
49 50	311	 Percentage of women who develop significant ketonaemia in both
51 52	312	groups (defined as ≥1.0mmol/L) as measured by participants
53 54	313	 Percentage of neonatal hypoglycaemic episodes requiring intervention
55	314	(blood glucose checked 2- hours post-delivery and 2-hours thereafter
56 57	315	for 12 hours according to local protocol), neonatal birth weight,
58 59 60	316	gestational age at delivery, hyperbilirubinaemia/jaundice, and/or

2	317	admission to Special Care Baby Unit or neonatal intensive care, and
3 ⊿	318	stillbirths
5	319	 The incidence and rate of other adverse events (e.g. headaches,
6 7	320	lethargy, constipation, or complications requiring hospital admission)
8 9	321	between the start of the trial intervention and delivery recorded as mild,
10 11	322	moderate and severe, as defined by Common Terminology Criteria for
12	323	Adverse Events version 5 (CTCAEv5)(34). Hospital admission for
13 14	324	routine labour and delivery will not be classified as an adverse event.
15 16	325	
17	326	Secondary outcomes
19	327	 Completeness of collection of trial endpoints including the percentage of
20 21	328	completed weight measurements, 4-day food diaries, and International
22 23	329	Physical Activity Questionnaire (IPAQ) scores
24	330	 Fidelity of delivery of the interventions will be measured through the number
26	331	and modality of completed planned patient contacts, electronic and paper
27 28	332	food diaries, and self-reported capillary glucose and ketone measurements
29 30	333	 Qualitative analysis of the acceptability and implementation of the
31	334	interventions will be explored amongst a subset of participants (~10 in each
32 33	335	group) and healthcare professionals through in-depth interviews
34 35	336	
36 37	337	Exploratory outcomes
38	338	The following outcomes will be explored without statistical inference.
39 40	339	1. Maternal outcomes:
41 42	340	 The percentage of women requiring metformin and/or insulin
43 44	341	 Four-point capillary glucose profiles during third trimester (four times daily
45	342	until delivery)
46 47	343	Change in fasting blood test results between baseline measurements, 36-
48 49	344	37 weeks' gestation, and 12 weeks post-delivery (including oral glucose
50 51	345	tolerance tests (OGTT)
52	346	 Mode of delivery, development of preeclampsia, polyhydramnios
53 54	347	(maximum liquor volume pool depth ≥8 cm)
55 56	348	 Quality of life and health status questionnaires (WHOQoL-BREF and SF-
57 58	349	36 questionnaires)(35,36)
59	350	2. Foetal outcomes:
60		

1 2	351	Foetal weight
3 4	352	Gestational age at delivery
5	353	
6 7	354	
8 9	355	
10 11	356	
12	357	
13 14	358	
15 16	359	
17 18	360	Measurements
19	361	The full schedule of assessments can be found in figure 3.
20 21	362	
22 23	363	Physical measurements
24 25	364	Height, weight and blood pressure will be measured using standardised calibrated
26	365	equipment in antenatal clinic.
27 28	366	
29 30	367	Blood samples
31 32	368	Fasting venous blood samples will be collected to assess maternal HbA1c, fasting
33	369	glucose, insulin, beta-hydroxybutyrate, liver function tests, free fatty acids, thyroid
34 35	370	function tests, and full blood count. A cord blood sample will be collected at the time
36 37	371	of delivery to measure neonatal glucose, and insulin and C-peptide where collection
38 30	372	is possible. At the end of the study all samples will be disposed of in accordance with
40	373	the Human Tissue Act (2004).
41 42	374	
43 44	375	Questionnaires
45	376	Participants will be asked to complete four questionnaires at four time points
40	377	throughout the trial (self-reported). Quality of life and health status will be assessed
48 49	378	using the World Health Organisation Quality of Life Questionnaire (brief version) and
50 51	379	the 36-Item Short Form Survey respectively(35,36). Physical activity will be
52	380	measured using the International Physical Activity Questionnaire – Short Form, and
53 54	381	diet quality will be assessed using the UK Diabetes and Diet Questionnaire(37,38).
55 56	382	These questionnaires are self-reported by participants and have been chosen as
57 58	383	they are widely used and validated tools.
59 60	384	

1		
1 2	385	Food Diaries
3 4	386	4-day dietary records will be completed using Libro (Nutritics Mobile Application) or
5	387	paper food diaries, which will be entered into Nutritics software (Nutritics, Dublin,
8 7	388	Ireland)(39). Participants who wish to use Libro will receive one to one training to use
8 9	389	this by the study dietitian. Diaries will provide the research team with information
10 11	390	about the intake of energy, carbohydrate, fat, protein, fibre, glycaemic index, and the
12	391	timing of meals for participants in both groups. Participants will be asked what other
13 14	392	dietary modifications, if any, they have made at their fortnightly dietitian reviews to
15 16	393	establish the adoption of any alternative dietary practices in the cohort.
17	394	
18 19	395	Adverse Events
20 21	396	Participants in both groups will be asked about any adverse effects that they have
22 23	397	experienced at each visit. These will include, but are not limited to, the potential
24	398	effects of a low-energy diet, e.g. headache, lethargy, dizziness, constipation,
25 26	399	indigestion, poor concentration, and hunger. Adverse events will be graded as per
27 28	400	CTAEv5(34). Participants will be issued with a participation/emergency card with
29	401	emergency contact details for the research team to be carried at all times and to be
30 31	402	shown to the attending physician in case of emergency admission to hospital. All
32 33	403	participants will be issued with clear instructions as to how to manage a
34 35	404	hypoglycaemic and/or ketonaemic event (see appendix).
36	405	
37 38	406	Data management
39 40	407	Participant data will be anonymised and will be stored in line with the Medicines for
41	408	Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act
42 43	409	(2018) and archived in line with the Medicines for Human Use (Clinical Trials)
44 45	410	Amended Regulations (2006) as defined in the MFT Clinical Trials Office Archiving
46 47	411	SOP (11; Retention of Data, Off-Site Archiving, and Destroying Documents).
48	412	Deidentified data will be stored in a study-specific Research Electronic Data Capture
49 50	413	(REDCap) database. The sponsor will periodically audit the site study file, a sample
51 52	414	of the case report form, consent forms, and source data, and check accuracy of the
53	415	study database to ensure satisfactory completion.
54 55	416	
56 57	417	Statistical methods
58 50	418	A statistical analysis plan specifying the full details of the primary and secondary
60	419	outcomes, other variables, and methods, will be produced prior to trial analysis. The

main analysis will be conducted via intention-to-treat population and will not undertake any significance tests. Descriptive, graphical (summary), and basic statistics (e.g. i. number, frequencies and percentages, ii. mean and standard deviation, or iii. median and quartiles as appropriate) will be presented as appropriate for each group respectively, for group difference jointly, and for each stratum. Per-protocol analysis will be considered as a secondary analysis. Levels of missing data will be investigated and used to inform future studies. No imputation will be used. The end of study guestionnaire will be analysed using appropriate descriptive statistics for closed questions and key themes will be extracted without formal analysis from open questions to inform future research.

Progression Criterion

The success of the feasibility trial will be defined by the progression criteria as outlined in table 1. Any concerns regarding a low retention rate will be discussed with the PPIE group. Interviews will include those who withdraw from the study to address potential reasons for withdrawal with the aim to improve retention in future.

	Feasible (green)	Feasible with modification of the protocol (amber)	Not feasible (red)
Recruitment	≥4 patients/month	>2 patients/month	≤2 patients/month
Uptake to the feasibility study	≥15%	10-15%	<10%
Retention to the feasibility study	>70%	50-70%	<50%
Adherence to the	>50% of the low-	30-50% of the low-	<30% of the low-
ILED intervention	energy days	energy days	energy days
	completed (2/week	completed (2/week	completed (2/week
	between weeks 24-	between weeks 24-	between weeks 24-
	28 and delivery)	28 and delivery)	28 and delivery)
Table 1: Trial progression criterion			

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Qualitative sub-study

Participants will be invited to take part in an optional qualitative sub-study at 11-13
weeks post-partum. Healthcare professionals delivering the interventions will also be
invited to take part in this study.

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We will undertake 11-12 semi-structured interviews with a subset of women from each group (ILED n=10 and best NHS Care n=10) at around 12 weeks post-delivery. The final sample size will be contingent on obtaining data saturation. We will also interview a sample of healthcare professionals (HCPs) involved in the delivery of care to study participants, including dieticians, obstetricians and midwives, including those with leadership and clinical managerial roles. Sampling will be purposive, aiming to obtain women from a range of ethnic groups, ages, socioeconomic backgrounds, and self-reported engagement with the intervention. Participants and HCPs will be asked about their experiences and thoughts regarding the intervention, including motivating factors, and facilitators/barriers to engagement. Interviews will be conducted by a researcher from the University of Manchester/MFT who is independent from the research staff involved in the delivery and assessment of the programmes. Analysis will be conducted by two independent researchers at the University of Manchester/MFT using Braun and Clarke's thematic analysis approach to identify key issues around the acceptability, usefulness of the programmes, and feasibility of a subsequent trial(40). Analysis will be inductive: open-ended, exploratory, and driven by the data.

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All participants will also be asked to complete an optional and anonymous end of study questionnaire developed by the study team at their post-partum visit (see appendix). This will give participants the opportunity to feedback on their experience and will enable the study team to identify improvements to the design of a possible follow-up study.

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⁵⁰₅₁ 467 **Trial Steering Committee (TSC)**

The trial steering committee will include an independent consultant endocrinologist, obstetrician, dietitian, and the patient representative. The committee will oversee the trial to ensure that it is carried out to the expected standards. The TSC will liaise with the CI to develop a schedule of meetings, proposed to occur every four months, with meetings to occur no less than annually. Minutes will be taken at TSC meetings and

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473 copies of the minutes will be filed in the Trial Master File; they will be shared with

- 474 relevant stakeholders as appropriate.
- 5 475

476 Patient and public involvement

Patient and public involvement was actively sought throughout the planning and design of this trial and continues to form a key part of the trial as it progresses. The patient and public involvement and engagement (PPIE) group assisted in the development of all participant materials and provided valuable insight into the wording of participant information and acceptability of the proposed intervention. The PPIE group will be updated as the trial progresses and a further focus group will be held to advise on the interview schedule and wording for the gualitative sub-study. The group will also be invited to aid in the development of summarising key findings for dissemination to relevant patient groups.

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- 26 487

28 488 Ethics and dissemination

This study has been approved by the Cambridge East Research Ethics Committee and is sponsored by MFT. Findings will be disseminated via publication in peer-reviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists. Anonymised data will be available upon formal request once the principal results of the study have been published. Planned modifications to the protocol will be approved by the research ethics committee before they are adopted into the study. An audit trail of ethical amendments and documentation will allow monitoring by the research team and external regulatory bodies.

This is the first study to assess the feasibility and safety of an ILED in GDM as compared to best NHS care. Given the increasing incidence of GDM and associated health risks this research is both pertinent and important. The study is not powered to show differences between ILED and best NHS care, however the planned guantitative and gualitative assessments will inform the feasibility of the programme and a future definitive trial.

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46 47	650	Δut	hors' contributions
48	651	Mich	nors contributions
49 50	652		na. Andrea Bilkington and Avni Vyas designed the study, wrote the protocol, and
51 52	052	1 1011	ha, Andrea Finnington and Avni vyas designed the study, whole the protocol, and
53	653	sect	ared the funding. Elizabeth Dapre drafted the manuscript for publication, with
54 55	654	inpu	t from Michelle Harvie, Basil G. Issa, Brian McMillan, and Ting-Li Su. All other
56 57	655	auth	ors have proofed and checked the manuscript.
57 58 59	656		
60	657	Ack	nowledgments

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4 5	660	Miss Lisa Brew-Butler, specialist midwives who continue to help identify suitable
6 7	661	candidates for the study.
8 9	662	
10 11	663	Funding statement:
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15 16	666	the study had no role in the study design or writing of the report. Dr Dapre is an
17 18	667	NIHR sponsored GP academic clinical fellow.
19	668	
20	669	Competing interests statement.
22 23	670	Michelle Harvie has co-authored three self-help books for the public to follow
24 25	671	intermittent diets. All author proceeds are paid directly to the charity Prevent Breast
26 27	672	Cancer (registered charity number 1109839) to fund breast cancer research.
27 28	673	
29 30	674	
31 32	675	
33 34	676	
34 35	677	
36 37	678	
38 39	679	
40 41	680	
42	681	
43 44	682	
45 46	683	
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59 60	691	
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1 2 3 4 5 6 7 8 9 10 11	692 693 694 695 696 697						
12	698	Appendix					
15 14	699	1.0 Patient Information	n Sheet (Supplementa	ry file 1 Patient infor	mation Sheet		
15 16	700	MIDDAS GDM v3.0 02032023 clean)					
17	701						
18 19	702	2.0 Consent Form (Sup	oplementary file 2_v2	Consent Form MIDDAS	SGDM v2.0		
20 21	703	19102022 Clean Up	dated)				
22	704						
23 24	705	3.0 Self-monitoring scl	hedule for capillary g	lucose and ketone mo	onitoring		
25 26		ILE	D	Best NI	IS Care		
27		Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose		
28 29		Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)		
30 21		the morning after each of		on 2 non-consecutive			
32		the low-energy days		days / week			
33 34		1 hour post evening meal	1hr post breakfast	1 hour post evening	1hr post breakfast		
35		on each of the low-energy		meal on 2 non-			
36 37		days		consecutive days / week			
38			1hr post lunch		1hr post lunch		
39 40	700		1hr post dinner		1hr post dinner		
41 42 43	706 707	4.0 Medical Management Protocols					
44	708	Hypoglycaemia					
45 46	709	Participants will be advised to take 15-20g of rapid acting carbohydrate in the event					
47 48	710	of hypoglycaemia, (defined as blood glucose <4 mmol/L) which is anticipated to raise					
49	711	blood glucose by 3 mmol/L. Examples of rapid acting carbohydrate include 170-					
50 51	712	225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6					
52	713	glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). Participants will					
53 54	714	be advised to repeat the	e treatment every 15 mi	inutes until blood aluco	se is ≥4 mmol/l		
55 56	715	The following table high	lights when participants	s should consider takin			
57	716	follow up clower acting	oarbobydrato:		gaaalona		
57 58 716 follow-up slower acting carbohydrate:							
59	717						

Less than 1 hour before the next meal Try and avoid 1-2 hour before the next meal 10g More than 2 hours before the next meal 15-20g 718 Try 720 Ketonaemia 721 Ketonaemia 722 Ketone levels ≥1.0 mmol/L on a fasting sample: 723 • Drink 1L fluids and repeat ketone levels after 4 hours. 724 • If ketone level has improved (<1.0mmol/L), no further action required. 725 • If ketone level has increased or remains the same, repeat ketone level after 2 hours. 726 • If ketone level is persistently increased, consume 40g carbohydrates and repeat in 2 hours. 729 • Continue to do this until ketone levels <1.0mmol/L. 730 Try 731 If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed. 734 Guidance for the introduction of diabetes medication (week 24-delivery) 735 Diabetes medication will be introduced according to the following protocol: 737 • If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence 740 Metformin MR 500 mg daily to be incr	1 2		Situation Acceptable slo	w acting carbohydrate			
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More than 2 hours before the next meal 15-20g 718 719 720 Ketonaemia 721 Ketonaemia 722 Ketonaemia 723 • Drink 1L fluids and repeat ketone levels after 4 hours. 724 • If ketone level has improved (<1.0mmol/L), no further action required.	5 6		1-2 hour before the next meal10g				
9 718 10 719 720 720 721 Ketonaemia 722 Ketone levels ≥1.0 mmol/L on a fasting sample: 723 Drink 1L fluids and repeat ketone levels after 4 hours. 724 If ketone level has improved (<1.0mmol/L), no further action required.	7 8 9 10 11 12 13 14 15 16 17 18		More than 2 hours before the next meal 15-20g				
10 719 720 721 721 Ketonaemia 722 Ketone levels ≥1.0 mmol/L on a fasting sample: 723 Drink 1L fluids and repeat ketone levels after 4 hours. 724 If ketone level has improved (<1.0mmol/L), no further action required.		718	·				
12 720 14 721 Ketonaemia 15 722 Ketone levels ≥1.0 mmol/L on a fasting sample: 16 723 Drink 1L fluids and repeat ketone levels after 4 hours. 17 723 If ketone level has improved (<1.0mmol/L), no further action required.		719					
14 721 Ketonaemia 15 722 Ketone levels ≥1.0 mmol/L on a fasting sample: 17 723 Drink 1L fluids and repeat ketone levels after 4 hours. 17 723 If ketone level has improved (<1.0mmol/L), no further action required.		720					
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 729 Continue to do this until ketone levels <1.0mmol/L. 730 731 731 If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed. 734 735 Guidance for the introduction of diabetes medication (week 24-delivery) Diabetes medication will be introduced according to the following protocol: 737 738 • If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence 740 Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated. 743 744 If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l, 		728	repeat in 2 hours.				
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 ³¹731 If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed. ⁷³⁴ ⁷³⁵ Guidance for the introduction of diabetes medication (week 24-delivery) Diabetes medication will be introduced according to the following protocol: ⁷³⁷ ⁷³⁸ • If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated. ⁷⁴² • If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l, 		730					
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 ³⁸ 735 Guidance for the introduction of diabetes medication (week 24-delivery) ³⁹ 736 Diabetes medication will be introduced according to the following protocol: ⁴¹ 737 ⁴³ 738 • If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour ⁴⁴ 739 postprandial glucose readings are >7 mmol/l in a 7 day period: commence ⁴⁷ 740 Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram ⁴⁸ 80 if tolerated. ⁵⁰ 743 • If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting ⁵¹ blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime ⁵² r44 blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime ⁵³ isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for ⁵⁴ a fasting glucose of ≤5 mmol/l, ⁵⁵ 747 	30 37	734					
 40 736 Diabetes medication will be introduced according to the following protocol: 737 738 If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour 739 postprandial glucose readings are >7 mmol/l in a 7 day period: commence 740 Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram 8D if tolerated. 742 743 If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime rod glucose readings are >5 mmol/l in a 7-day period: commence bedtime rod glucose of ≤5 mmol/l, 747 	38 39	735	Guidance for the introduction of diabetes medication (v	veek 24-delivery)			
 737 738 If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour 739 postprandial glucose readings are >7 mmol/l in a 7 day period: commence 740 Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram 741 BD if tolerated. 742 743 If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting 744 blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime risophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for ria fasting glucose of ≤5 mmol/l, 	40 41	736	Diabetes medication will be introduced according to the follo	owing protocol:			
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 ⁴⁵ 739 postprandial glucose readings are >7 mmol/l in a 7 day period: commence ⁴⁷ 740 Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram ⁴⁸ BD if tolerated. ⁵⁰ 742 ⁵² 743 • If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting ⁵⁴ 744 blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime ⁵⁵ 745 isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for ⁵⁷ 746 a fasting glucose of ≤5 mmol/l, ⁵⁹ 747 	45 44	738	 If ≥25% fasting blood glucose readings are >5 mmol/l ar 	nd/or ≥25% of 1 hour			
47740Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram48741BD if tolerated.5074252743If after reaching optimal or maximum tolerated dose Metformin \geq 25% fasting535474454744blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime55745isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for57746a fasting glucose of \leq 5 mmol/l,59747	45 46	739	postprandial glucose readings are >7 mmol/l in a 7 day	period: commence			
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54744blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime5556745isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for57746a fasting glucose of ≤ 5 mmol/l,59747	52 53	743	If after reaching optimal or maximum tolerated dose Met	tformin ≥25% fasting			
56 745isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for 57 746a fasting glucose of ≤ 5 mmol/l, 59 747	54 55	744	blood glucose readings are >5 mmol/l in a 7-day period:	commence bedtime			
746 a fasting glucose of ≤ 5 mmol/l, 747 747	56	745	isophane insulin 4 units and uptitrate the dose by 2 units	s every 3 days aiming for			
⁵⁹ 747	57 58	746	a fasting glucose of ≤5 mmol/l,				
DU	59 60	747					

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1 2	748	 and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day
3 4	749	period: commence prandial fast acting insulin analogue (Humalog or Novorapid)
5	750	2-4 units with the relevant meal. Uptitrate the dose by 2 units every 3 days aiming
6 7	751	for a 1 hour postprandial glucose of ≤7 mmol/l.
8 9	752	
10 11	753	Medication adjustment will be made in accordance with the above guidance.
12	754	
13 14	755	5.0 Intermittent Low Energy Diet Day Example (Supplementary file 3 _ Example
15 16	756	of 1 days meal plan for 1000kcal with 3 options 12.12.22)
17	757	
19	758	6.0 End of Study Questionnaire (Supplementary file 4 _ MIDDASGDM End of
20 21	759	study Questionniare v1.0 28042022)
22 23	760	
23	761	
25 26	762	
27 28	763	
29	764	
30 31	765	LEGENDS
32 33	766	 <image 1=""/>: Figure 1: Inclusion and exclusion criteria
34 35	767	 <image 2=""/>: Figure 2: Participant flow through trial
36	768	 <image 3=""/>: Figure 3: Schedule of assessments
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Inc	Inclusion Criteria					
AA A A	 Pregnant women ≥18 years BMI of ≥27.5kg/m2 or a BMI ≥25 kg/m² in high risk minority ethnic group (i.e. South Asian, Black African, African Caribbean) and <50 kg/m2 at booking appointment (8-12 weeks' gestation) Newly diagnosed GDM according to local diagnostic criteria (fasting glucose ≥5.3mmol/l and/or 2-hour postprandial glucose ≥8.5mmol/l in a 75g OGTT) scheduled to receive first line diet and physical activity (best NHS care) 24-30 weeks' pregnant at screening appointment 					
Exe	clusion Criteria					
AA AAA	Pregestational type 1 or type 2 diabetes. Fasting glucose of ≥7 or 2-hour postprandial of ≥11 on OGTT (immediate intervention with medication would be required in this group of women) Current multiple pregnancy Maturity Onset Diabetes of the Young (MODY) Significant comorbid disease that in PI's opinion would preclude participation in the study e.g.					
AA	severe psychological problems. Current participation in a GDM medication treatment trial People who are not capable of providing informed consent or adhering to the monitoring and safety protocols					
>	People who have previously had bariatric surgery for weight loss including gastric bypass and sleeve gastrectomy, and/or those prescribed weight loss medications (e.g. orlistat).					
A A A	Medications at the time of the OGTT that may interfere with results (e.g. high dose oral steroids, immunosuppressants) Previous history of intrauterine growth restriction Women who have lost more than 5% of their weight from booking appointment to screening					
	appointment.					

Figure 1: Inclusion and exclusion criteria

159x144mm (220 x 220 DPI)





154x245mm (220 x 220 DPI)

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	Study Visit							
	1	2	3	4	5	6	7	8
Gestation (weeks)	~24-30	~24-30	~30-34	~32-36	~34-38	~36-40	delivery	11-13 post- partum
Eligibility confirmed	x							
Informed consent	x							
Randomisation	x							
Tailored dietitian review (face to face or remote)	x	×	x	x	x	×		x
Height	x							
Weight ^s	x	×	×	x	×	×	×	x
Blood Pressure ^A	x	x	x	x	x	x	x	x
Fasting blood sample*	x				×			x
Questionnaires#	x		x		x			x
4-day food diary			x		x			x
Foetal growth scan	x		x		x			
Review of glucose and ketone measurements		x	x	x	x	x		
Neonatal measurements®							x	
Oral glucose tolerance test								x
Exit interview / end of study questionnaires								x
Invitation to optional qualitative sub-study ⁵								x

hydroxybutyrate, free fatty acids, full blood count, fasting glucose, insulin #Questionnaires: World Health Organisation Quality of Life (brief version), 36-Item Short Form Survey, International Physical Activity Questionnaire (short form), UK Diabetes and Diet Questionnaire

Physical Activity Questionnaire (short form), UK Diabetes and Diet Questionnaire #Neonatal measurements include gestational age at delivery, mode of delivery, neonatal weight, cord blood glucose ⁵Sub-study involves semi-structured interviews exploring participants' thoughts and experiences of the trial

Figure 3: Schedule of assessments

154x236mm (72 x 72 DPI)



NHS Foundation Trust

Consultant Endocrinologist – Dr. Basil Issa Research Dietitian – Dr. Michelle Harvie Email: mft.middas.gdm@nhs.net Tel: 07815987910





Nightingale Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester</u> Intermittent <u>Diet</u> in Gestational <u>Diabetes</u> <u>Acceptability</u> <u>Study</u>

Participant information sheet

We would like to invite you to take part in a research study that is testing two different diet programmes which aim to help people with gestational diabetes control their blood sugars.

If you decide to take part:

- You will be assigned to one of two diet programmes for the duration of your pregnancy. One involves following the standard NHS healthy diet recommendations for pregnancy, and the other follows the standard NHS healthy diet for 5 days/week plus two nonconsecutive calorie restricted days of 1,000 kcal per week (both groups will be encouraged to be physically active).
- You will be asked to attend your routine appointments at Wythenshawe or St Marys Hospital and will have fortnightly appointments until delivery of your baby (some appointments may be virtual depending on COVID-19 restrictions). You will be asked to attend the hospital for a blood test 12 weeks after having your baby.
- You will be supported by a diabetes specialist dietitian, midwife, consultant endocrinologist, and your obstetric team throughout the study to help manage your pregnancy and blood glucose safely.
- Throughout the study you will be asked to monitor your food intake via a smartphone/tablet app, or on paper if you prefer, and you will receive feedback on this during your dietary reviews. Comprehensive dietary advice and recipes will be provided.
- Throughout the study you will be asked to monitor your blood sugar using a blood sugar meter four times a day, and you will also be asked to monitor your ketone levels three times on two days of the week (ketones indicate how well your body is using sugar or fat as an energy source). You will be taught how to check your blood sugar and ketone levels.
- If you would like to take part, or you have any questions, then please contact mft.middas.gdm@nhs.net





This study is being carried out by a team of trained dietitians, doctors, nurses, midwives and researchers under the supervision of Dr. Basil Issa and Dr. Michelle Harvie at Wythenshawe and St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what taking part would involve for you. Please take your time to read the following information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.

Please ring the research team at the number at the top of the first page, or e-mail mft.middas.gdm@nhs.net if there is anything that is not clear, or if you would like more information. You can attend an information session about the diets and the study before agreeing to take part if you would like to.

Your participation in the study is entirely voluntary; you do not have to take part if you do not want to and you can opt out of the study at any time without giving a reason. Thank you for reading this information. We hope this research will be of interest to you.

Why are we doing this research?

Around 1 in 8 pregnant women can develop gestational diabetes. This condition causes risks to mother and baby from high blood sugar, high blood pressure, induced labours, caesareansections, and larger babies. Women often need medication to control blood sugar despite following recommended NHS healthy eating plans for pregnancy. Intermittent low-calorie diets (two non-consecutive days over the course of the week) improve blood sugar control and reduce the need for medication in patients with type 2 diabetes. We want to find out whether intermittent low-calorie diets might also improve blood sugar control in gestational diabetes and reduce the need for medication as it is a similar condition to type 2 diabetes.

What is the purpose of this research?

This study aims to assess the acceptability (to you) and safety of an intermittent low-calorie diet compared to the usual recommended NHS healthy eating and lifestyle plan for gestational diabetes. A computer system will randomly allocate you to one of the two diets. We want to find out which diet is most acceptable to women, whether there is any difference in the two diets' effect on blood sugar control, and any side effects experienced by women. The findings of this study will inform a larger study which will be designed to more closely compare the effect of the two diets on blood sugar control in women with gestational diabetes.

Why have I been asked to take part?

You have been invited to take part in this study because you have been diagnosed with gestational diabetes. We hope to recruit around 48 people to take part in this study.

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What happens if you agree to take part?

If you agree to take part you will be randomly allocated via a computer system to one of two diet and lifestyle programmes for the remaining weeks of your pregnancy.

Best NHS Care Healthy Diet programme

You will receive personalised advice from a specialist dietician. Recommendations will include increased fruit/vegetable intake, low glycaemic index starchy foods (i.e starchy foods which are slowly absorbed and take a while to raise your blood sugar level), reducing refined sugar, and having regular mealtimes. You will be advised how to design your diet to include the right amount of protein, fats, carbohydrates, and fibre, and will be given meal plans and recipes. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Intermittent Low-Calorie Diet programme

If you are allocated to this group you will receive personalised advice to follow a low-calorie diet of 1,000 kcal on two non-consecutive days of the week and the NHS healthy diet on the other five days of the week. The 1,000 kcal days include a set number of portions of protein, carbohydrates and fat foods, fruits, vegetables and dairy/dairy alternatives typically including \sim 210g (7 oz) of lean protein foods and 3-4 portions of wholegrain carbohydrates, 5 portions of vegetables, 2 of fruit, and 3 of dairy or dairy alternatives and a small amount of healthy fat. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Monitoring

You will have all of your usual routine antenatal appointments including checks on your weight, blood pressure, blood tests and ultrasound scans. Extra blood tests will be done as part of the study and these will be added on to samples taken during your routine blood tests.

You will be asked to monitor your blood sugar at home four times a day until your baby is born, and your ketone levels on two days of the week (you will be taught how to do this using a finger prick machine). The results will be recorded when you attend clinic.

We would like to collect a sample of blood from the umbilical cord at delivery to check blood sugar and insulin levels, and your baby's birthweight will be documented. Guidelines currently recommend that wherever possible the umbilical cord is clamped after 1-2 minutes; this is referred to as 'delayed cord clamping' and means that babies receive as much blood as possible from the placenta. This is normal practice. The cord blood sample will not affect your ability to have delayed cord clamping and will not cause any harm to your baby. It will not be possible, however, to delay clamping of the cord for so long that all blood has left the cord (the sample needs to be taken whilst there is still some blood left in the cord).

When babies are born to mothers with gestational diabetes it is normal that their birth weight is recorded and that their blood sugar is monitored for 12 hours following delivery; these results will be recorded by the research team.

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You will be asked to attend an additional glucose tolerance test at the hospital 12 weeks after delivery to assess whether you have any residual diabetes (95% of women do not) and also to assess how sensitive your body is to insulin (an important risk factor for the development of diabetes in the future). You will be asked to attend at 9:00am having fasted (no food or drink apart from water) from midnight. A blood sample (around 10 mL/2 teaspoons) will be taken for glucose and insulin and you will be asked to drink a sugary drink with 75 grams of glucose. A further blood sample will be taken after 2 hours for glucose and insulin. You will need to remain in hospital during this time. The reason for this is to help us to understand whether there could be any difference in the body's ability to process sugar between the two diet groups, and also to find out whether any women still have signs of diabetes after pregnancy.

Any blood samples taken as part of the study will be identifiable only using your study identification number and will have none of your personal details. Part of the sample will be sent for immediate analysis and any remaining will be stored securely, accessible only by the research team. At the end of the study any left over samples will be disposed of in accordance with the Human Tissue Act (2004).

You will be asked to record your food intake via the Libro smartphone/tablet app or in a paper diary for four days during four weeks throughout the study. You will also be asked to complete three questionnaires to assess your wellbeing and level of physical activity in these weeks, and a final end of study questionnaire at the final appointment.

Ongoing support from a specialist team of healthcare professionals

Your specialist team includes a Consultant Endocrinologist, Consultant Obstetrician, diabetes specialist dietitian, midwives, and a GP trainee with a special interest in women's health. The specialist team work closely with the usual obstetric teams involved in your care. Reviews with the team will be either face to face when you attend clinic or remotely using video calls.

Mobile Applications and Glucose Meters

The study will use a smartphone application called 'Libro' to help you record information. Libro is a smartphone application which allows you to record your dietary intake during the study. We will ask you to record 4 days of food and drink intake during 4 weeks across the study. Your diaries will be viewed by your allocated dietitian who will provide personalised dietary feedback via the app. You are also free to record more days of your diet should you wish, which some people find helpful. If you do not want to use the mobile app you can use paper instead. You will be supported to set up and use the Nutritics Libro App at your appointments. You do not have to use the application to be part of the study.

Your blood sugar will be monitored using a glucose monitoring device which checks your blood sugar using a 'fingerprick' blood test. You will be shown how to do this yourself. With your permission the research team will make a note of your glucose readings at every visit, either by checking your glucose monitoring device, or by uploading your glucose meter readings onto the computer if you are using a mobile application.

The self-monitoring schedule is as follows:

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Intermittent low-ene	ergy diet monitoring	Best NHS care monitoring		
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose	
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)	
the morning after each		on 2 non-consecutive		
of the low calorie days		days / week		
1 hour post evening	1hr post breakfast	1 hour post evening	1hr post breakfast	
meal on each of the low		meal on 2 non		
calorie days		consecutive days / week		
	1hr post lunch		1hr post lunch	
	1hr post dinner		1hr post dinner	

What should I do if my blood glucose or ketones are out of range?

Low Blood Sugar

You are advised to take 15-20g of 'rapid acting' carbohydrate if your blood glucose is <4 mmol/L). Examples include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). You will need to repeat the treatment every 15 minutes until your blood glucose is ≥4 mmol/l.

The following table highlights when you need to consider an additional slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate	
Less than 1 hour before the next meal	Try and avoid	
1-2 hour before the next meal	10g (eg half of one of the items below)	
More than 2 hours before the next meal	15-20g (eg slice of toast, piece of fruit, small	
	bowl of cereal, glass of milk)	

Raised Ketones

If your ketone levels are \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If your ketone level has improved (<1.0mmol/L), no further action is required.
- If your ketone level has increased or remains the same, repeat your ketone level after 2 hours.
- If your ketone level is persistently increased, consume 40g carbohydrates (eg one bagel, bowl of cereal and a banana, small jacket potato), and repeat in 2 hours.
- Continue to do this until your ketone levels are <1.0mmol/L.

Make Immediate Contact with the research team if:

Blood glucose	• Your blood glucose is <3.0 mmol/l or you have symptoms requiring medical	1
	attention which are thought to be due to low blood glucose,	

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	 Your fasting blood glucose is >5.2 mmol/L on more than a quarter of your measurements on two days in a row, Your 1 hour post-meal blood glucose is >7.7 mmol/L on more than a quarter of your measurements on two days in a row
etones	 Your blood ketones are >1.0 mmol/L

Will I need medications?

If your blood sugars are found to be high despite following the recommended diet and lifestyle programmes you may be advised to start medication to help control your blood sugar. You will be advised on changes to your medications by a diabetes specialist nurse/diabetes midwife and also a Consultant Endocrinologist if required. This is usual practice regardless of whether you are taking part in the study.

What care will I receive after the study has stopped?

At the end of the study, you will be provided appropriate ongoing dietary advice from the study dietitian following your final glucose tolerance test to follow the NHS healthy eating and lifestyle plan. You will receive routine postnatal care from your GP, hospital team, and dietitian if required. You will be advised to see your GP for an annual blood test to check your blood sugar levels (this is routine care for women with gestational diabetes). Approximately 5% of women with gestational diabetes have residual diabetes after delivery. This will be identified from your glucose tolerance test/HbA1c; if this is the case you and your GP will be informed. Your GP will take over the management of your diabetes as per routine care outside the study.

Interview sub study

Women in this study may be invited to take part in an interview at the end of the study. You will be asked about your views and experiences on trying to follow your allocated diet programme. This interview can be arranged at a time that suits you, either at Wythenshawe or St Marys Hospital, at your home, or over the telephone. There is no obligation to take part in this interview study.

Frequently asked questions

Do I have to take part?

No, you do not have to take part if you do not wish to and your decision will not affect any standard of care you receive at Wythenshawe or St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

What happens if I change my mind?

It is OK if you agree to take part in the study but later change your mind. You do not need to give a reason and it will not affect the standard of care you receive. The study team may also choose to withdraw you if it is necessary for your health or safety due to unexpected findings during the study. If you decide to withdraw from the study, or the study is stopped for any reason, you will be asked whether or not you are happy for us to keep the data that may have already been collected. If you do withdraw from the study you will continue to be cared for by your usual specialist diabetes and obstetric teams for the duration of your pregnancy. You will

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still have the option of completing the end of study questionnaire and/or interview to provide feedback; this is very useful for the research team to help us understand potential reasons you may have chosen to withdraw from the study.

You will also have the option that if you withdraw, researchers may still collect relevant information about your pregnancy and/or gestational diabetes from your medical records within the 18-month study duration. This will be an option on the consent form.

Are there any benefits from taking part?

You will receive frequent personalised advice and support to follow two diet and lifestyle programmes which may help to control your blood sugar levels throughout your pregnancy. The information gained from this study will also help inform the future NHS care of patients with gestational diabetes.

Are there any risks from taking part?

Research has found that diets consisting of two low-calorie days a week are very low risk. Pregnant women will develop slightly higher levels of ketones when following low calorie diets than women who are not pregnant. Ketones are produced naturally by the body when the body uses fat stores for energy (i.e. when we follow a low calorie diet or haven't eaten enough because we are ill).

Some research suggests that very high levels of ketones throughout pregnancy may cause a higher risk of babies being slightly smaller than average. It is very unlikely that you will develop high levels of ketones by following this diet. You will be provided with a ketone meter and you will be asked to check your ketone levels before your lunch and evening meal on your low-calorie days, and the following morning, to make sure that your ketone levels are normal.

On your low-calorie days you may feel slightly more hungry, or you may experience other effects such as increased nausea, light headedness, or tiredness. It is important that you eat regularly throughout the day to reduce the risk of this happening. You will be asked to report any side effects of following the diet to the team at each appointment.

What happens if my baby or I become unwell during the study?

The safety of you and your baby are of utmost importance and remain our priority. In the instance that either of you become unwell your case will be reviewed by our specialist team and your suitability for continuing in the trial will be decided. Although it remains exceptionally rare, were you to experience the unexpected loss of your baby you will be withdrawn from the trial and supported by the dedicated specialist bereavement team at the hospital. Any information which has been collected as part of the trial will be stored securely and once we have finished the study we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What will happen to blood samples which are taken?

Some blood samples taken as part of the study will be sent to the laboratory immediately for analysis and any remaining will be stored securely for the duration of the study. Only your 'study ID' will be used – the samples will have none of your personal details on them. At the end of

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the study any remaining samples will be disposed of in accordance with the Human Tissue Act (2004).

What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (**Dr. Basil Issa** or **Dr. Michelle Harvie – via the study office – via michelle.harvie@manchester.ac.uk or telephone 0161 291 4410**). If you remain unhappy and wish to complain formally, you can do so through the NHS complaints procedure. Details can be obtained from the NHS Patient and Liaison Service (PALS) on Tel: 0161 276 8686 or contact the team by email pals@mft.nhs.uk.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme. If something did go wrong and you were harmed or suffered deterioration in your health as a result of taking part in this study then you may have grounds for legal action or compensation.

Additional information about the study

Will my lifestyle be affected if I take part?

An essential aspect of this study is a change to your diet and physical activity patterns with support from a specialist team of healthcare professionals.

Payments

We are able to offer free parking at Wythenshawe/St Marys Hospitals for study visits and offer reimbursement for reasonable travel expenses (car, bus or tram) linked to visits for this study. There are no other payments for taking part.

Will my details be kept confidential?

Yes. The study team and any associated regulatory authorities follow strict ethical and legal guidance regarding participant confidentiality. Any information we have about you will be handled in confidence and will only be used for the purposes of this study. All data recorded will be coded and your name will remain anonymous.

During the study we will inform your GP via letter of your participation in the study and your ongoing results, including your weight, blood tests, any abnormal findings and any recommendations for treatment.

If you join the study, some relevant parts of your medical records may be looked at by authorised personnel at Wythenshawe or St Marys hospitals prior to starting the study. These records may also be looked at by an independent auditing body and regulatory authorities to check that the study is being carried out correctly. We will only access parts of your medical records that are relevant to this research and all information accessed will be kept strictly confidential.

How will we use information about you?

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We will need to use information from you and from your medical records for this research project.

This information will include the following:

- · Initials
- · NHS number
- · Name

- Contact details
 - Medical History including test results

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Other researchers from outside the Trust may ask to see this data for the purposes of furthering their research. We will only share this upon written request to the Trust. The external researchers will be asked to sign a Confidentiality Agreement before any data is shared.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health during pregnancy from your hospital records. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
 - by sending an email to mft.middas.gdm@nhs.net or
- · by ringing us on 07815987910

How will my details be used to access the Mobile Applications?

None of your personal details (other than the telephone number from which an application is downloaded) will be needed to access the mobile applications. Once you have given your consent to take part in the study you will be issued with a 'dummy' e-mail and password under a pseudonym (fake name). Only the research team will know the dummy e-mail address you have been assigned to, in order to be able to review your data. The application will not contain your identifiable data. If you choose to use a mobile application to monitor your blood sugar

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levels the relevant terms of service for the app and the app developers privacy policy will apply. It will be your responsibility to read and understand these prior to download.

Will my insurance be affected if I take part in this study?

It is unlikely that your insurance premiums will be affected by participation in this study as the study has the potential to improve your diabetic control and reduce your risk of ill health. However, if you are at all concerned, then we advise that you contact your insurers and seek expert advice before agreeing to participate.

Who has reviewed this study?

Research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is made up of experts, non-experts and members of the general public. Together they review research applications to ensure your safety, rights, wellbeing and dignity are protected at all times. This study has been reviewed and given favourable opinion by REC.

What will happen to the study results?

It is intended that the results of this study will be presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. To do this our study information is double-checked by other professionals in research and healthcare. There is a possibility that the study and its results may be publicised for example on radio, television, magazines, books and websites. You will not be identified in any publicity, reports or publication arising from this study. If you would like a general summary of the results of the study you can select this on the consent form or please contact the research team.

Who is organising and funding the research?

Researchers from Wythenshawe hospital, have designed this study and will be carrying out this research. This study has been funded by the National Institute of Health and Research.

Further information and contact details

For further information about this study, please contact mft.middas.gdm@nhs.net or 07815987910

Thank you for taking the time to read this information sheet. We hope it has been of interest to you.





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Consultant Endocrinologist – Dr. Basil Issa Tel: 0161 291 7070 Research Dietitian – Dr. Michelle Harvie Tel: 07815987910 Email: <u>mft.middas.gdm@nhs.net</u>

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Nightingale Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>

I confirm that I have read and understand the participant information sheet

(version 3.0) for the above study. I have had the opportunity to consider the

I understand that my participation is voluntary and that I am free to withdraw

at any time, without giving any reason, without my medical care or legal rights

I understand that relevant sections of my medical notes and data collected

during the study may be looked at by individuals from Manchester University

NHS Foundation Trust and regulatory authorities, where it is relevant to my

taking part in the research. I give permission for these individuals to have

I consent to the collection of blood samples to be collected as described in the

I consent to the collection of cord blood to be collected at the time of delivery

I understand that the information collected about me will be used to support

other research in the future and may be shared anonymously with other

I agree to my GP being informed of my participation in this study and changes

to my weight, body measurements, blood results, guestionnaire results and

I agree that my blood sugar readings can be recorded by the study team.

information and ask questions, and have had these answered satisfactorily.

Participant Informed Consent Form

Participant Identification Number:

being affected.

researchers.

medications as required.

access to my records.

participant information sheet.

as described in the participant information sheet.

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- 9. I understand that to use the mobile applications as described in the Patient Information Sheet, I will need to provide my personal mobile number to be able to access the app.
- 10. I understand that the information I provide to mobile applications as described in the Patient Information Sheet will be treated in line with the relevant terms of service and the app developers privacy policy at the time of downloading the application.
- 11. I have informed the study team of any health issues, including those which may affect my ability to follow the diet, and I will inform the study team of any unusual symptoms that occur during the diet. I will inform the study team of changes to my health status during the study.
- 12. I have informed the study team of any health issues, including those which may affect my ability to exercise, and I will inform the study team of changes to my health status during the study.
- 13. I consent to the storage of personal information (including electronic) for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.
- 14. I agree to take part in the above study.
- 15. I agree that relevant information about my pregnancy and/or gestational diabetes can be obtained from my medical records within the 18-month study duration if I withdraw from the study early.
- 16. I am aware that my non-identifiable trial data may be shared with other researchers for the purposes of research.

Optional (delete as appropriate)

17.	I agree to be approached to take part in sub-study 1 (interview study), and understand that I will be approached to take part in the sub-study regardless of whether I withdraw from the	
	main study	YES/NO
18.	I would like to receive a summary of the final study results	YES/NO

19. I agree to be contacted regarding future research opportunities YES/NO

My preferred contact (please tick and include email if preferred)

Post

Email 🗌

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S	Signatures		
N	lame of participant	Date	Signature
N	Name of person taking consent	Date	Signature
١	When completed: 1 for participar	nt; 1 for patient file; 1 for me for site file	edical notes; 1 for GP; 1 (original)

Example of 1 day meal plan for Diet Day

The diet days aim to limit the calories to 1000 calories per day. You are aiming to include 2 (not consecutive) diet days each week. The other 5 days, follow the Mediterranean diet as described earlier. To keep the calories to 1000, the diet day will look like this:

Mixed diet		Vegetarian/ vegan diet
4	Carbohydrate portions	3
6	Protein portions	7
5	Vegetable portions	5
2	Fruit portions	2
3	Dairy portions	3
1	Fat portions	1

Below are some examples of meals that can be used to help you follow a 1000 calorie diet.. There are options for a mixed diet or vegan or vegetarian options, if you feel you wanted to try meat free days. Filling up on vegetables will make you feel less hungry

Mixed diet options

Breakfast	Portion	Dairy	Protein	Carb	Veg	Fruit	Fat
Grilled lean bacon	1 rasher	0	1	0	0	0	0
Grilled tomatoes	7 cherry tomatoes	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Diet or natural yogurt	1 small carton	1	0	0	0	0	0
Lunch							
Wholegrain bread	2 medium slices	0	0	2	0	0	0
Tuna	⅓ of a 120g can	0	1	0	0	0	0
Green salad	Cereal bowl full / 80 g with oil-free dressing	0	0	0	1	0	0
Satsumas	2	0	0	0	0	1	0
Mid afternoon							
Low fat cheese	30g / match box size	1	0	0	0	0	0
Apple slices	I medium apple 🔌 (80g)	0	0	0	0	1	0
Tea/ coffee		0	0	0	0	0	0
Evening							
Vegetable rice	4 tablespoons cooked rice 160g of mix vegetables	0	0	2	2	0	0
Chicken curry	90g /average chicken breast (no skin) & ½ can tomatoes, 1 desertspoon oil	0	3	0	1	0	1
Bedtime							
Low fat houmous	1 level tablespoon	0	1	0	0	0	0
Pepper sticks	1/2 red pepper	0	0	0	1	0	0
Milk	1 small glass	1	0	0	0	0	0
Total portions	a day	3	6	4	5	2	1
		portions	portions	portions	portions	portions	portion

Vegetarian option

Breakfast		Dairy	Protein	Carb	Veg	Fruit	Fat
Egg	2 poached	0	2	0	0	0	0
Mushrooms	2 cupped handfuls / 80g	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Cheddar cheese	1 match box size / 30g	1	0	0	0	0	0
Cucumber	Sliced handful	0	0	0	1	0	0
Lunch							
Baked beans	2 tablespoons	0	1	0	0	0	0
Seeded bread toasted	1 medium sliced	0	0	1	0	0	0
Blueberries	1 handful	0	0	0	0	1	0
Mid afternoon							
Meat free ham	2 slice small	0	1	0	0	0	0
Pepper	1⁄2 sliced	0	0	0	1	0	0
Avocado	1/4	0	0	0	0	0	1
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Vegetarian sausage casserole Jacket potato (100g)	1 grilled sausage 2 cereal bowls vegetables 1 ½ egg sized (100 g)	0	2	1	2	0	0
Bedtime							
Pear	1 medium	0	0	0	0	1	0
Low fat cream cheese	1 tablespoon	1	0	0	0	0	0
Whole wheat cracker	2 biscuits	0	0	1	0	0	0
Milk	1 small glass	1	1	0	0	0	0
Total portion	s a day	3 portions	7 portions	3 portions	5 portions	2 portions	1 portions
		portions	portions	portions	portions	portions	portions

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Vegan options

Breakfast		Dairy equivalent	Protein	Carb	Veg	Fruit	Fat
Branflakes	3 tablespoons	0	0	1	0	0	0
Milk- soya	200 ml	1	0	0	0	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Soya yogurt	3 tablespoons	1	0	0	0	0	0
Lunch							
Kidney bean & Vegetable chilli Wholemeal	3 tablespoons of beans 60g with 1 cereal bowl mixed vegetables & 1/2 can chopped tomatoes ½ pitta	0	2	1	2	0	0
Banana	1 medium	0	0	0	0	1	0
Mid	Thealam	U	U	U	U		0
afternoon							
Low fat	2 level	0	2	0	0	0	0
hummus	tablespoon						
1 carrot	I medium carrot (80g)	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Quinoa	2 tablespoon cooked	0	0	1	0	0	0
Tofu	4 matchbox	0	2	0	0	0	0
Mixed salad with edamame beans	2 x Cereal bowl full with oil free dressing & 1 tablespoons of edamame	0	1	0	2	0	0
Bedtime							
Peanut	1 heaped	0	0	0	0	0	1
butter	teaspoon						
Apple	1 medium sliced	0	0	0	0	1	0
Milk	1 small glass	1	0	0	0	0	0
Total portion	is a day	3 portions	7	2	5	2	1
			portions	portions	portions	portions	portions

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To help with estimation of portions the following tables outline weight and measures of the different food groups. Where possible household measures are given to make things a little easier. Use these to help you plan your 2 days in the week of 1000 calories.

Carbohydrate 4 portions - mixed diet 3 portions - vegan/vegetarian	Equal to
Wholewheat or oat breakfast cereal, e.g. wholewheat biscuit, malted wholewheat squares, Grapenuts, bran flakes, fruit & fibre	24g or 3 tablespoons or 1 whole wheat biscuit
Porridge oats or no-added sugar muesli	20g or 1 heaped tablespoon
Wholegrain, wholemeal, rye, granary bread	36g or medium slice of bread (other than rye), 1½ slices of rye, or ½ roll
Wholemeal or multigrain pitta bread or tortilla wrap, chapatti made without fat	60g or 1x 8" tortilla or 1 standard pitta or small thin chapatti
Rye crispbread, crackers, oak cakes	22g or 2 crispbreads/ 2 oatcakes
Wholegrain rice cake	16g or 2 rice cakes
Wholewheat pasta or rice - cooked amount Cous cous, Bulgar wheat, Quinoa, Pearl barley	1 tablespoon uncooked 2 tablespoons cooked 30g- raw weight or 60g cooked
Lasagne (wholemeal if possible)	20g raw weight or 1 large sheet or 1½ smaller sheets
Noodles (wholemeal if possible)	25g raw weight or ½ block/nest
Baked or boiled potato (in skin), cassava, sweet potato	1½ egg sized potatoes or 100g raw weight
Wholemeal pizza base (topping is from other food groups)	35g or $^{1}/_{6}$ of thin 10" pizza base
Unsweetened popcorn	20g or 2 handfuls
	•

Protein 6 portions – mixed diet 7 portions – vegan/vegetarian	Equal to
Fresh or smoked white fish (e.g. haddock or cod)	60g or 2oz 2 fish finger size
Seafood, e.g. prawns, mussels, crab	45g or 1½oz
Canned tuna or salmon in brine or spring water	45g or 1½oz ⅓ standard tin (120g)
Oily fish (fresh or tinned in tomato sauce or olive oil - drained), e.g. mackerel, sardines, salmon, fresh tuna, kippers, smoked salmon or trout	30g or 1oz or ¼ standard tin (120g) or ¼ fillet of salmon
Chicken, turkey, duck, pheasant (cooked without skin) Lean beef, pork, lamb, rabbit, venison, offal (fat removed) Quorn fillets, steak, mince or pieces Vegetarian mince frozen	30g or 1oz or 1 slice size of playing card
Lean grilled bacon Quorn ham	25g or ¾oz or 1 rasher
Lean ham Quorn bacon rashers (not slices)	30g or 1oz or 1 medium, 2 small or 4 wafer thin slices
Eggs	60 g or 2 oz or 1 egg
Tofu	50g or $1^2/_3$ oz or Size of 2 match boxes
Tempeh	25 g or 1 oz or Size of 1 match box
Baked beans (reduced sugar)	60 g or 2 oz or 2 tablespoons
Lentils, chickpeas and kidney beans, mung beans, black eye beans, puy lentils, toor dahl, urad dahl, Raw weight	20g or ⅔ oz or 1 tablespoon raw
Cooked or tinned weight	65g or 2oz or 1½ tablespoons cooked /tinn or 1 cupped handful
Soya beans (frozen or cooked) or edamame beans	30g or 1oz or 1 tablespoon
Vegetarian sausage	25g or ¾ oz or ½ sausage
Textured vegetable protein (TVP)	10g or ⅓ oz uncooked or 1 heaped tablespoon uncooł
Low fat hummus	30g or 1oz or 1 level tablespoon

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Vegetables – min 5 portions 1 portion = 80g or 2⅔oz	1 portion is equal to
Asparagus, Aubergines, Broccoli, Brussel sprouts, Carrots, Cabbage, Cauliflower, Chinese leaves, Courgettes, Cucumber, Curly kale, Green beans, Lettuce (mixed leaves), Mange tout, Methi, Mushrooms, Okra, Pak choi, Peas, Sugar snap, Spinach, Spring greens cooked, Sweetcorn, Tomatoes, Watercress fresh	80g or 2 ³ / ₃ oz or 2 spears of broccoli, 8 cauliflower florets. 3 heaped tablespoons of vegetables or large cereal bowl of salad.
Fruit - 2 portions.	1 portion is equal to
1 portion = 80g or 2 ² / ₃ oz (30g or 1oz dried fruits)	
Berries (e.g. blackberries, blueberries, redcurrants, raspberries, strawberries) Cherries or grapes	80g or 2⅔oz 1 handful
Grapefruit, guava and mango	80g or 2⅔oz or ½ a whole fruit
Large fruit (e.g. melon, pineapple, papaya)	80g or 2⅔oz or 1 medium slice
Medium fruits (e.g. apple, pear, nectarine, orange, peach, banana, pomegranate)	80g or 2⅔oz 1 fruit
Small fruit (e.g. fresh apricots, kiwi, clementine, passion fruit, plums)	80g or 2⅔oz or 2 fruits
Any stewed fruit—unsweetened or with calorie-free sweetener e.g. apple, rhubarb	80g or 2⅔oz or 3 tablespoons
Kumquats, lychees, physalis	5 fruits
Dried fruits (raising currants apricots)	30g or 1oz or

¹ ∕ ₃ pint or 200ml or
1 small glass
120-150g or 4-5oz or
1 small pot or
3 tablespoons
80g or 1 ² / ₃ oz or
2 tablespoons
75g or 1½oz or
1/4 pot, 2 tablespoons
30g or 1oz or
1 tablespoon
30g or 1oz or Matchbox size
No more than 180g or 6oz a
week
-

** we recommend soya milk as coconut, oat and almond milks are lower in protein and calcium

Fat – 2 portions only	Equal to
Margarine or low-fat spread (avoid the buttery types) Olive oil or other oil Oil based dressing Pesto Mayonnaise	8g or 1 teaspoon 1 dessertspoon of oil
Seeds (e.g. linseed, pumpkin, sunflower, sesame, chia, hemp)	7g or 1 dessertspoon
Unsalted or salted or dry roasted nuts	7g or 1 dessertspoon 3 walnut halves, 3 Brazil, 4 almonds, 8 peanuts, 10 cashews or pistachios
Olives	50g or 10 olives
Low fat mayonnaise, Curry paste or Harissa paste	15g or ½ oz or 1 tablespoon
Peanut butter (without palm oil)	11g or ⅓ oz or 1 heaped teaspoon
Cocoa powder	12 g or ⅓ oz or 2 heaped teaspoons
Avocado	40g or 1⅓ oz or 1/4 of an average pear
Low fat guacamole	40g or 1 ¹ ⁄₃ oz or 2 tablespoons

BMJ Open



MIDDAS-GDM End of Study Questionnaire

Thank you for taking part in the MIDDAS-GDM Study.

 This is one of the first studies of its kind. We hope to learn as much as possible from this study, in particular the views of people who have taken part. We are inviting you to provide your views on different aspects of the study and following the diet, and how we can improve our programmes and research studies in future.

Please complete the following questions and return this questionnaire to the MIDDAS-GDM study team in the envelope provided. If there is anything else you would like to say about your experiences of the study, please use the section at the end. Your answers to the questions below will remain anonymous.

1. What w	/ere your	reasons	for joini	ng the st	udy?				
		• • • • • • • • • • • • • • • •	• • • • • • • • • • • • • • • • • • • •						
2. How sa	atisfied w	ere you v	with stuc	ly overal	l (recruit	ment, ap	pointmen	its etc)?	(circle)
1	2	3	4	5	6	7	8	9	10
Not at all	2	Sligh	tly .	Qu	ite	' Ve	ry	U	Extreme
satisfied		satisf	ied	satis	fied	satis	fied		satisfied
Comments	:								
	•••••	•••••							
			-	Study Ap	pointme	<u>ents</u>			
- \/							.,		
3. You we	ere asked	to attend	d	additio	nal face	to face a _l	opointme	nts at tl	he hospit



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Manchester University NHS Foundation True
4. You were asked to attend additional virtual (i.e. video call or telephone)
appointments by the study team (please fill in the number)
5. How do you feel about the number of additional appointments you were asked to
attend? (tick)
I was happy with the number of appointments
I would have preferred fewer face to face appointments
I would have preferred more face to face appointments
I would have preferred fewer virtual appointments
I would have preferred more virtual appointments
Comments:
6. How do you feel about virtual (i.e. video call or telephone) appointments?
□ I prefer virtual appointments to face to face appointments (please explain why below)
□ I prefer face to face appointments to virtual appointments (please explain why below)
Comments:
<u>Diet</u>
7 Which distances asked to follow? (slopes tist)
7. Which diet were you asked to follow? (<i>please tick</i>)
□ Best NHS Care (i.e. increased fruit/vegetable intake, low-GI foods, reduction in free sugars
regular meals)
□ Intermittent low energy diet (5 days of the best NHS care diet plus 2 non-consecutive days of
1000 kcal each week)

8. Was the diet easy to follow?

•••••••									
1	2	3	4	5	6	7	8	9	10
Not at all		Slig	ghtly	Mode	erately	Ve	əry		Extremely

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					Manch	ester Univers
12. Would y	ou make ar	ny chang	jes to	the reviews (call	s/face to face a	ppointments) you
with the	dietitian du	ring you	r pre	gnancy ?		,,,
□ Yes		0,7	•			
🗆 No						
Comments:						
13. How use	eful was you	ır final a	ppoin	tment with the die	titian at 12 wee	ks post-delivery?
1	2 3		4	5 6	7 8	9 10
Not at all		Slightly		Quite	Very	Extreme
Comments:				0		
				N		
14. Did you	feel confide	ent to exe	ercise	e whilst on the diet	t plan?	
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				Additional suppor	rt	
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				NITS FOUNDATION INUS
Additional support from			Face to face / phone	
the doctors in the clinic				
More contact with other			Face to face / phone	
women in the study				
following the diets				
g are area				
Other, please specify:				
·				
16. Did you receive any ຣເ	upport	outs	ide of the study team help	to keep you on track as you
progressed through th	e stu	dy?		
⊐ No				
⊐ Yes				
f yes, what support did you	recei	ve?		
17. How did you find the	fingeı	[,] pric	Record keeping k testing requirements on	the study? (tick all those the
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	NHS Foundation Trust
Not challenging a	t all
□ I felt it was <u>neces</u>	sary to test this often to ensure my safety
□ I felt it was <u>unneo</u>	essary to test this often to ensure my safety
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☐ Straightforward	
□ Challenging but o	n the whole <u>achievable</u>
Challenging and	not achievable
□ I felt uncomfortat	le using computer software to keep track of my medical details
□ I felt comfortable	using computer software to keep track of my medical details
Comments:	
20. How did you find o	ompleting the food diary during the study? (tick all those that apply)
□ Challenging but o	n the whole <u>achievable</u>
□ Challenging and	not achievable
□ Not challenging a	t all
Comments:	
21. How did you find tl	e physical activity questionnaires on the study? (tick all those that apply)
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□ Challenging and	not achievable
□ Not challenging a	t all
Comments:	

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32. What did you e	enjoy least about the study and could be improved?
	Any other comments about the study
ТЬ	ank you for completing this guestion pairs, places return to:
111	MIDDAS CDM Study Toom Nightingalo Contro
	Middas-Gdivi Study Team, Nightingale Centre,
	vvytnensnawe Hospital, Manchester, M23 9L1

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T	DieR	The TIDieR (Template for Intervention Description and Replice	tion) Checklist*:	
emplate f escription	or Intervention and Replication	Information to include when describing an intervention and the location	of the information	
Item Item		ding	Where le	ocated **
number		for uses relations and the second sec	Rerimary paper	Other [†] (details)
1.	BRIEF NAME Provide the name	e or a phrase that describes the intervention.	24. DowNload	
2.	WHY Describe any rati	ionale, theory, or goal of the elements essential to the intervention.	ad fro ⁴⁴ http ur (ABES) .	
	WHAT		://bm	
3.	Materials: Descri	be any physical or informational materials used in the intervention, including those	1 2, 15	_appendix
	Provided to partic	ion on where the materials can be accessed (e.g. online appendix, URL).	bmj.com/ c	
4.	Procedures: Des including any ena	cribe each of the procedures, activities, and/or processes used in the intervention, to abling or support activities.	n 5-12 June 12, 20	
	WHO PROVIDE	D)25 at	
5.	For each categor expertise, backgr	ry of intervention provider (e.g. psychologist, nursing assistant), describe their round and any specific training given.	^T Ag1, 7-12, 17-18 Bibliog	
	нош		raphiqu	

	BMJ Open	open-2	
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or	<u>8</u> <u>8</u> 6-18	
	telephone) of the intervention and whether it was provided individually or in a group.	78264 (
	WHERE fo	on 10	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary	<u>п</u> 26-18	
	infrastructure or relevant features.	nseiqi	
	WHEN and HOW MUCH	1024. D	
В.	Describe the number of times the intervention was delivered and over what period of time including	£256-18	
	the number of sessions, their schedule, and their duration, intensity or dose.	loade	
		d from r (ABI	
۵	If the intervention was planned to be personalised, titrated or adapted, then describe what why	S)	
J.	when and how		
		njope	
	MODIFICATIONS	n.bm	
10. [‡]	If the intervention was modified during the course of the study, describe the changes (what, why,	§N/A	
	when, and how).	ر on ر	
	HOW WELL	une 12	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if anv	2013-14	
	strategies were used to maintain or improve fidelity, describe them.	25 at /	
		Agenc	
12. [‡]	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	ëN/A ⊞	
	intervention was delivered as planned.	blio	

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ttp://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique

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ig, Al training, and similar technologies

** Authors - use N/A if an item is not applicable for the intervention being described. Reviewers	s – use '?' if informatign about the element is not reported/not
sufficiently reported.	t, in

- + If the information is not provided in the primary paper, give details of where this information is available. This may ingeluge locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL). + If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains a second and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study ether elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist $\mathbf{\hat{P}}_{\mathbf{\hat{k}}}$ a randomised trial is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of the CONSORT 2010 Statement. When a clinical trial protocol is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement a statement Statement (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropria study design (see (ABES ata mini www.equator-network.org). cer review on

TIDieR checklist

SPIRIT CHECKLIST

Section/Item	ltem no	
Title	1	
Trial Registration	2a	
	2b	
Protocol Version	3	
Funding	4	
Roles and responsibilities	5a	
	5b	
	5c 5d	
Introduction		- •
Background and rationale	6a	e
	6b	
Objectives	7	
Trial Design	8	31
Methods: Participants, interventions, and	loutcomes	
Study setting	9	
Eligibility criteria	10	
Interventions	11a	
	1	J



	11b	
	11c	
	11d	
Outcomes	12	
Participant Timeline	13	
Sample Size	14	
Recruitment	15	
Methods: Assignment of interventions (fo	r controlled tri	4
Allocation		
Sequence generation	16a	
Allocation concealment mechanism	16b	
Implementation	16c	



	1	1
Blinding (masking)	17a	
	17b	
Methods: Data collection, management, a	and analysis	
Data collection methods	18a	
	18b	
Data management	19	·C
Statistical methods	20a	20
	20b	1
	20c	
Methods: Monitoring		
Data monitoring	21a	

	21b	
Harms	22	
Auditing	23	
Ethics and dissemination		
Research ethics approval	24	
Protocol amendments	25	
Consent or assent	26a	
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Declaration of interests	28	2/
Access to data	29	
Ancillary and post-trial care	30	
Dissemination policy	31a	

31b 31c endices rmed consent materials 32 ogical specimens 33	
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Description	Location
Descriptive title identifying the study design, population,	1
nterventions, and, if applicable, trial acronym	±
Trial identifier and registry name. If not yet registered, name	2
of intended registry	5
All items from the World Health Organization Trial	throughout
Registration Data Set	throughout
Date and version identifier	n/a
Sources and types of financial, material, and other support	23
Names, affiliations, and roles of protocol contributors	1
Name and contact information for the trial sponsor	name only, 23
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	23
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)	18
Departmention of response supplier and institution for	
Description of research question and justification for undertaking the trial, including summary of relevant studies published and unpublished) examining benefits and harms or each intervention	4-5
Explanation for choice of comparators	4-5
Specific objectives or hypotheses	13-14
Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and ramework (eg, superiority, equivalence, noninferiority, exploratory)	6
Description of study settings (eg, community clinic, academic nospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
nalusion and ovalusion oritoria for participants. If applicable	7
eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	,

Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	13-14
Time schedule of enrolment, interventions (including any run- ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Strategies for achieving adequate participant enrolment to reach target sample size	n/a
als)	
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	δ
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 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	8

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Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
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	9-15
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	supplementary PIS
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 wher details of data management procedures can be found, if not in the protocol	e 16
Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistica analysis plan can be found, if not in the protocol	16
Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Composition of data monitoring committee (DMC); summar	,

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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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 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) Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	n/a 13, 16 16 n/a 19
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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 Financial and other competing interests for principal	n/a
Financial and other competing interests for principal	16
investigators for the overall trial and each study site	23
Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	supplementary PIS
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	

Authorship eligibility guidelines and any intended use of professional writers Plans, if any, for granting public access to the full protocol,	n/a
Plans, if any, for granting public access to the full protocol,	
participant- level dataset, and statistical code	19
Model consent form and other related documentation given to participants and authorised surrogates	supplementary materials
Plans for collection, laboratory evaluation, and storage of piological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	15

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1 2 3 4		MeSH Descriptors
6 7	Infant, newborn	
8	Pregnancy	
9	Glucose Intolerance	
10 11	Diabetes, Gestational	
12	Insuin	
13	Rediabatia stata	
14 15	Metformin	
16	Glycated Hemoglobin	
17 19	Overweight	
19	Obesity	
20	Diabetes Mellitus Type 2	
21 22	Diet. Healthy	
23	Feasibility Studies	
24 25	Mobile Applications	
25 26	Body Weight	
27	Hypoglycaemic agents	
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Manchester Intermittent Diet in Gestational Diabetes Acceptability Study (MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater Manchester

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-078264.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2023
Complete List of Authors:	Dapre, Elizabeth; Wythenshawe Hospital Issa, Basil; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Harvie, Michelle; University Hospital of South Manchester NHS Foundation Trust, Genesis prevention centre Su, Ting-Li; University of Manchester, Dentistry McMillan, Brian; The University of Manchester, Centre for Primary Care and Health Services Research Pilkington, A.; Wythenshawe Hospital Hanna, F.; University Hospitals of North Midlands NHS Trust Vyas, Avni; Manchester Metropolitan University Faculty of Health Psychology and Social Care, Health Professionals Mackie, S.; Wythenshawe Hospital Yates, James; Manchester University NHS Foundation Trust Evans, Benjamin; Manchester University NHS Foundation Trust Mubita, Womba; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Lombardelli, Cheryl; Manchester University NHS Foundation Trust
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Obstetrics and gynaecology, Reproductive medicine
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, DIABETES & ENDOCRINOLOGY, Obesity, NUTRITION & DIETETICS, Feasibility Studies, Maternal medicine < OBSTETRICS



Manchester Intermittent Diet in Gestational Diabetes Acceptability Study		
(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent		
Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater		
	Manchester	
uthors: Dapre. E., Issa	. B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,	
A., Vvas, A., Yates, J., Mackie, S., Evans, B. Mubita, W. Lombardelli, C.		
, <u>,</u> , , , - ,		
Or Elizabeth Danre	elizabeth.dapre@hotmail.com	
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	Midlands, UK	
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Benjamin Evans	Division of Clinical Trials, Manchester Foundation Trust, UK	
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Cheryl Lombardelli	The Nightingale Centre, Wythenshawe Hospital, Manchester, UK	

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1 2	18	
3 4 5 6 7 8 9	19	<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>
	20	(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent
	21	Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater
	22	Manchester
10	23	
12	24	Authors: Dapre, E., Issa, B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,
13 14	25	A., Vyas, A., Yates, J., Mackie, S., Evans, B., Mubita, W., Lombardelli, C.
15 16	26	
17	27	Corresponding Author: elizabeth.dapre@nhs.net
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43	28	
	29	Abstract (word count 298)
	30	Introduction: The prevalence of gestational diabetes mellitus (GDM) is rising in the
	31	UK and is associated with maternal and neonatal complications. National Institute for
	32	Health and Care Excellence (NICE) guidance advises first line management with
	33	healthy eating and physical activity which is only moderately effective for achieving
	34	glycaemic targets. Approximately 30% of women require medication with metformin
	35	and/or insulin. There is currently no strong evidence base for any particular dietary
	36	regimen to improve outcomes in GDM. Intermittent low-energy diets (ILEDs) are
	37	associated with improved glycaemic control and reduced insulin resistance in type 2
	38	diabetes (T2DM) and could be a viable option in the management of GDM. This
	39	study aims to test the safety, feasibility and acceptability of an ILED intervention
	40	amongst women with GDM compared to best National Health Service (NHS) care.
	41	
	42	Method and analysis: We aim to recruit 48 women with GDM diagnosed between 24-
45	43	28 weeks gestation from antenatal clinics at Wythenshawe and St Mary's hospitals,
46 47	44	Manchester Foundation Trust, over 13 months starting in November 2022.
48 49	45	Participants will be randomised (1:1) to ILED (2 low-energy diet days/week of
50	46	1000kcal and 5 days/week of the best NHS care healthy diet and physical activity
52	47	advice) or best NHS care 7 days/week until delivery of their baby. Primary outcomes
53 54	48	include uptake and retention of participants to the trial, and adherence to both dietary
55 56	49	interventions. Safety outcomes will include birthweight, gestational age at delivery,
57	50	neonatal hypoglycaemic episodes requiring intervention, neonatal
58 59	51	hyperbilirubinaemia, admission to special care baby unit or neonatal intensive care
60	52	unit, stillbirths, the percentage of women with hypoglycaemic episodes requiring

1 2	53	third-party assistance, and significant maternal ketonaemia (defined as ≥1.0mmol/L)
3	54	Secondary outcomes will assess the fidelity of delivery of the interventions, and
4 5 6 7	55	qualitative analysis of participant and healthcare professionals' experiences of the
	56	diet. Exploratory outcomes include the number of women requiring metformin and/or
8 9	57	insulin.
10	58	
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48 49	80	
50 51	81	Ethics and dissemination: Ethical approval has been granted by the Cambridge
52	82 83	publication in peer-reviewed journals, conference presentations, and shared with
53 54	84	diabetes charitable bodies and organisations in the UK, such as Diabetes UK and
55 56	85	the Association of British Clinical Diabetologists.
57 58	86	
59	87	
60	88	Irial Registration Number: NC105344066

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3		Strengths and limitations of this study					
4 5		Strengths					
6		 This study adds to the limited literature of safety of low-calorie diets amongst 					
8		we may with gestetional dishetes					
9 10		women with gestational diabetes					
11		This study has been informed by an experienced patient and public involvement					
12 13		and engagement group					
14		Limitations					
15 16		This study involves a small sample size and is not powered to show efficacy of					
17		the intervention					
18 19		Women joining this study are likely to be highly motivated and adherence may					
20 21		not reflect that seen in the wider general population					
22	00						
23 24	90	INTRODUCTION (word county 2520)					
25	91	INTRODUCTION (word could: 3539)					
26 27	92	Background					
28 29 30 31 32 33 34 35	93	In the UK up to 16% of pregnant women develop gestational diabetes (GDM) and					
	94	the incidence is rising, in part due to increasing rates of obesity and maternal					
	95	age(1,2). GDM is associated with maternal and neonatal complications (the risk					
	96	increases with poor glycaemic control), including macrosomia, shoulder dystocia,					
	97	caesarean-sections, neonatal hypoglycaemia and/or hyperbilirubinaemia, preterm					
36 27	98	delivery, preeclampsia, and stillbirth(2). Women who have had GDM have an					
37 38	99	estimated seven to ten-fold risk of developing type 2 diabetes (T2DM) later in life.					
39 40	100	and their children have a higher risk of developing adult obesity and T2DM(2–4).					
41	101						
42 43	101	Evenesive weight gain in programmy is a particular problem for woman with CDM(E)					
44	102	Excessive weight gain in pregnancy is a particular problem for women with GDM(5).					
45 46	103	Harper et al demonstrated that, in women with GDM, every additional 1lb/week					
47	104	gained following diagnosis of GDM resulted in a 36-83% increased risk of pre-					
48 49	105	eclampsia, caesarean-section, macrosomia, and large for gestational age babies(5).					
50 51	106	Such studies highlight the importance of adequate weight control throughout					
51 52	107	pregnancy in women with GDM in order to reduce both maternal and neonatal					
53 54	108	complications.					
55	109						
56 57	110	First-line therapy for GDM is diet and physical activity. National Institute for Health					
58	111	and Care Excellence (NICE) guidance encourages a healthy dist with increased fruit					
59 60	TTT	and our Excention (MOE) guidance encourages a reality det with increased full					

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- and vegetables, low-glycaemic index (GI) foods, reduced refined sugars, regular mealtimes and regular physical activity(6,7). These dietary measures fail to achieve glycaemic targets in ~30% of women who require medication with metformin and/or insulin(8). A range of dietary approaches have been studied including daily diets promoting low-GI diets (limiting refined and promoting complex carbohydrates), continuous modest energy-restriction (1800 Kcal/day), and low carbohydrate diets(9). There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM. Intermittent Low-Energy Diets (ILED) The pathogenesis of GDM is strongly linked to obesity and chronic insulin resistance with many clinicians viewing GDM as a form of evolving T2DM. ILEDs typically include several days of a food based or meal replacement (e.g. drinks/bars) low-energy diet (650-1000kcal) diet, with a standard healthy (non-restrictive) diet recommended on the remaining days of the week. These diets are associated with significant reductions in weight, insulin resistance and hyperglycaemia in patients with prediabetes (HbA1c between 42-47mmol/mol, impaired glucose tolerance, or impaired fasting glycaemia), those with T2DM, and otherwise healthy subjects with overweight/obesity(10–17). These changes are equivalent to, or greater than, those achieved with standard daily energy restriction. A popular intermittent diet involves 2 consecutive or non-consecutive days/week of a low-energy diet (650-1000kcal) and 5 days of normal eating/week, known as the 5:2 diet. The Manchester Intermittent
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- participants in the ILED group completed the study and achieved a 6% reduction of their baseline body weight. Forty two percent achieved an HbA1c of <48 mmol/mol(18). Given the strong overlap between GDM and T2DM, an ILED may be a promising dietary intervention for those with GDM. A successful dietary approach to glycaemic control could empower women to take charge of the management of their GDM. Women with GDM are motivated to modify their diet driven by a desire to improve foetal outcomes(19-21).

vs. Daily Diabetes App Study (MIDDAS), a study comparing an ILED and a

continuous low-energy diet in T2D conducted in our unit, has shown the feasibility

including those using insulin(18). At the end of the study approximately 70% of

and safety of an ILED (800kcal for 2 days/week) in patients with T2DM and obesity.

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Our Patient and Public Involvement and Engagement (PPIE) work indicates that women find the current National Institute for Health and Care Excellence (NICE) healthy eating guidance(6,7) confusing and vague. Our PPIE work has indicated that women are keen to try alternative dietary approaches, particularly if alternative diets are more effective in preventing the need to progress to medications such as metformin and insulin.

Aim

The aim of this trial is to test the safety, feasibility, and acceptability of an ILED in GDM to inform a future large-scale RCT.

METHODS

Trial Design

The study is a 28-week feasibility two-arm RCT in one NHS trust performed in patients with GDM and BMI ≥27.5 kg/m², or ≥25 kg/m² in high-risk minority ethnic groups (i.e. South Asian, Black African, African Caribbean) in Greater Manchester, between December 2022 and July 2024(22,23). There will be an embedded qualitative sub-study for participants and healthcare professionals. Due to the nature of the intervention, it will not be possible to blind the participants, clinicians, or study team to the treatment allocation after randomisation (the statistician and laboratory technicians will remain blinded).

Trial Setting and Recruitment

Participants will be recruited from antenatal clinics at Wythenshawe and St Mary's Hospitals, Manchester Foundation Trust (MFT) between November 2022 and December 2023. This is an urban area within Greater Manchester, and MFT serves patients from a wide range of minority ethnic and socio-demographic backgrounds. Women may self-refer to the antenatal clinic or be referred by their primary care team. Assessments will be carried out at MFT, or remotely if required by COVID-19 restrictions. The qualitative sub-study will be carried out at MFT, remotely, or at a location of the participant's choosing. We aim to recruit eligible participants over a period of 13 months. Potential participants will be given written information about the study and the opportunity to ask questions about the study prior to providing written consent (figure 1).

1 2	182	Eligibility Criteria			
3 4 5 6 7 8 9	183				
	184	<image exclusion="" figure1="" inclusion="" jpg="" one;=""/>			
	185				
	186				
10	187	Participant Flow			
11	188	Participants who fulfil the broad eligibility criteria will be notified about the trial by the			
13 14	189	GDM nurse/midwife at the time of their diagnosis. Those who are interested will be			
15 16	190	provided with a comprehensive patient information sheet (see appendix) and more			
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	191	detailed eligibility screening questions. They will be asked to attend their first			
	192	appointment having fasted for at least 6 hours and complete a four-day food diary (in			
	193	line with our departments usual care). On attending their first routine clinic			
	194	appointment, interested participants will receive further information from the research			
	195	team. They will have the opportunity to ask questions, have their eligibility confirmed,			
	196	and will be asked for their written consent to take part. Baseline assessments will be			
	197	taken and participants will be randomised to their allocated treatment group using an			
	198	online randomisation platform. Participant flow through the study is demonstrated in			
	199	figure 2.			
	200				
	201	Sample Size			
	202	We plan to recruit 24 participants per study arm (n=48) which, when considering an			
	203	estimated attrition rate of 15%, will provide complete outcome data on 40			
	204	participants(24–26). It has been estimated that 24 participants per group will be			
41 42	205	sufficient to determine study outcomes, in line with sample size recommendations for			
43	206	feasibility studies(27–29).			
44 45	207				
46 47	208	This number will allow us to enable estimation of recruitment/retention parameters			
48	209	with sufficient precision. For example, based on 40 completed participants, it will			
49 50	210	enable recruitment rates in the region of 25% to be estimated with an error of +/-			
51 52	211	13.42% at most; retention of 85% will be estimated with error of +/-11.07% at most. It			
53 54	212	is also sufficient for estimation of variability (e.g. standard deviation) in gestational			
55	213	weight gain and capillary glucose concentrations (proposed outcomes for the future			
56 57	214	definitive trial) with negligible bias (30).			
58 59	215				
60	216				

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1 2	217	Randomisation
3 1	218	The randomisation schedule will be independently set up and known only by the trial
5	219	statistician. The trial statistician will be blinded to the participant's identity using
6 7	220	"sealed envelope" software (https://www.sealedenvelope.com/). Randomisation will
8 9	221	be carried out by generating an online pseudo-random list with random permuted
10	222	blocks of varying size, known only to the statistician, and will be stratified for two
12	223	variables:
13 14	224	- Age (18-35, >35 years)
15 16	225	- BMI (27.5-34.99kg/m ² and >35kg/m2, >25-32.49kg/m ² and >32.5kg/m ² for
17	226	high-risk minority ethnic groups (i.e. South Asian, Black African, African
18 19	227	Caribbean)
20 21	228	These stratification variables have been chosen to reduce potential bias as we
22 23	229	expect varying severity of GDM with increasing age and BMI, and possible
24	230	differences in diet adherence(31).
25 26	231	
27 28	232	Treatment to intervention and control groups will be allocated in a 1:1 ratio. A
29	233	member of the research team who will be unaware of the randomisation algorithm
30 31	234	(principal investigator, clinical research nurse, clinical research fellow or project
32 33	235	manager) will trigger the randomisation procedure onsite; participants and clinicians
34 35	236	will then be informed of the allocated treatment group. Clinicians will not be blinded
36	237	due to the need to remain astute to safety, adherence, and side effects, requiring
37 38	238	open and honest discussions with patients at each appointment. The statistician will
39 40	239	remain blinded to treatment allocation until all outcome measures for all subjects
41 42	240	have been collected.
43	241	
44 45	242	Interventions
46 47	243	Study Arm 1: Best NHS Care Diet
48	244	All dietetic advice will be face to face or via video calls or the telephone. Participants
49 50	245	will receive one to one personalised written and verbal advice from a dietitian to
51 52	246	follow NICE diet and physical activity recommendations(6,7). Dietitians and midwives
53 54	247	will receive training to ensure standardised delivery of information in clinic, and
55	248	standardised patient information leaflets will be supplied to include information about
56 57	249	increased fruit/vegetable intake, low-glycaemic index foods, and a reduction in free
58 59	250	sugars. Information will include advice about the importance of regular meals; dietary
60	251	advice aims to ensure that participants include at least 70g protein/28g fibre, and

predominantly mono- and polyunsaturated fats as per American Diabetes Association recommendations(32). Participants will be advised to be physically active, for example walking for 30 minutes after a meal. Participants will receive ongoing dietetic education and support every 2 weeks until delivery. This level of support is higher than typically provided in NHS GDM antenatal clinics due to limited resources but has been utilised to reflect best NHS care. They will receive suggested menus and recipes to follow the NICE recommended healthy diet for GDM. Participants will be asked to measure their capillary glucose four times each day and their ketones on two random (recorded) days of the week of their choosing (see appendix). Study Arm 2: Intermittent Low-Energy Diet (ILED) Participants will receive the same level of dietetic support as the best NHS care group. They will be given advice on adopting an ILED which involves 2 non-consecutive low-energy diet days/week (1000kcal to include 100g low-GI carbohydrate and 70g of protein) and 5 days/week of the NICE healthy eating low-GI diet and physical activity recommended for the best NHS care group. The low-energy days involve women selecting a set number of portions of protein. carbohydrate, fat, fruit, vegetables, and dairy/dairy alternatives as described in previous studies(33). Each low-energy day includes ~210g of lean protein foods, 3-4 portions of wholegrain carbohydrates, 1x7g portion of fat, 5 portions of vegetables, 2 of fruit, and 3 of dairy/dairy alternatives. Food and drink will be self-selected and not provided by the study team. Participants will be provided with comprehensive food lists, advice on portion sizes for the low-energy days and suggested menus and recipes to follow for both the low-energy and NICE recommended healthy diet days. Both diets can be successfully adapted for people of different ethnicities and those following omnivorous, vegetarian and vegan diets. Participants will be asked to measure their capillary glucose four times each day and their ketones on (and the morning after) the two low-energy days (see appendix). <IMAGE 2: figure 2 flow jpg> <IMAGE 3: figure 3 sched assessments jpg>

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2	287	
3 4	288	
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6 7	290	Outcomes
8 9	291	Primary outcomes
10 11	292	Uptake rate measured as a percentage of eligible participants who consent to
12	293	take part, including the proportion of women who were screened who did not
13 14	294	meet the eligibility criteria, and the number of women who did not give
15 16	295	consent to take part
17	296	Recruitment rate measured as the number of eligible participants who consent
19	297	to take part per month
20 21	298	Retention rate measured as the number of randomised participants who
22 23	299	complete the trial (those who attend the final visit) and the percentage of
24 25	300	participants who attend all 8 visits
26	301	Adherence to the dietary interventions assessed from self-reported adherence
27 28	302	to the potential low-calorie days between randomisation and delivery
29 30	303	 Completion of self-assessed glucose and ketone readings assessed as a
31 32	304	percentage of the required readings
33	305	
34 35	306	Safety outcomes:
36 37	307	 Percentage of women following ILED/best NHS care with
38 39	308	hypoglycaemia (episodes of blood glucose of <3.0mmol/mol) and
40	309	hypoglycaemia requiring third-party assistance as measured by
41 42	310	participants
43 44	311	 Percentage of women who develop significant ketonaemia in both
45 46	312	groups (defined as ≥1.0mmol/L) as measured by participants
47	313	 Percentage of neonatal hypoglycaemic episodes requiring intervention
48 49	314	(blood glucose checked 2- hours post-delivery and 2-hours thereafter
50 51	315	for 12 hours according to local protocol), neonatal birth weight,
52	316	gestational age at delivery, hyperbilirubinaemia/jaundice, and/or
53 54 55 56	317	admission to Special Care Baby Unit or neonatal intensive care, and
	318	stillbirths
57 58	319	\circ The incidence and rate of other adverse events (e.g. headaches,
59 60	320	lethargy, constipation, or complications requiring hospital admission)

1 2	321	between the start of the trial intervention and delivery recorded as mild,
3 4	322	moderate and severe, as defined by Common Terminology Criteria for
5	323	Adverse Events version 5 (CTCAEv5)(34). Hospital admission for
6 7	324	routine labour and delivery will not be classified as an adverse event.
8 9	325	
10 11	326	Secondary outcomes
12	327	 Completeness of collection of trial endpoints including the percentage of
13 14	328	completed weight measurements, 4-day food diaries, and International
15 16	329	Physical Activity Questionnaire (IPAQ) scores
17	330	 Fidelity of delivery of the interventions will be measured through the number
18 19 20 21	331	and modality of completed planned patient contacts, electronic and paper
	332	food diaries, and self-reported capillary glucose and ketone measurements
22 23	333	 Qualitative analysis of the acceptability and implementation of the
24 25	334	interventions will be explored amongst a subset of participants (~10 in each
25 26	335	group) and healthcare professionals through in-depth interviews
27 28	336	
29 30	337	Exploratory outcomes
31 32 33 34 35 36 37 38 39 40	338	The following outcomes will be explored without statistical inference.
	339	1. Maternal outcomes:
	340	 The percentage of women requiring metformin and/or insulin
	341	Four-point capillary glucose profiles during third trimester (four times daily
	342	until delivery)
	343	 Change in fasting blood test results between baseline measurements, 36-
41 42	344	37 weeks' gestation, and 12 weeks post-delivery (including oral glucose
43 44	345	tolerance tests (OGTT)
45	346	 Mode of delivery, development of preeclampsia, polyhydramnios
40 47	347	(maximum liquor volume pool depth ≥8 cm)
48 49	348	 Quality of life and health status questionnaires (WHOQoL-BREF and SF-
50 51	349	36 questionnaires)(35,36)
52 52	350	2. Foetal outcomes:
53 54	351	Foetal weight
55 56	352	Gestational age at delivery
57 58	353	
59 60	354	

1 2	355	
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8 9	359	
10	360	Measurements
11 12	361	The full schedule of assessments can be found in figure 3.
13 14	362	
15 16	363	Physical measurements
17	364	Height, weight and blood pressure will be measured using standardised calibrated
18 19	365	equipment in antenatal clinic.
20 21	366	
22	367	Blood samples
23	368	Fasting venous blood samples will be collected to assess maternal HbA1c, fasting
25 26	369	glucose, insulin, beta-hydroxybutyrate, liver function tests, free fatty acids, thyroid
27 28	370	function tests, and full blood count. A cord blood sample will be collected at the time
29	371	of delivery to measure neonatal glucose, and insulin and C-peptide where collection
30 31	372	is possible. At the end of the study all samples will be disposed of in accordance with
32 33	373	the Human Tissue Act (2004).
34 35	374	
36	375	Questionnaires
37 38	376	Participants will be asked to complete four questionnaires at four time points
39 40	377	throughout the trial (self-reported). Quality of life and health status will be assessed
41 42	378	using the World Health Organisation Quality of Life Questionnaire (brief version) and
43	379	the 36-Item Short Form Survey respectively(35,36). Physical activity will be
44 45	380	measured using the International Physical Activity Questionnaire – Short Form, and
46 47	381	diet quality will be assessed using the UK Diabetes and Diet Questionnaire(37,38).
48	382	These questionnaires are self-reported by participants and have been chosen as
49 50	383	they are widely used and validated tools.
51 52	384	
53 54	385	Food Diaries
55	386	4-day dietary records will be completed using Libro (Nutritics Mobile Application) or
56 57	387	paper food diaries, which will be entered into Nutritics software (Nutritics, Dublin,
58 59	388	Ireland)(39). Participants who wish to use Libro will receive one to one training to use
60	389	this by the study dietitian. Diaries will provide the research team with information

1 2	390	about the intake of energy, carbohydrate, fat, protein, fibre, glycaemic index, and the
3 4 5 6 7 8 9	391	timing of meals for participants in both groups. Participants will be asked what other
	392	dietary modifications, if any, they have made at their fortnightly dietitian reviews to
	393	establish the adoption of any alternative dietary practices in the cohort.
	394	
10	395	Adverse Events
12	396	Participants in both groups will be asked about any adverse effects that they have
13 14	397	experienced at each visit. These will include, but are not limited to, the potential
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	398	effects of a low-energy diet, e.g. headache, lethargy, dizziness, constipation,
	399	indigestion, poor concentration, and hunger. Adverse events will be graded as per
	400	CTAEv5(34). Participants will be issued with a participation/emergency card with
	401	emergency contact details for the research team to be carried at all times and to be
	402	shown to the attending physician in case of emergency admission to hospital. All
	403	participants will be issued with clear instructions as to how to manage a
	404	hypoglycaemic and/or ketonaemic event (see appendix).
	405	
	406	Data management
	407	Participant data will be anonymised and will be stored in line with the Medicines for
	408	Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act
	409	(2018) and archived in line with the Medicines for Human Use (Clinical Trials)
	410	Amended Regulations (2006) as defined in the MFT Clinical Trials Office Archiving
	411	SOP (11; Retention of Data, Off-Site Archiving, and Destroying Documents).
	412	Deidentified data will be stored in a study-specific Research Electronic Data Capture
41 42	413	(REDCap) database. The sponsor will periodically audit the site study file, a sample
43	414	of the case report form, consent forms, and source data, and check accuracy of the
44 45	415	study database to ensure satisfactory completion.
46 47	416	
48 49	417	Statistical methods
50	418	A statistical analysis plan specifying the full details of the primary and secondary
51 52	419	outcomes, other variables, and methods, will be produced prior to trial analysis. The
53 54	420	main analysis will be conducted via intention-to-treat population and will not
55	421	undertake any significance tests. Descriptive, graphical (summary), and basic
56 57 58 59 60	422	statistics (e.g. i. number, frequencies and percentages, ii. mean and standard
	423	deviation, or iii. median and quartiles as appropriate) will be presented as
	424	appropriate for each group respectively, for group difference jointly, and for each

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1 2 3 4 5 6 7 8 9	425	stratum. Per-protocol analysis will be considered as a secondary analysis. Levels of
	426	missing data will be investigated and used to inform future studies. No imputation will
	427	be used. The end of study questionnaire will be analysed using appropriate
	428	descriptive statistics for closed questions and key themes will be extracted without
	429	formal analysis from open questions to inform future research.
10 11	430	
12	431	Progression Criterion
13 14	432	The success of the feasibility trial will be defined by the progression criteria as
15 16	433	outlined in table 1. Any concerns regarding a low retention rate will be discussed with
17 18	434	the PPIE group. Interviews will include those who withdraw from the study to address
19	435	potential reasons for withdrawal with the aim to improve retention in future.
20 21	436	
22 23		Feasible with

	Feasible (green)	Feasible with modification of the protocol (amber)	Not feasible (red)
Recruitment	≥4 patients/month	>2 patients/month	≤2 patients/month
Uptake to the feasibility study	≥15%	10-15%	<10%
Retention to the feasibility study	>70%	50-70%	<50%
Adherence to the	>50% of the low-	30-50% of the low-	<30% of the low-
ILED intervention	energy days	energy days	energy days
	completed (2/week	completed (2/week	completed (2/week
	between weeks 24-	between weeks 24-	between weeks 24-
	28 and delivery)	28 and delivery)	28 and delivery)

Table 1: Trial progression criterion

438 Qualitative sub-study

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We will undertake 11-12 semi-structured interviews with a subset of women from
 443 each group (ILED n=10 and best NHS Care n=10) at around 12 weeks post-delivery.
 445 The final sample size will be contingent on obtaining data saturation. We will also

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interview a sample of healthcare professionals (HCPs) involved in the delivery of care to study participants, including dieticians, obstetricians and midwives, including those with leadership and clinical managerial roles. Sampling will be purposive, aiming to obtain women from a range of ethnic groups, ages, socioeconomic backgrounds, and self-reported engagement with the intervention. Participants and HCPs will be asked about their experiences and thoughts regarding the intervention, including motivating factors, and facilitators/barriers to engagement. Interviews will be conducted by a researcher from the University of Manchester/MFT who is independent from the research staff involved in the delivery and assessment of the programmes. Analysis will be conducted by two independent researchers at the University of Manchester/MFT using Braun and Clarke's thematic analysis approach to identify key issues around the acceptability, usefulness of the programmes, and feasibility of a subsequent trial(40). Analysis will be inductive: open-ended, exploratory, and driven by the data.

26 460

All participants will also be asked to complete an optional and anonymous end of study questionnaire developed by the study team at their post-partum visit (see appendix). This will give participants the opportunity to feedback on their experience and will enable the study team to identify improvements to the design of a possible follow-up study.

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³⁸ 39 ³⁹ 467 Trial Steering Committee (TSC)

The trial steering committee will include an independent consultant endocrinologist, obstetrician, dietitian, and the patient representative. The committee will oversee the trial to ensure that it is carried out to the expected standards. The TSC will liaise with the CI to develop a schedule of meetings, proposed to occur every four months, with meetings to occur no less than annually. Minutes will be taken at TSC meetings and copies of the minutes will be filed in the Trial Master File; they will be shared with relevant stakeholders as appropriate.

52 475

5354 476 Patient and public involvement

Patient and public involvement was actively sought throughout the planning and
 design of this trial and continues to form a key part of the trial as it progresses. The
 patient and public involvement and engagement (PPIE) group assisted in the

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development of all participant materials and provided valuable insight into the wording of participant information and acceptability of the proposed intervention. The PPIE group will be updated as the trial progresses and a further focus group will be held to advise on the interview schedule and wording for the gualitative sub-study. The group will also be invited to aid in the development of summarising key findings for dissemination to relevant patient groups. Ethics and dissemination This study has been approved by the Cambridge East Research Ethics Committee and is sponsored by MFT. Findings will be disseminated via publication in peer-reviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists. Anonymised data will be available upon formal request once the principal results of the study have been published. Planned modifications to the protocol will be approved by the research ethics committee before they are adopted into the study. An audit trail of ethical amendments and documentation will allow monitoring by the research team and external regulatory bodies. This is the first study to assess the feasibility and safety of an ILED in GDM as compared to best NHS care. Given the increasing incidence of GDM and associated health risks this research is both pertinent and important. The study is not powered to show differences between ILED and best NHS care, however the planned quantitative and qualitative assessments will inform the feasibility of the programme and a future definitive trial.

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	669	the recruitment and follow up of participants throughout the trial.
	670	
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	675	NIHR sponsored GP academic clinical fellow.
	676	
	677	Competing interests statement.
	678	Michelle Harvie has co-authored three self-help books for the public to follow
	679	intermittent diets. All author proceeds are paid directly to the charity Prevent Breast
	680	Cancer (registered charity number 1109839) to fund breast cancer research.
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13 14	705	
15	706	Appendix
16 17	707	1.0 Patient Information Sheet (supplementary document 1)
18 19 20 21 22 23 24 25 26	708	
	709	2.0 Consent Form (supplementary document 2)
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	711	3.0 Self-monitoring schedule for capillary glucose and ketone monitoring
	712	(supplementary document 3)
27	713	4.0 Medical Management Protocols (supplementary document 4)
28 29	714	
30 31	715	5.0 Intermittent Low Energy Diet Day Example (supplementary document 5)
32	716	
34	717	6.0 End of Study Questionnaire (supplementary document 6)
35 36	718	
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44 45	723	LEGENDS
46 47	724	 <image 1=""/>: Figure 1: Inclusion and exclusion criteria
48 49	725	 <image 2=""/>: Figure 2: Participant flow through trial
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IIIC	lusion Criteria
AA A A	Pregnant women ≥18 years BMI of ≥27.5kg/m2 or a BMI ≥25 kg/m ² in high risk minority ethnic group (i.e. South Asian, Black African, African Caribbean) and <50 kg/m2 at booking appointment (8-12 weeks' gestation) Newly diagnosed GDM according to local diagnostic criteria (fasting glucose ≥5.3mmol/l and/or 2-hour postprandial glucose ≥8.5mmol/l in a 75g OGTT) scheduled to receive first line diet and physical activity (best NHS care) 24-30 weeks' pregnant at screening appointment
Ex	clusion Criteria
AA AAA	Pregestational type 1 or type 2 diabetes. Fasting glucose of ≥7 or 2-hour postprandial of ≥11 on OGTT (immediate intervention with medication would be required in this group of women) Current multiple pregnancy Maturity Onset Diabetes of the Young (MODY) Significant comorbid disease that in PI's opinion would preclude participation in the study e.g. chronic kidney disease, significant cardiac disease, significant history of disordered eating or

Figure 1: Inclusion and exclusion criteria

159x144mm (220 x 220 DPI)





154x245mm (220 x 220 DPI)

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	Study Visit							
11	1	2	3	4	5	6	7	8
Gestation (weeks)	~24-30	~24-30	~30-34	~32-36	~34-38	~36-40	delivery	11-13 post- partum
Eligibility confirmed	x							
Informed consent	x							
Randomisation	x							
Tailored dietitian review (face to face or remote)	x	×	×	x	×	x		x
Height	х							
Weight*	x	×	x	x	×	x	×	x
Blood Pressure ^A	x	x	x	x	x	x	x	x
Fasting blood sample*	x				×			x
Questionnaires#	x		x		x			x
4-day food diary			x		x			x
Foetal growth scan	x		x		x			
Review of glucose and ketone measurements		x	x	x	×	x		
Neonatal measurements#							x	
Oral glucose tolerance test								x
Exit interview / end of study questionnaires								x
Invitation to optional qualitative sub-study ⁵								x
^A Frequency of assessm COVID-19 restrictions *Fasting bloods: urea a hydroxybutyrate, free f #Questionnaires: Worl Physical Activity Questi #Neonatal measureme ⁵ Sub-study involves ser	ent will be 2 ind electroly fatty acids, ft d Health Org onnaire (sho nts include g ni-structured	-4 weekly de tes, liver fun all blood cou panisation Qu art form), UK restational ap d interviews	pending on ction tests, b nt, fasting gl ality of Life Diabetes an ge at delivery exploring pa	whether app one profile, ucose, insulii (brief versior d Diet Quest y, mode of di rticipants' th	ipids, thyroi n 1), 36-Item S ionnaire elivery, neon oughts and e	face-to-face d function te hort Form Su atal weight, experiences	or virtual du sts, HbA1c, I urvey, Intern cord blood g of the trial	e to oeta ational lucose

Figure 3: Schedule of assessments

154x236mm (72 x 72 DPI)



NHS Foundation Trust

Consultant Endocrinologist – Dr. Basil Issa Research Dietitian – Dr. Michelle Harvie Email: mft.middas.gdm@nhs.net Tel: 07815987910





Nightingale Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester</u> Intermittent <u>Diet</u> in Gestational <u>D</u>iabetes <u>A</u>cceptability <u>S</u>tudy

Participant information sheet

We would like to invite you to take part in a research study that is testing two different diet programmes which aim to help people with gestational diabetes control their blood sugars.

If you decide to take part:

- You will be assigned to one of two diet programmes for the duration of your pregnancy. One involves following the standard NHS healthy diet recommendations for pregnancy, and the other follows the standard NHS healthy diet for 5 days/week plus two nonconsecutive calorie restricted days of 1,000 kcal per week (both groups will be encouraged to be physically active).
- You will be asked to attend your routine appointments at Wythenshawe or St Marys Hospital and will have fortnightly appointments until delivery of your baby (some appointments may be virtual depending on COVID-19 restrictions). You will be asked to attend the hospital for a blood test 12 weeks after having your baby.
- You will be supported by a diabetes specialist dietitian, midwife, consultant endocrinologist, and your obstetric team throughout the study to help manage your pregnancy and blood glucose safely.
- Throughout the study you will be asked to monitor your food intake via a smartphone/tablet app, or on paper if you prefer, and you will receive feedback on this during your dietary reviews. Comprehensive dietary advice and recipes will be provided.
- Throughout the study you will be asked to monitor your blood sugar using a blood sugar meter four times a day, and you will also be asked to monitor your ketone levels three times on two days of the week (ketones indicate how well your body is using sugar or fat as an energy source). You will be taught how to check your blood sugar and ketone levels.
- If you would like to take part, or you have any questions, then please contact mft.middas.gdm@nhs.net




This study is being carried out by a team of trained dietitians, doctors, nurses, midwives and researchers under the supervision of Dr. Basil Issa and Dr. Michelle Harvie at Wythenshawe and St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what taking part would involve for you. Please take your time to read the following information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.

Please ring the research team at the number at the top of the first page, or e-mail mft.middas.gdm@nhs.net if there is anything that is not clear, or if you would like more information. You can attend an information session about the diets and the study before agreeing to take part if you would like to.

Your participation in the study is entirely voluntary; you do not have to take part if you do not want to and you can opt out of the study at any time without giving a reason. Thank you for reading this information. We hope this research will be of interest to you.

Why are we doing this research?

Around 1 in 8 pregnant women can develop gestational diabetes. This condition causes risks to mother and baby from high blood sugar, high blood pressure, induced labours, caesareansections, and larger babies. Women often need medication to control blood sugar despite following recommended NHS healthy eating plans for pregnancy. Intermittent low-calorie diets (two non-consecutive days over the course of the week) improve blood sugar control and reduce the need for medication in patients with type 2 diabetes. We want to find out whether intermittent low-calorie diets might also improve blood sugar control in gestational diabetes and reduce the need for medication as it is a similar condition to type 2 diabetes.

What is the purpose of this research?

This study aims to assess the acceptability (to you) and safety of an intermittent low-calorie diet compared to the usual recommended NHS healthy eating and lifestyle plan for gestational diabetes. A computer system will randomly allocate you to one of the two diets. We want to find out which diet is most acceptable to women, whether there is any difference in the two diets' effect on blood sugar control, and any side effects experienced by women. The findings of this study will inform a larger study which will be designed to more closely compare the effect of the two diets on blood sugar control in women with gestational diabetes.

Why have I been asked to take part?

You have been invited to take part in this study because you have been diagnosed with gestational diabetes. We hope to recruit around 48 people to take part in this study.

BMJ Open: first published as 10.1136/bmjopen-2023-078264 on 10 February 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Manchester University



MANCHESTER

NHS Foundation Trust

What happens if you agree to take part?

If you agree to take part you will be randomly allocated via a computer system to one of two diet and lifestyle programmes for the remaining weeks of your pregnancy.

Best NHS Care Healthy Diet programme

You will receive personalised advice from a specialist dietician. Recommendations will include increased fruit/vegetable intake, low glycaemic index starchy foods (i.e starchy foods which are slowly absorbed and take a while to raise your blood sugar level), reducing refined sugar, and having regular mealtimes. You will be advised how to design your diet to include the right amount of protein, fats, carbohydrates, and fibre, and will be given meal plans and recipes. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Intermittent Low-Calorie Diet programme

If you are allocated to this group you will receive personalised advice to follow a low-calorie diet of 1,000 kcal on two non-consecutive days of the week and the NHS healthy diet on the other five days of the week. The 1,000 kcal days include a set number of portions of protein, carbohydrates and fat foods, fruits, vegetables and dairy/dairy alternatives typically including \sim 210g (7 oz) of lean protein foods and 3-4 portions of wholegrain carbohydrates, 5 portions of vegetables, 2 of fruit, and 3 of dairy or dairy alternatives and a small amount of healthy fat. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week in addition to strength exercises on at least two days of the week.

Monitoring

You will have all of your usual routine antenatal appointments including checks on your weight, blood pressure, blood tests and ultrasound scans. Extra blood tests will be done as part of the study and these will be added on to samples taken during your routine blood tests.

You will be asked to monitor your blood sugar at home four times a day until your baby is born, and your ketone levels on two days of the week (you will be taught how to do this using a finger prick machine). The results will be recorded when you attend clinic.

We would like to collect a sample of blood from the umbilical cord at delivery to check blood sugar and insulin levels, and your baby's birthweight will be documented. Guidelines currently recommend that wherever possible the umbilical cord is clamped after 1-2 minutes; this is referred to as 'delayed cord clamping' and means that babies receive as much blood as possible from the placenta. This is normal practice. The cord blood sample will not affect your ability to have delayed cord clamping and will not cause any harm to your baby. It will not be possible, however, to delay clamping of the cord for so long that all blood has left the cord (the sample needs to be taken whilst there is still some blood left in the cord).

When babies are born to mothers with gestational diabetes it is normal that their birth weight is recorded and that their blood sugar is monitored for 12 hours following delivery; these results will be recorded by the research team.

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You will be asked to attend an additional glucose tolerance test at the hospital 12 weeks after delivery to assess whether you have any residual diabetes (95% of women do not) and also to assess how sensitive your body is to insulin (an important risk factor for the development of diabetes in the future). You will be asked to attend at 9:00am having fasted (no food or drink apart from water) from midnight. A blood sample (around 10 mL/2 teaspoons) will be taken for glucose and insulin and you will be asked to drink a sugary drink with 75 grams of glucose. A further blood sample will be taken after 2 hours for glucose and insulin. You will need to remain in hospital during this time. The reason for this is to help us to understand whether there could be any difference in the body's ability to process sugar between the two diet groups, and also to find out whether any women still have signs of diabetes after pregnancy.

Any blood samples taken as part of the study will be identifiable only using your study identification number and will have none of your personal details. Part of the sample will be sent for immediate analysis and any remaining will be stored securely, accessible only by the research team. At the end of the study any left over samples will be disposed of in accordance with the Human Tissue Act (2004).

You will be asked to record your food intake via the Libro smartphone/tablet app or in a paper diary for four days during four weeks throughout the study. You will also be asked to complete three questionnaires to assess your wellbeing and level of physical activity in these weeks, and a final end of study questionnaire at the final appointment.

Ongoing support from a specialist team of healthcare professionals

Your specialist team includes a Consultant Endocrinologist, Consultant Obstetrician, diabetes specialist dietitian, midwives, and a GP trainee with a special interest in women's health. The specialist team work closely with the usual obstetric teams involved in your care. Reviews with the team will be either face to face when you attend clinic or remotely using video calls.

Mobile Applications and Glucose Meters

The study will use a smartphone application called 'Libro' to help you record information. Libro is a smartphone application which allows you to record your dietary intake during the study. We will ask you to record 4 days of food and drink intake during 4 weeks across the study. Your diaries will be viewed by your allocated dietitian who will provide personalised dietary feedback via the app. You are also free to record more days of your diet should you wish, which some people find helpful. If you do not want to use the mobile app you can use paper instead. You will be supported to set up and use the Nutritics Libro App at your appointments. You do not have to use the application to be part of the study.

Your blood sugar will be monitored using a glucose monitoring device which checks your blood sugar using a 'fingerprick' blood test. You will be shown how to do this yourself. With your permission the research team will make a note of your glucose readings at every visit, either by checking your glucose monitoring device, or by uploading your glucose meter readings onto the computer if you are using a mobile application.

The self-monitoring schedule is as follows:

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Intermittent low-ene	ergy diet monitoring	Best NHS care monitoring				
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose			
Fasting before breakfast the morning after each	Fasting (morning)	Fasting before breakfast on 2 non-consecutive	Fasting (morning)			
of the low calorie days		days / week				
1 hour post evening meal on each of the low calorie days	1hr post breakfast	1 hour post evening meal on 2 non consecutive days / week	1hr post breakfast			
	1hr post lunch		1hr post lunch			
	1hr post dinner		1hr post dinner			

What should I do if my blood glucose or ketones are out of range?

Low Blood Sugar

You are advised to take 15-20g of 'rapid acting' carbohydrate if your blood glucose is <4 mmol/L). Examples include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). You will need to repeat the treatment every 15 minutes until your blood glucose is ≥4 mmol/l.

The following table highlights when you need to consider an additional slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g (eg half of one of the items below)
More than 2 hours before the next meal	15-20g (eg slice of toast, piece of fruit, small
	bowl of cereal, glass of milk)

Raised Ketones

If your ketone levels are \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If your ketone level has improved (<1.0mmol/L), no further action is required.
- If your ketone level has increased or remains the same, repeat your ketone level after 2 hours.
- If your ketone level is persistently increased, consume 40g carbohydrates (eg one bagel, bowl of cereal and a banana, small jacket potato), and repeat in 2 hours.
- Continue to do this until your ketone levels are <1.0mmol/L.

Make Immediate Contact with the research team if:

Blood glucose	• Your blood glucose is <3.0 mmol/l or you have symptoms requiring medical	1
	attention which are thought to be due to low blood glucose,	

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Your fasting	blood	gluc	ose i	s >	5.2	mmc	ol/L o	on n	nore	tha	n a	qua	rte	r of	yοι	ur		

	measurements on two days in a row,
	• Your 1 hour post-meal blood glucose is >7.7 mmol/L on more than a
	quarter of your measurements on two days in a row
Ketones	Your blood ketones are >1.0 mmol/L

Will I need medications?

If your blood sugars are found to be high despite following the recommended diet and lifestyle programmes you may be advised to start medication to help control your blood sugar. You will be advised on changes to your medications by a diabetes specialist nurse/diabetes midwife and also a Consultant Endocrinologist if required. This is usual practice regardless of whether you are taking part in the study.

What care will I receive after the study has stopped?

At the end of the study, you will be provided appropriate ongoing dietary advice from the study dietitian following your final glucose tolerance test to follow the NHS healthy eating and lifestyle plan. You will receive routine postnatal care from your GP, hospital team, and dietitian if required. You will be advised to see your GP for an annual blood test to check your blood sugar levels (this is routine care for women with gestational diabetes). Approximately 5% of women with gestational diabetes have residual diabetes after delivery. This will be identified from your glucose tolerance test/HbA1c; if this is the case you and your GP will be informed. Your GP will take over the management of your diabetes as per routine care outside the study.

Interview sub study

Women in this study may be invited to take part in an interview at the end of the study . You will be asked about your views and experiences on trying to follow your allocated diet programme. This interview can be arranged at a time that suits you, either at Wythenshawe or St Marys Hospital, at your home, or over the telephone. There is no obligation to take part in this interview study.

Frequently asked questions

Do I have to take part?

No, you do not have to take part if you do not wish to and your decision will not affect any standard of care you receive at Wythenshawe or St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

What happens if I change my mind?

It is OK if you agree to take part in the study but later change your mind. You do not need to give a reason and it will not affect the standard of care you receive. The study team may also choose to withdraw you if it is necessary for your health or safety due to unexpected findings during the study. If you decide to withdraw from the study, or the study is stopped for any reason, you will be asked whether or not you are happy for us to keep the data that may have already been collected. If you do withdraw from the study you will continue to be cared for by your usual specialist diabetes and obstetric teams for the duration of your pregnancy. You will

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still have the option of completing the end of study questionnaire and/or interview to provide feedback; this is very useful for the research team to help us understand potential reasons you may have chosen to withdraw from the study.

You will also have the option that if you withdraw, researchers may still collect relevant information about your pregnancy and/or gestational diabetes from your medical records within the 18-month study duration. This will be an option on the consent form.

Are there any benefits from taking part?

You will receive frequent personalised advice and support to follow two diet and lifestyle programmes which may help to control your blood sugar levels throughout your pregnancy. The information gained from this study will also help inform the future NHS care of patients with gestational diabetes.

Are there any risks from taking part?

Research has found that diets consisting of two low-calorie days a week are very low risk. Pregnant women will develop slightly higher levels of ketones when following low calorie diets than women who are not pregnant. Ketones are produced naturally by the body when the body uses fat stores for energy (i.e. when we follow a low calorie diet or haven't eaten enough because we are ill).

Some research suggests that very high levels of ketones throughout pregnancy may cause a higher risk of babies being slightly smaller than average. It is very unlikely that you will develop high levels of ketones by following this diet. You will be provided with a ketone meter and you will be asked to check your ketone levels before your lunch and evening meal on your low-calorie days, and the following morning, to make sure that your ketone levels are normal.

On your low-calorie days you may feel slightly more hungry, or you may experience other effects such as increased nausea, light headedness, or tiredness. It is important that you eat regularly throughout the day to reduce the risk of this happening. You will be asked to report any side effects of following the diet to the team at each appointment.

What happens if my baby or I become unwell during the study?

The safety of you and your baby are of utmost importance and remain our priority. In the instance that either of you become unwell your case will be reviewed by our specialist team and your suitability for continuing in the trial will be decided. Although it remains exceptionally rare, were you to experience the unexpected loss of your baby you will be withdrawn from the trial and supported by the dedicated specialist bereavement team at the hospital. Any information which has been collected as part of the trial will be stored securely and once we have finished the study we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What will happen to blood samples which are taken?

Some blood samples taken as part of the study will be sent to the laboratory immediately for analysis and any remaining will be stored securely for the duration of the study. Only your 'study ID' will be used – the samples will have none of your personal details on them. At the end of

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the study any remaining samples will be disposed of in accordance with the Human Tissue Act (2004).

What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (Dr. Basil Issa or Dr. Michelle Harvie – via the study office – via michelle.harvie@manchester.ac.uk or telephone 0161 **291** 4410). If you remain unhappy and wish to complain formally, you can do so through the NHS complaints procedure. Details can be obtained from the NHS Patient and Liaison Service (PALS) on **Tel:** 0161 276 8686 or contact the team by email pals@mft.nhs.uk.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme. If something did go wrong and you were harmed or suffered deterioration in your health as a result of taking part in this study then you may have grounds for legal action or compensation.

Additional information about the study

Will my lifestyle be affected if I take part?

An essential aspect of this study is a change to your diet and physical activity patterns with support from a specialist team of healthcare professionals.

Payments

We are able to offer free parking at Wythenshawe/St Marys Hospitals for study visits and offer reimbursement for reasonable travel expenses (car, bus or tram) linked to visits for this study. There are no other payments for taking part.

Will my details be kept confidential?

Yes. The study team and any associated regulatory authorities follow strict ethical and legal guidance regarding participant confidentiality. Any information we have about you will be handled in confidence and will only be used for the purposes of this study. All data recorded will be coded and your name will remain anonymous.

During the study we will inform your GP via letter of your participation in the study and your ongoing results, including your weight, blood tests, any abnormal findings and any recommendations for treatment.

If you join the study, some relevant parts of your medical records may be looked at by authorised personnel at Wythenshawe or St Marys hospitals prior to starting the study. These records may also be looked at by an independent auditing body and regulatory authorities to check that the study is being carried out correctly. We will only access parts of your medical records that are relevant to this research and all information accessed will be kept strictly confidential.

How will we use information about you?

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We will need to use information from you and from your medical records for this research project.

This information will include the following:

- Initials
- NHS number .
- Name .

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- Contact details
 - Medical History including test results

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Other researchers from outside the Trust may ask to see this data for the purposes of furthering their research. We will only share this upon written request to the Trust. The external researchers will be asked to sign a Confidentiality Agreement before any data is shared.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health during pregnancy from your hospital records. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
 - by sending an email to mft.middas.gdm@nhs.net or
- by ringing us on 07815987910

How will my details be used to access the Mobile Applications?

50 None of your personal details (other than the telephone number from which an application is 51 52 downloaded) will be needed to access the mobile applications. Once you have given your 53 consent to take part in the study you will be issued with a 'dummy' e-mail and password under 54 a pseudonym (fake name). Only the research team will know the dummy e-mail address you 55 have been assigned to, in order to be able to review your data. The application will not contain 56 your identifiable data. If you choose to use a mobile application to monitor your blood sugar 57

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levels the relevant terms of service for the app and the app developers privacy policy will apply. It will be your responsibility to read and understand these prior to download.

Will my insurance be affected if I take part in this study?

It is unlikely that your insurance premiums will be affected by participation in this study as the study has the potential to improve your diabetic control and reduce your risk of ill health. However, if you are at all concerned, then we advise that you contact your insurers and seek expert advice before agreeing to participate.

Who has reviewed this study?

Research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is made up of experts, non-experts and members of the general public. Together they review research applications to ensure your safety, rights, wellbeing and dignity are protected at all times. This study has been reviewed and given favourable opinion by REC.

What will happen to the study results?

It is intended that the results of this study will be presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. To do this our study information is double-checked by other professionals in research and healthcare. There is a possibility that the study and its results may be publicised for example on radio, television, magazines, books and websites. You will not be identified in any publicity, reports or publication arising from this study. If you would like a general summary of the results of the study you can select this on the consent form or please contact the research team.

Who is organising and funding the research?

Researchers from Wythenshawe hospital, have designed this study and will be carrying out this research. This study has been funded by the National Institute of Health and Research.

Further information and contact details

For further information about this study, please contact mft.middas.gdm@nhs.net or 07815987910

> Thank you for taking the time to read this information sheet. We hope it has been of interest to you.





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Consultant Endocrinologist – Dr. Basil Issa Tel: 0161 291 7070 Research Dietitian – Dr. Michelle Harvie Tel: 07815987910 Email: <u>mft.middas.gdm@nhs.net</u>

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Nightingale Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>

Participant Informed Consent Form

Participant Identification Number:

- Please initial box
- 1. I confirm that I have read and understand the participant information sheet (version 3.0) for the above study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Manchester University NHS Foundation Trust and regulatory authorities, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records.
- 4. I consent to the collection of blood samples to be collected as described in the participant information sheet.
- 5. I consent to the collection of cord blood to be collected at the time of delivery as described in the participant information sheet.
- 6. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.
- 7. I agree that my blood sugar readings can be recorded by the study team.
- 8. I agree to my GP being informed of my participation in this study and changes to my weight, body measurements, blood results, questionnaire results and medications as required.

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- 9. I understand that to use the mobile applications as described in the Patient Information Sheet, I will need to provide my personal mobile number to be able to access the app.
- 10. I understand that the information I provide to mobile applications as described in the Patient Information Sheet will be treated in line with the relevant terms of service and the app developers privacy policy at the time of downloading the application.
- 11. I have informed the study team of any health issues, including those which may affect my ability to follow the diet, and I will inform the study team of any unusual symptoms that occur during the diet. I will inform the study team of changes to my health status during the study.
- 12. I have informed the study team of any health issues, including those which may affect my ability to exercise, and I will inform the study team of changes to my health status during the study.
- 13. I consent to the storage of personal information (including electronic) for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.
- 14. I agree to take part in the above study.
- 15. I agree that relevant information about my pregnancy and/or gestational diabetes can be obtained from my medical records within the 18-month study duration if I withdraw from the study early.
- 16. I am aware that my non-identifiable trial data may be shared with other researchers for the purposes of research.

Optional (delete as appropriate)

17.	I agree to be approached to take part in sub-study 1 (interview study), and understand that I will be approached to take part in the sub-study regardless of whether I withdraw from the	
	main study	YES/NO
18.	I would like to receive a summary of the final study results	YES/NO

19. I agree to be contacted regarding future research opportunities YES/NO

My preferred contact (please tick and include email if preferred)

Post

Do not contact

Email

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Self-monitoring schedule for capillary glucose and ketone monitoring

ILE	D	Best Nł	IS Care
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)
the morning after each of		on 2 non-consecutive	
the low-energy days		days / week	
1 hour post evening meal	1hr post breakfast	1 hour post evening	1hr post breakfast
on each of the low-energy		meal on 2 non-	
days		consecutive days / week	
	1hr post lunch		1hr post lunch
	1hr post dinner		1hr post dinner

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Medical Management Protocols

Hypoglycaemia

Participants will be advised to take 15-20g of rapid acting carbohydrate in the event of hypoglycaemia, (defined as blood glucose <4 mmol/L) which is anticipated to raise blood glucose by 3 mmol/L. Examples of rapid acting carbohydrate include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). Participants will be advised to repeat the treatment every 15 minutes until blood glucose is ≥4 mmol/l. The following table highlights when participants should consider taking additional follow-up slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g
More than 2 hours before the next meal	15-20g

Ketonaemia

Ketone levels ≥1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If ketone level has improved (<1.0mmol/L), no further action required.
- If ketone level has increased or remains the same, repeat ketone level after 2 hours.
- If ketone level is persistently increased, consume 40g carbohydrates and repeat in 2 hours.
- Continue to do this until ketone levels <1.0mmol/L.

If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed.

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Guidance for the introduction of diabetes medication (week 24-delivery)

Diabetes medication will be introduced according to the following protocol:

- If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated.
- If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l,
- and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence prandial fast acting insulin analogue (Humalog or Novorapid)
 2-4 units with the relevant meal. Uptitrate the dose by 2 units every 3 days aiming for a 1 hour postprandial glucose of ≤7 mmol/l.
- Medication adjustment will be made in accordance with the above guidance.

Example of 1 day meal plan for Diet Day

The diet days aim to limit the calories to 1000 calories per day. You are aiming to include 2 (not consecutive) diet days each week. The other 5 days, follow the Mediterranean diet as described earlier. To keep the calories to 1000, the diet day will look like this:

Mixed diet		Vegetarian/ vegan diet
4	Carbohydrate portions	3
6	Protein portions	7
5	Vegetable portions	5
2	Fruit portions	2
3	Dairy portions	3
1	Fat portions	1

Below are some examples of meals that can be used to help you follow a 1000 calorie diet.. There are options for a mixed diet or vegan or vegetarian options, if you feel you wanted to try meat free days. Filling up on vegetables will make you feel less hungry

Mixed diet options

Breakfast	Portion	Dairy	Protein	Carb	Veg	Fruit	Fat
Grilled lean bacon	1 rasher	0	1	0	0	0	0
Grilled tomatoes	7 cherry tomatoes	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning	Ť						
Diet or natural yogurt	1 small carton	1	0	0	0	0	0
Lunch							
Wholegrain bread	2 medium slices	0	0	2	0	0	0
Tuna	⅓ of a 120g can	0	1	0	0	0	0
Green salad	Cereal bowl full / 80 g with oil-free dressing	0	0	0	1	0	0
Satsumas	2	0	0	0	0	1	0
Mid afternoon							
Low fat cheese	30g / match box size	1	0	0	0	0	0
Apple slices	I medium apple	0	0	0	0	1	0
Tea/ coffee		0	0	0	0	0	0
Evening							
Vegetable rice	4 tablespoons cooked rice 160g of mix vegetables	0	0	2	2	0	0
Chicken curry	90g /average chicken breast (no skin) & ½ can tomatoes, 1 desertspoon oil	0	3	0	1	0	1
Bedtime							
Low fat houmous	1 level tablespoon	0	1	0	0	0	0
Pepper sticks	1/2 red pepper	0	0	0	1	0	0
Milk	1 small glass	1	0	0	0	0	0
Total portions	a day	3 portions	6 portions	4 portions	5 portions	2 portions	1 portio

Vegetarian option

Breakfast		Dairy	Protein	Carb	Veg	Fruit	Fat
Egg	2 poached	0	2	0	0	0	0
Mushrooms	2 cupped handfuls / 80g	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Cheddar cheese	1 match box size / 30g	1	0	0	0	0	0
Cucumber	Sliced handful	0	0	0	1	0	0
Lunch							
Baked beans	2 tablespoons	0	1	0	0	0	0
Seeded bread toasted	1 medium sliced	0	0	1	0	0	0
Blueberries	1 handful	0	0	0	0	1	0
Mid afternoon							
Meat free ham	2 slice small	0	1	0	0	0	0
Pepper	1⁄2 sliced	0	0	0	1	0	0
Avocado	1/4	0	0	0	0	0	1
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Vegetarian sausage casserole Jacket potato (100g)	1 grilled sausage 2 cereal bowls vegetables 1 ½ egg sized (100 g)	0	2	1	2	0	0
Bedtime							_
Pear	1 medium	0	0	0	0	1	0
Low fat cream cheese	1 tablespoon	1	0	0	0	0	0
Whole wheat cracker	2 biscuits	0	0	1	0	0	0
Milk	1 small glass	1	1	0	0	0	0
Total portions	s a day	3 portions	7 portions	3 portions	5 portions	2 portions	1 portions

Vegan options

Breakfast		Dairy equivalent	Protein	Carb	Veg	Fruit	Fat
Branflakes	3 tablespoons	0	0	1	0	0	0
Milk- sova	200 ml	1	0	0	0	0	0
Tea/ coffee	1 mua	0	0	0	0	0	0
Midmorning			_				-
Soya vogurt	3 tablespoons	1	0	0	0	0	0
Lunch							
Kidney bean & Vegetable chilli Wholemeal pitta	3 tablespoons of beans 60g with 1 cereal bowl mixed vegetables & 1/2 can chopped tomatoes ½ pitta	0	2	1	2	0	0
Banana	1 medium	0	0	0	0	1	0
Mid							
afternoon							
Low fat hummus	2 level tablespoon	0	2	0	0	0	0
1 carrot	I medium carrot (80g)	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Quinoa	2 tablespoon cooked	0	0	21	0	0	0
Tofu	4 matchbox	0	2	0	0	0	0
Mixed salad with edamame beans	2 x Cereal bowl full with oil free dressing & 1 tablespoons of edamame	0	1	0	2	0	0
Bedtime							
Peanut butter	1 heaped teaspoon	0	0	0	0	0	1
Apple	1 medium sliced	0	0	0	0	1	0
Milk	1 small glass	1	0	0	0	0	0
Total portion	s a day	3 portions	7	2	5	2	1
			portions	portions	portions	portions	portions

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59 60 To help with estimation of portions the following tables outline weight and measures of the different food groups. Where possible household measures are given to make things a little easier. Use these to help you plan your 2 days in the week of 1000 calories.

Carbohydrate 4 portions - mixed diet 3 portions - vegan/vegetarian	Equal to
Wholewheat or oat breakfast cereal, e.g. wholewheat biscuit, malted wholewheat squares, Grapenuts, bran flakes, fruit & fibre	24g or 3 tablespoons or 1 whole wheat biscuit
Porridge oats or no-added sugar muesli	20g or 1 heaped tablespoon
Wholegrain, wholemeal, rye, granary bread	36g or medium slice of bread (other than rye), $1\frac{1}{2}$ slices of rye, or $\frac{1}{2}$ roll
Wholemeal or multigrain pitta bread or tortilla wrap, chapatti made without fat	60g or 1x 8" tortilla or 1 standard pitta or small thin chapatti
Rye crispbread, crackers, oak cakes	22g or 2 crispbreads/ 2 oatcakes
Wholegrain rice cake	16g or 2 rice cakes
Wholewheat pasta or rice - cooked amount	1 tablespoon uncooked 2 tablespoons cooked
Cous cous, bulgar wheat, guinoa, r earl baney	30g- raw weight or 60g cooked
Lasagne (wholemeal if possible)	20g raw weight or 1 large sheet or 1½ smaller sheets
Noodles (wholemeal if possible)	25g raw weight or ½ block/nest
Baked or boiled potato (in skin), cassava, sweet potato	1½ egg sized potatoes or 100g raw weight
Wholemeal pizza base (topping is from other food groups)	35g or $^{1}/_{6}$ of thin 10" pizza base
Unsweetened popcorn	20g or 2 handfuls

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Protein 6 portions – mixed diet 7 portions – vegan/vegetarian	Equal to
Fresh or smoked white fish (e.g. haddock or cod)	60g or 2oz 2 fish finger size
Seafood, e.g. prawns, mussels, crab	45g or 1½oz
Canned tuna or salmon in brine or spring water	45g or 1½oz ⅓ standard tin (120g)
Oily fish (fresh or tinned in tomato sauce or olive oil - drained), e.g. mackerel, sardines, salmon, fresh tuna, kippers, smoked salmon or trout	30g or 1oz or ¼ standard tin (120g) or ¼ fillet of salmon
Chicken, turkey, duck, pheasant (cooked without skin) Lean beef, pork, lamb, rabbit, venison, offal (fat removed) Quorn fillets, steak, mince or pieces Vegetarian mince frozen	30g or 1oz or 1 slice size of playing card
Lean grilled bacon Quorn ham	25g or ¾oz or 1 rasher
Lean ham Quorn bacon rashers (not slices)	30g or 1oz or 1 medium, 2 small or 4 wafer thin slices
Eggs	60 g or 2 oz or 1 egg
Tofu	50g or $1^2/_3$ oz or Size of 2 match boxes
Tempeh	25 g or 1 oz or Size of 1 match box
Baked beans (reduced sugar)	60 g or 2 oz or 2 tablespoons
Lentils, chickpeas and kidney beans, mung beans, black (eye beans, puy lentils, toor dahl, urad dahl, Raw weight	20g or ⅔ oz or 1 tablespoon raw
Cooked or tinned weight	65g or 2oz or 1 ¹ / ₂ tablespoons cooked /tinned or 1 cupped handful
Soya beans (frozen or cooked) or edamame beans	30g or 1oz or 1 tablespoon
Vegetarian sausage	25g or ¾ oz or ½ sausage
Textured vegetable protein (TVP)	10g or ¹ / ₃ oz uncooked or 1 heaped tablespoon uncooked
Low fat hummus	30g or 1oz or 1 level tablespoon

Vegetables – min 5 portions 1 portion = 80g or 2⅔oz	1 portion is equal to
Asparagus, Aubergines, Broccoli, Brussel sprouts, Carrots, Cabbage, Cauliflower, Chinese leaves, Courgettes, Cucumber, Curly kale, Green beans, Lettuce (mixed leaves), Mange tout, Methi, Mushrooms, Okra, Pak choi, Peas, Sugar snap, Spinach, Spring greens cooked, Sweetcorn, Tomatoes, Watercress fresh	80g or 2 ² / ₃ oz or 2 spears of broccoli, 8 cauliflower florets. 3 heaped tablespoons of vegetables or large cereal bowl of salad.
Fruit - 2 portions	1 portion is equal to
1 portion = 80g or $2^{2}/_{3}$ oz (30g or 1oz dried fruits)	
Berries (e.g. blackberries, blueberries, redcurrants, raspberries, strawberries) Cherries or grapes	80g or 2⅔oz 1 handful
Grapefruit, guava and mango	80g or 2⅔oz or ½ a whole fruit
Large fruit (e.g. melon, pineapple, papaya)	80g or 2⅔oz or 1 medium slice
Medium fruits (e.g. apple, pear, nectarine, orange, peach, banana, pomegranate)	80g or 2⅔oz 1 fruit
Small fruit (e.g. fresh apricots, kiwi, clementine, passion fruit, plums)	80g or 2⅔oz or 2 fruits
Any stewed fruit—unsweetened or with calorie-free sweetener e.g. apple, rhubarb	80g or 2⅔oz or 3 tablespoons
Kumquats, lychees, physalis	5 fruits
Dried fruits (raisins, currants, apricots)	30g or 1oz or 1 tablespoon
Milk and dairy foods - 3 portions	Equal to
Milk (semi-skimmed or skimmed) Alternative 'milks' with added calcium, e.g. soya **	¹ ⁄₃ pint or 200ml or 1 small glass
Diet yoghurts, Low fat/fat-free Greek or Greek Style or natural yoghurts, fromage frais or plain soya yoghurt, high protein yogurt	120-150g or 4-5oz or 1 small pot or 3 tablespoons
Whole milk natural yogurt	80g or 1 ⅔ oz or 2 tablespoons
Cottage cheese	75g or 1½oz or ¼ pot, 2 tablespoons
Cream cheese (light or extra light)	30g or 1oz or

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** we recommend soya milk as coconut, oat and almond milks are lower in protein and calcium

Lower fat hard cheeses e.g.:

Reduced fat cheddar, Edam,

Bavarian smoked, feta, ricotta, mozzarella, reduced fat

halloumi, paneer made from semi-skimmed milk

1 tablespoon

week

30g or 1oz or Matchbox size

No more than 180g or 6oz a

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8g or 1 teaspoon 1 dessertspoon of oil 7g or 1 dessertspoon 7g or 1 dessertspoon
7g or 1 dessertspoon 7g or 1 dessertspoon
7g or 1 dessertspoon
3 walnut halves, 3 Brazil, 4 almonds, 8 peanuts, 10 cashews or pistachios
50g or 10 olives
15g or $\frac{1}{2}$ oz or 1 tablespoon
11g or ⅓ oz or 1 heaped teaspoon
12 g or ⅓ oz or 2 heaped teaspoons
40g or 1⅓ oz or 1/4 of an average pear
40g or 1 ¹ / ₃ oz or 2 tablespoons

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MIDDAS-GDM End of Study Questionnaire

Thank you for taking part in the MIDDAS-GDM Study.

This is one of the first studies of its kind. We hope to learn as much as possible from this study, in particular the views of people who have taken part. We are inviting you to provide your views on different aspects of the study and following the diet, and how we can improve our programmes and research studies in future.

Please complete the following questions and return this questionnaire to the MIDDAS-GDM study team in the envelope provided. If there is anything else you would like to say about your experiences of the study, please use the section at the end. Your answers to the questions below will remain anonymous.

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2. How sa 1 Not at all satisfied Comments	2	3 Sligh satis	4 htly fied	i dy overall 5 Quit satisfi	6 e ed	ment, 7 	8 Very atisfied	9 	1 Extra sati

3. You were asked to attend additional face to face appointments at the hospital by the study team (please fill in the number)

4. You were asked to attend additional virtual (i.e. video call or telephone)



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appointments by the study team (please fill in the number)	
5. How do you feel about the number of additional appointments you attend? (tick)	u were asked to
I was happy with the number of appointments	
I would have preferred fewer face to face appointments	
I would have preferred more face to face appointments	
I would have preferred fewer virtual appointments	
I would have preferred more virtual appointments	
Comments:	
6. How do you feel about virtual (i.e. video call or telephone) appoint	tments?
□ I prefer virtual appointments to face to face appointments (please expla	in why below)
□ I prefer face to face appointments to virtual appointments (please expla	in why below)
Comments:	
<u>Diet</u>	
7. Which diet were you asked to follow? (<i>please tick</i>)	
	and a time in factor and a
Best NHS Care (i.e. increased fruit/vegetable intake, low-GI foods, r	reduction in free sugars,
regular meals)	a second
L Intermittent low energy diet (5 days of the best NHS care diet plus 2 not	n-consecutive days of
1000 kcal each week)	
v. was the diet easy to follow?	9 10
Not at all Slightly Moderately Very	Extremely



Comments:				
9. Did you enjoy	following the diet	plan?	7 0	0 10
Not at all	3 4 Slightly	b 6 Moderately	ہ Very	9 10 Extreme
Comments:				
10. Would you ma	ake any changes to	the written infor	mation (i.e. diet b	ooklets, recipes)
were given on	how to follow the	diet plan?	-	
□ Yes				
□ No				
If ves what chang	es would vou make	2		
in yes, what onding				
Commonts:				
			2	••••••
				•••••
11. How was you	first appointment	with the distition	2 (tick all that apply	40
11. How was your	r first appointment	with the dietitian	? (tick all that apply	/)?
11. How was your	r first appointment of information I rece	with the dietitian eived was OK	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece	with the dietitian eived was OK eived was too little	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece of information I rece	with the dietitian eived was OK eived was too little eived was too muc	? <i>(tick all that appl</i> y	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u> □ I was happy	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec	with the dietitian eived was OK eived was too little eived was too muc ceived	? (tick all that apply	/)?
 11. How was your □ The amount □ The amount □ The amount □ The amount □ I was happy □ The advice I 	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/) ?
11. How was your The <u>amount</u> The <u>amount</u> The <u>amount</u> I was happy The <u>advice</u> I Comments:	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/)?

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	diatitian a							
	dietitian c	auring yo	ur pre	gnancy ?				
⊔ Yes								
□ No								
Comments:								
13. How use	ful was yo	our final a	appoin	tment with the die	titian at 1	2 week	s post-c	delivery?
			•••		_	•	•	
1 Not at all	2	3 Slightly	4	5 6 Quite	7 Ver	8 У	9	10 Extreme
Comments:			2					
14. Did you f	feel confid	dent to ex	ercise	e whilst on the diet	plan?			
-	0	2	4	E C C		o		10
	2	.)	/1				~ ~ ~	
Not at all	-	Slightly	4	5 0 Quite	/ Very	0	9	Extremely
Not at all confident	-	Slightly confiden	t	Quite confident	/ Very confide	ent	9	Extremely confident
Not at all confident	_	Slightly confiden	t	Quite confident	/ Very confide	ent	9	Extremely confident
Not at all confident	-	Slightly confiden	t	Quite confident	/ Very confide	ent	g	Extremely confident
Not at all confident Comments:	-	Slightly confiden	+ t	S G Quite confident	7 Very confide	ent	9	Extremely confident
Not at all confident Comments:	-	Slightly confiden	+ t	S O Quite confident	Very confide	•nt	y 	Extremely confident
Not at all confident	- 	Slightly confiden	+ t	S G Quite confident	7 Very confide	o nt	9	Extremely confident
Not at all confident Comments:	_ 	Slightly confiden	+ t	S G Quite confident	7 Very confide	o nt	9 	Extremely confident
Not at all confident Comments:		Slightly confiden	+ t	Additional suppor	very confide	o Int	9 	Extremely confident
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Not at all confident Comments:	ny of the f	Slightly confiden	+ t have Ye	Additional suppor been useful & if so	t bod of	ent	9 	Extremely confident
Not at all confident	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	•nt •nt • n ?	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	ent	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s	ny of the f	following	+ t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	o nt 	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s dietitian	ny of the f	Slightly confiden	+ t have Ye s	Additional suppor been useful & if so Preferred metho contact Face to face / p	very confide	•nt	9 	Extremely confident
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Not at all confident Comments: 15. Would ar Additional s dietitian	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact Face to face / p	very confide	nt 	9 	Extremely confident



				NHS Foundation Trus
Additional support from			Face to face / phone	
the doctors in the clinic				
More contact with other			Face to face / phone	
women in the study				
following the diets				
Other, please specify:				
		4		
16. Did you receive any si	uppor	t outs	ide of the study team help	o to keep you on track as you
progressed through th	ne stu	dy?		
🗆 No				
□ Yes				
If ves, what support did you	ı recei	ve?		
in yoo, milat ouppoint and you	. 1000			
		•••••		
			Record keeping	
17. How did you find the	finge	r pric	k testing requirements on	the study? (tick all those that
apply)				
Challenging but on the contract of the cont	ne who	ole <u>ac</u> ł	nievable	
□ Challenging and <u>not</u>	achiev	<u>able</u>		
Not challenging at all				
□ I felt it was <u>necessary</u>	<u>/</u> to te	st this	often to ensure my safety	
□ I felt it was <u>unnecess</u>	<u>ary</u> to	test th	nis often to ensure my safety	/
Comments:				
18 How did you find the	katan	a tast	ing requirements on the s	tudy? (tick all those that and
io. now ala you fina the	NELUII		ing requirements on the s	i uon an uiose uiaι appi
	ie who	bie <u>act</u>	nevable	
Challenging and not a	achiev	able		



2	NHS Foundation Trust
3 4	□ Not challenging at all
5 6	□ I felt it was <u>necessary</u> to test this often to ensure my safety
7	I felt it was <u>unnecessary</u> to test this often to ensure my safety
9 10	
10 11	Comments:
12 13 14	
15 16	19. How did you find using Diasend software?
17 18	□ Straightforward
19	□ Challenging but on the whole <u>achievable</u>
20 21	□ Challenging and <u>not achievable</u>
22 23	I felt uncomfortable using computer software to keep track of my medical details
24 25	I felt comfortable using computer software to keep track of my medical details
26	
28	Comments:
29 30 31	
32 33	20. How did you find completing the food diary during the study? (tick all those that apply)
34 35	□ Challenging but on the whole <u>achievable</u>
36 37	□ Challenging and <u>not achievable</u>
38	□ Not challenging at all
40	
41 42	Comments:
43 44	
45 46	
40 47 48 40	21. How did you find the physical activity questionnaires on the study? (tick all those that apply)
50	□ Challenging but on the whole <u>achievable</u>
51 52	□ Challenging and <u>not achievable</u>
53 54	□ Not challenging at all
55 56	
57	Comments:
58 59	
60	

		Manches	NHS Foundation
22. How did you find the quality of lif	e questionnaires	on the study? (ticl	k all those that a
□ Challenging but on the whole a	<u>chievable</u>		
□ Challenging and not achievable			
□ Not challenging at all			
Comments:			
	Libro® app		
23. Did you use the Libro® app?			
□ Yes			
□ No (please move to question 25)			
24. Did you find the App helpful?			
1 2 3 4 Not at all Slightly	5 6 Moderately	7 8 Very	9 10 Extrem
Comments	10.		
25. What did you like about the App?			
		5	
		4	
26 What did you dislike about the Ar	on and could be in	proved?	
27. If you didn't use the app what	were the reasons	for this? (tick all th	at apply)

NILC

Manchester University

							NHS Fo	undation in
🗆 Don	't like usir	ng apps in general	🗆 No	t user frie	endly			
🗆 Labo	our intens	ive / time consumi	ng 🗆 Pre	efer to us	e pen ar	nd pape	ər	
□ Find	mobile d	evices challenging	l					
🗆 Lack	c of regula	ar internet access						
Othe	er (provide	e details below)						
			Diasend So	oftware				
28. Did you fi	nd the Di	iasend software h	nelpful?					
1 Not at all	2	3 4	5 Moderate	6 M	7 Verv	8	9	10 Extremely
NOT at all		Signity		ıy	very			Lynemery
0								
Comments								
Comments								
Comments								
			<u> </u>					
29. What did	you like a	about the Diasen	d software?					
29. What did	you like a	about the Diasen	d software?					
29. What did	you like a	about the Diasen	d software?					
29. What did	you like a	about the Diasen	d software?					
29. What did	you like a	about the Diasen	d software?					
29. What did	you like a	about the Diasend	d software?					
29. What did	you like a you disli	about the Diasend	d software?	re and c	ould be	impro	ved?	
29. What did	you like a	about the Diasen ke about the Dias	d software?	re and c	ould be	impro	ved?	
29. What did	you like a	about the Diasen ke about the Dias	d software?	re and c	ould be	impro	ved?	
29. What did	you like a	about the Diasen ke about the Dias	d software?	re and c	ould be	impro	ved?	
29. What did	you like a	about the Diasend	d software?	re and c	ould be	impro	ved?	
29. What did	you like a	about the Diasen ke about the Dias <u>Stu</u>	d software? end softwa	re and c	ould be	impro	ved?	
29. What did	you like a you dislii	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa	are and c	ould be	impro	ved?	
29. What did	you like a you dislii	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa idy Improve study?	are and c	ould be	impro	ved?	
29. What did	you like a you dislii	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa	re and c	ould be	impro	ved?	
29. What did	you like a you dislii	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa idy Improve study?	re and c	ould be	impro	ved?	
29. What did	you like a you dislil	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa idy Improve study?	are and c	ould be	impro	ved?	
29. What did	you like a you dislii	about the Diasen ke about the Dias <u>Stu</u> y most about the	d software? end softwa idy Improve study?	are and c	ould be	impro	•ved?	



	NHS Foundation Trust
22 M/hat did you a	value of about the study and sould be improved?
32. What did you e	njoy least about the study and could be improved?
	Any other comments about the study
	\sim
Tha	ank you for completing this guestionnaire, please return to:
	MIDDAS-GDM Study Team, Nightingale Centre,
	Wythenshawe Hospital, Manchester, M23 9LT

T DieR Template for Intervention

BMJ Open The TIDieR (Template for Intervention Description and Repliced tion) Checklist*:

Information to include when describing an intervention and the location and the location

Description	and Replication Information to include when describing an intervention and the location	E C C		1
Item	Item	ina	Wher	e located **
number		for	rimary paper	Other [†] (details)
		Ens	ବୁ କ୍ରିage or append	lix
		rela	Rumber)	
		ted	024.	
	BRIEF NAME	to h te co	Dov	
1.	Provide the name or a phrase that describes the intervention.	iupe ext a	\$2 0	
	WHY	rieur (nd da	aded	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	(ABE	10 14-5	
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2	Materials: Describe any physical or informational materials used in the intervention, including these	trai	3 0 12 15	appondix
5.	materials. Describe any physical of informational materials used in the intervention, including those	nina		
	provided to participants or used in intervention delivery or in training of intervention providers.	.an	<u>ь</u>	
	Provide information on where the materials can be accessed (e.g. online appendix, URL).	d sii	COT	
		nila	on	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention,	r tec	5 6-12	
	including any enabling or support activities.	hno	lē 12	
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	WHO PROVIDED	Š	25 at	
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their	c	 ₽_1, 7-12, 17-18	
	expertise, background and any specific training given.		ence	
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	HOW	-	raph	
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TIDieR che	cklist For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtm	I	de l	

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6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or	6 -18	
	telephone) of the intervention and whether it was provided individually or in a group.	78264 (
	WHERE	on 10	
7.	្ទុ Describe the type(s) of location(s) where the intervention occurred, including any necessary គួក	1 2 6-18	
	infrastructure or relevant features.	uary 2	
	WHEN and HOW MUCH	о 24. Г	
8.	Describe the number of times the intervention was delivered and over what period of time including	ĕ <u>≰</u> 6-18	
	the number of sessions, their schedule, and their duration, intensity or dose.	loaded 1	
		from	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why,	6-18	
	when, and how.	//bmjop	
	MODIFICATIONS	ben.bm	
10. [‡]	If the intervention was modified during the course of the study, describe the changes (what, why, 👸	§N/A	
	when, and how).	n/ on Ju	
	HOW WELL	ne 12	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any	2013-14	
	strategies were used to maintain or improve fidelity, describe them.	5 at Ag	
12. [‡]	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	ence N/A	
	intervention was delivered as planned.	libliogr	
		aphiqu	
TIDieR cl	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	le de	

- BMJ Open ** Authors use N/A if an item is not applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. sufficiently reported. sufficiently reported.
- or other published papers (provide citation details) or a website (provide the URL). + If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.
- * We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains an elaboration and elaboration for each item.
- * The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study ether elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist $\mathbf{\hat{P}}_{\mathbf{\hat{k}}}$ a randomised trial is being reported, the Li conjunction with th .et can be used in conjunction w TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of the CONSORT 2010 Statement. When a clinical trial protocol is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement a statement Statement (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropria to that study design (see (ABES) ta mini www.equator-network.org).

ttp://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique

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SPIRIT CHECKLIST

Section/Item	ltem no	
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Trial Registration	2a	
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Funding	4	
Roles and responsibilities	5a	
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	5c	
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Background and rationale	6a	C
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Methods: Participants, interventions, and	outcomes	
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Implementation	16c	



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Blinding (masking) 17a 17b Methods: Data collection, management, and analysis Data collection methods 18a 18b 18b 18b Data management 19 Statistical methods 20b 20b 20c Methods: Monitoring			ı
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Data monitoring 21a	Data monitoring	21a	

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Protocol amendments	25	
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Declaration of interests	28	2/
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Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
	1
I rial identifier and registry name. If not yet registered, name of intended registry	3
All items from the World Health Organization Trial Registration Data Set	throughout
Date and version identifier	n/a
Sources and types of financial, material, and other support	23
Names, affiliations, and roles of protocol contributors	1
Name and contact information for the trial sponsor	name only, 23
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	23
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)	18
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Explanation for choice of comparators	4-5
Specific objectives or hypotheses	13-14
Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	¹ 6
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	6
Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions for each group with sufficient detail to allow	9

Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	13-14
Time schedule of enrolment, interventions (including any run- ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Strategies for achieving adequate participant enrolment to reach target sample size	n/a
ils)	
Method of generating the allocation sequence (eg, computer-	0
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	8
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 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	8

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Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
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	9-15
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	supplementary PIS
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	16
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	16
Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
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	18

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
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 16
Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	n/a
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)	19
Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, supplementary conser
Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	16
Financial and other competing interests for principal investigators for the overall trial and each study site	23
Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	supplementary PIS
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	19
	l

Authorship eligibility guidelines and any intended use of professional writers	n/a
Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	19
Model consent form and other related documentation given to participants and authorised surrogates	supplementary mater
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	15

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6	Infant, newborn
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8	Glucose Intolerance
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17	Insulin
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21	Diet. Healthy
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Manchester Intermittent Diet in Gestational Diabetes Acceptability Study (MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater Manchester

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-078264.R3
Article Type:	Protocol
Date Submitted by the Author:	05-Jan-2024
Complete List of Authors:	Dapre, Elizabeth; Wythenshawe Hospital Issa, Basil; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Harvie, Michelle; University Hospital of South Manchester NHS Foundation Trust, Genesis prevention centre Su, Ting-Li; University of Manchester, Dentistry McMillan, Brian; The University of Manchester, Centre for Primary Care and Health Services Research Pilkington, A.; Wythenshawe Hospital Hanna, F.; University Hospitals of North Midlands NHS Trust Vyas, Avni; Manchester Metropolitan University Faculty of Health Psychology and Social Care, Health Professionals Mackie, S.; Wythenshawe Hospital Yates, James; Manchester University NHS Foundation Trust Evans, Benjamin; Manchester University NHS Foundation Trust Mubita, Womba; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Lombardelli, Cheryl; Manchester University NHS Foundation Trust
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Obstetrics and gynaecology, Reproductive medicine
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, DIABETES & ENDOCRINOLOGY, Obesity, NUTRITION & DIETETICS, Feasibility Studies, Maternal medicine < OBSTETRICS



<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>			
(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent			
Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater			
	Manchester		
uthors: Dapre. E., Issa	. B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,		
., Vyas, A., Yates, J., N	Aackie, S., Evans, B., Mubita, W., Lombardelli, C.		
, <u>,</u> , , , - ,			
Or Elizabeth Danre	elizabeth.dapre@hotmail.com		
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Cheryl Lombardelli	The Nightingale Centre, Wythenshawe Hospital, Manchester, UK		

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1 2	18	
3	19	<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>
5	20	(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent
6 7	21	Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater
8 9	22	Manchester
10	23	
12	24	Authors: Dapre, E., Issa, B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,
13 14	25	A., Vyas, A., Yates, J., Mackie, S., Evans, B., Mubita, W., Lombardelli, C.
15 16	26	
17	27	Corresponding Author: elizabeth.dapre@nhs.net
18 19	28	
20 21	29	Abstract (word count 298)
22 23	30	Introduction: The prevalence of gestational diabetes mellitus (GDM) is rising in the
24	31	UK and is associated with maternal and neonatal complications. National Institute for
25 26	32	Health and Care Excellence (NICE) guidance advises first line management with
27 28	33	healthy eating and physical activity which is only moderately effective for achieving
29 30	34	glycaemic targets. Approximately 30% of women require medication with metformin
31	35	and/or insulin. There is currently no strong evidence base for any particular dietary
32 33	36	regimen to improve outcomes in GDM. Intermittent low-energy diets (ILEDs) are
34 35	37	associated with improved glycaemic control and reduced insulin resistance in type 2
36 37	38	diabetes (T2DM) and could be a viable option in the management of GDM. This
38	39	study aims to test the safety, feasibility and acceptability of an ILED intervention
39 40	40	amongst women with GDM compared to best National Health Service (NHS) care.
41 42	41	
43	42	Method and analysis: We aim to recruit 48 women with GDM diagnosed between 24-
45	43	28 weeks gestation from antenatal clinics at Wythenshawe and St Mary's hospitals,
46 47	44	Manchester Foundation Trust, over 13 months starting in November 2022.
48 49	45	Participants will be randomised (1:1) to ILED (2 low-energy diet days/week of
50	46	1000kcal and 5 days/week of the best NHS care healthy diet and physical activity
52	47	advice) or best NHS care 7 days/week until delivery of their baby. Primary outcomes
53 54	48	include uptake and retention of participants to the trial, and adherence to both dietary
55 56	49	interventions. Safety outcomes will include birthweight, gestational age at delivery,
57	50	neonatal hypoglycaemic episodes requiring intervention, neonatal
58 59	51	hyperbilirubinaemia, admission to special care baby unit or neonatal intensive care
60	52	unit, stillbirths, the percentage of women with hypoglycaemic episodes requiring

1 2	53	third-party assistance, and significant maternal ketonaemia (defined as ≥1.0mmol/L)
3	54	Secondary outcomes will assess the fidelity of delivery of the interventions, and
4 5	55	qualitative analysis of participant and healthcare professionals' experiences of the
6 7	56	diet. Exploratory outcomes include the number of women requiring metformin and/or
8 9	57	insulin.
10	58	
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50 51	81	Ethics and dissemination: Ethical approval has been granted by the Cambridge
52	82 83	publication in peer-reviewed journals, conference presentations, and shared with
53 54	84	diabetes charitable bodies and organisations in the UK, such as Diabetes UK and
55 56	85	the Association of British Clinical Diabetologists.
57 58	86	
59	87	
60	88	Irial Registration Number: NC105344066

1 2	89					
3		Strengths and limitations of this study				
4 5		Strengths				
6		 This study adds to the limited literature of safety of low-calorie diets amongst 				
8		we may with gestetional dishetes				
9 10		women with gestational diabetes				
11		This study has been informed by an experienced patient and public involvement				
12 13		and engagement group				
14		Limitations				
15 16		This study involves a small sample size and is not powered to show efficacy of				
17		the intervention				
18 19		Women joining this study are likely to be highly motivated and adherence may				
20 21		not reflect that seen in the wider general population				
22	00					
23 24	90	INTRODUCTION (word county 2520)				
25	91	INTRODUCTION (word could: 3539)				
26 27	92	Background				
28	93	In the UK up to 16% of pregnant women develop gestational diabetes (GDM) and				
29 30	94	the incidence is rising, in part due to increasing rates of obesity and maternal				
31 32 33	95	age(1,2). GDM is associated with maternal and neonatal complications (the risk				
	96	increases with poor glycaemic control), including macrosomia, shoulder dystocia,				
34 35	97	caesarean-sections, neonatal hypoglycaemia and/or hyperbilirubinaemia, preterm				
36 27	98	delivery, preeclampsia, and stillbirth(2). Women who have had GDM have an				
37 38	99	estimated seven to ten-fold risk of developing type 2 diabetes (T2DM) later in life,				
39 40	100	and their children have a higher risk of developing adult obesity and $T2DM(2-4)$				
41	101					
42 43	101	Evenesive weight gain in programmy is a particular problem for woman with CDM(E)				
44	102	Excessive weight gain in pregnancy is a particular problem for women with GDM(5).				
45 46	103	Harper et al demonstrated that, in women with GDM, every additional 1lb/week				
47	104	gained following diagnosis of GDM resulted in a 36-83% increased risk of pre-				
40 49	105	eclampsia, caesarean-section, macrosomia, and large for gestational age babies(5).				
50 51	106	Such studies highlight the importance of adequate weight control throughout				
52	107	pregnancy in women with GDM in order to reduce both maternal and neonatal				
53 54	108	complications.				
55	109					
56 57	110	First-line therapy for GDM is diet and physical activity. National Institute for Health				
58	111	and Care Excellence (NICE) guidance encourages a healthy dist with increased fruit				
59 60	TTT	and our Excention (MOE) guidance encourages a reality det with increased full				

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- and vegetables, low-glycaemic index (GI) foods, reduced refined sugars, regular mealtimes and regular physical activity(6,7). These dietary measures fail to achieve glycaemic targets in ~30% of women who require medication with metformin and/or insulin(8). A range of dietary approaches have been studied including daily diets promoting low-GI diets (limiting refined and promoting complex carbohydrates), continuous modest energy-restriction (1800 Kcal/day), and low carbohydrate diets(9). There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM. Intermittent Low-Energy Diets (ILED) The pathogenesis of GDM is strongly linked to obesity and chronic insulin resistance with many clinicians viewing GDM as a form of evolving T2DM. ILEDs typically include several days of a food based or meal replacement (e.g. drinks/bars) low-energy diet (650-1000kcal) diet, with a standard healthy (non-restrictive) diet recommended on the remaining days of the week. These diets are associated with significant reductions in weight, insulin resistance and hyperglycaemia in patients with prediabetes (HbA1c between 42-47mmol/mol, impaired glucose tolerance, or impaired fasting glycaemia), those with T2DM, and otherwise healthy subjects with overweight/obesity(10–17). These changes are equivalent to, or greater than, those achieved with standard daily energy restriction. A popular intermittent diet involves 2 consecutive or non-consecutive days/week of a low-energy diet (650-1000kcal) and 5 days of normal eating/week, known as the 5:2 diet. The Manchester Intermittent
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- participants in the ILED group completed the study and achieved a 6% reduction of their baseline body weight. Forty two percent achieved an HbA1c of <48 mmol/mol(18). Given the strong overlap between GDM and T2DM, an ILED may be a promising dietary intervention for those with GDM. A successful dietary approach to glycaemic control could empower women to take charge of the management of their GDM. Women with GDM are motivated to modify their diet driven by a desire to improve foetal outcomes(19-21).

vs. Daily Diabetes App Study (MIDDAS), a study comparing an ILED and a

continuous low-energy diet in T2D conducted in our unit, has shown the feasibility

including those using insulin(18). At the end of the study approximately 70% of

and safety of an ILED (800kcal for 2 days/week) in patients with T2DM and obesity.

⁶⁰ 146

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1 2	147	Our Patient and Public Involvement and Engagement (PPIE) work indicates that
3 4 5	148	women find the current National Institute for Health and Care Excellence (NICE)
	149	healthy eating guidance(6,7) confusing and vague. Our PPIE work has indicated that
6 7	150	women are keen to try alternative dietary approaches, particularly if alternative diets
8 9	151	are more effective in preventing the need to progress to medications such as
10 11 12 13 14 15 16	152	metformin and insulin.
	153	
	154	Aim
	155	The aim of this trial is to test the safety, feasibility, and acceptability of an ILED in
17	156	GDM to inform a future large-scale RCT.
18 19	157	
20 21	158	METHODS
22 23	159	Trial Design
24	160	The study is a 28-week feasibility two-arm RCT in one NHS trust performed in
25 26	161	patients with GDM and BMI ≥27.5 kg/m², or ≥25 kg/m² in high-risk minority ethnic
27 28	162	groups (i.e. South Asian, Black African, African Caribbean) in Greater Manchester,
29 30 31 32 33 34 35	163	between December 2022 and July 2024(22,23). There will be an embedded
	164	qualitative sub-study for participants and healthcare professionals. Due to the nature
	165	of the intervention, it will not be possible to blind the participants, clinicians, or study
	166	team to the treatment allocation after randomisation (the statistician and laboratory
36	167	technicians will remain blinded).
37 38	168	
39 40	169	Trial Setting and Recruitment
41	170	Participants will be recruited from antenatal clinics at Wythenshawe and St Mary's
43	171	Hospitals, Manchester Foundation Trust (MFT) between November 2022 and
44 45	172	December 2023. This is an urban area within Greater Manchester, and MFT serves
46 47	173	patients from a wide range of minority ethnic and socio-demographic backgrounds.
48 49 50 51 52 53 54 55	174	Women may self-refer to the antenatal clinic or be referred by their primary care
	175	team. Assessments will be carried out at MFT, or remotely if required by COVID-19
	176	restrictions. The qualitative sub-study will be carried out at MFT, remotely, or at a
	177	location of the participant's choosing. We aim to recruit eligible participants over a
	178	period of 13 months. Potential participants will be given written information about the
56 57	179	study and the opportunity to ask questions about the study prior to providing written
58 59	180	consent (supplementary files 1 and 2).
60	181	

1 2	182	Eligibility Criteria
3 ⊿	183	
5	184	<image exclusion="" figure1="" inclusion="" jpg="" one;=""/>
6 7	185	
8 9	186	
10	187	Participant Flow
12	188	Participants who fulfil the broad eligibility criteria will be notified about the trial by the
13 14	189	GDM nurse/midwife at the time of their diagnosis. Those who are interested will be
 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 	190	provided with a comprehensive patient information sheet (supplementary file 1) and
	191	more detailed eligibility screening questions. They will be asked to attend their first
	192	appointment having fasted for at least 6 hours and complete a four-day food diary (in
	193	line with our department's usual care). On attending their first routine clinic
	194	appointment, interested participants will receive further information from the research
	195	team. They will have the opportunity to ask questions, have their eligibility confirmed,
	196	and will be asked for their written consent to take part. Baseline assessments will be
	197	taken and participants will be randomised to their allocated treatment group using an
	198	online randomisation platform. Participant flow through the study is demonstrated in
	199	figure 2.
	200	
	201	Sample Size
	202	We plan to recruit 24 participants per study arm (n=48) which, when considering an
	203	estimated attrition rate of 15%, will provide complete outcome data on 40
	204	participants(24–26). It has been estimated that 24 participants per group will be
	205	sufficient to determine study outcomes, in line with sample size recommendations for
42	206	feasibility studies(27–29).
44 45	207	
46 47	208	This number will allow us to enable estimation of recruitment/retention parameters
48	209	with sufficient precision. For example, based on 40 completed participants, it will
49 50	210	enable recruitment rates in the region of 25% to be estimated with an error of +/-
51 52	211	13.42% at most; retention of 85% will be estimated with error of +/-11.07% at most. It
53 54	212	is also sufficient for estimation of variability (e.g. standard deviation) in gestational
55	213	weight gain and capillary glucose concentrations (proposed outcomes for the future
56 57	214	definitive trial) with negligible bias (30).
58 59	215	
60	216	

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1 2	217	Randomisation
3 1	218	The randomisation schedule will be independently set up and known only by the trial
5	219	statistician. The trial statistician will be blinded to the participant's identity using
6 7	220	"sealed envelope" software (https://www.sealedenvelope.com/). Randomisation will
8 9	221	be carried out by generating an online pseudo-random list with random permuted
10	222	blocks of varying size, known only to the statistician, and will be stratified for two
12	223	variables:
13 14	224	- Age (18-35, >35 years)
15 16	225	- BMI (27.5-34.99kg/m ² and >35kg/m2, >25-32.49kg/m ² and >32.5kg/m ² for
17	226	high-risk minority ethnic groups (i.e. South Asian, Black African, African
18 19	227	Caribbean)
20 21	228	These stratification variables have been chosen to reduce potential bias as we
22 23	229	expect varying severity of GDM with increasing age and BMI, and possible
24	230	differences in diet adherence(31).
25 26	231	
27 28	232	Treatment to intervention and control groups will be allocated in a 1:1 ratio. A
29	233	member of the research team who will be unaware of the randomisation algorithm
30 31	234	(principal investigator, clinical research nurse, clinical research fellow or project
32 33	235	manager) will trigger the randomisation procedure onsite; participants and clinicians
34 35	236	will then be informed of the allocated treatment group. Clinicians will not be blinded
36	237	due to the need to remain astute to safety, adherence, and side effects, requiring
37 38	238	open and honest discussions with patients at each appointment. The statistician will
39 40	239	remain blinded to treatment allocation until all outcome measures for all subjects
41 42	240	have been collected.
43	241	
44 45	242	Interventions
46 47	243	Study Arm 1: Best NHS Care Diet
48	244	All dietetic advice will be face to face or via video calls or the telephone. Participants
49 50	245	will receive one to one personalised written and verbal advice from a dietitian to
51 52	246	follow NICE diet and physical activity recommendations(6,7). Dietitians and midwives
53 54	247	will receive training to ensure standardised delivery of information in clinic, and
55	248	standardised patient information leaflets will be supplied to include information about
56 57	249	increased fruit/vegetable intake, low-glycaemic index foods, and a reduction in free
58 59	250	sugars. Information will include advice about the importance of regular meals; dietary
60	251	advice aims to ensure that participants include at least 70g protein/28g fibre, and

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1 2	252	predominantly mono- and polyunsaturated fats as per American Diabetes
3	253	Association recommendations(32). Participants will be advised to be physically
5	254	active, for example walking for 30 minutes after a meal. Participants will receive
6 7	255	ongoing dietetic education and support every 2 weeks until delivery. This level of
8 9	256	support is higher than typically provided in NHS GDM antenatal clinics due to limited
10 11 12 13 14 15 16	257	resources but has been utilised to reflect best NHS care. They will receive suggested
	258	menus and recipes to follow the NICE recommended healthy diet for GDM.
	259	Participants will be asked to measure their capillary glucose four times each day and
	260	their ketones on two random (recorded) days of the week of their choosing
17	261	(supplementary file 3).
18 19	262	
20 21	263	Study Arm 2: Intermittent Low-Energy Diet (ILED)
22 23	264	Participants will receive the same level of dietetic support as the best NHS care
24	265	group. They will be given advice on adopting an ILED which involves 2 non-
25 26	266	consecutive low-energy diet days/week (1000kcal to include 100g low-GI
27 28	267	carbohydrate and 70g of protein) and 5 days/week of the NICE healthy eating low-GI
29 30	268	diet and physical activity recommended for the best NHS care group. The low-
30 31 32 33	269	energy days involve women selecting a set number of portions of protein,
	270	carbohydrate, fat, fruit, vegetables, and dairy/dairy alternatives as described in
34 35	271	previous studies(33). Each low-energy day includes ~210g of lean protein foods, 3-4
36 37	272	portions of wholegrain carbohydrates, 1x7g portion of fat, 5 portions of vegetables, 2
37 38	273	of fruit, and 3 of dairy/dairy alternatives. Food and drink will be self-selected and not
39 40	274	provided by the study team. Participants will be provided with comprehensive food
41 42	275	lists, advice on portion sizes for the low-energy days and suggested menus and
43	276	recipes to follow for both the low-energy and NICE recommended healthy diet days
44	277	(supplementary file 4). Both diets can be successfully adapted for people of different
46 47	278	ethnicities and those following omnivorous, vegetarian and vegan diets. Participants
48 49	279	will be asked to measure their capillary glucose four times each day and their
50	280	ketones on (and the morning after) the two low-energy days (supplementary file 3).
51 52	281	
53 54	282	
55 56	283	<image 2="" 2:="" figure="" flow="" jpg=""/>
57 58	284 285	
59 60	286	<image 3="" 3:="" assessments="" figure="" jpg="" sched=""/>

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2	287	
3 4	288	
5	289	
6 7	290	Outcomes
8 9	291	Primary outcomes
10 11 12 13	292	Uptake rate measured as a percentage of eligible participants who consent to
	293	take part, including the proportion of women who were screened who did not
13 14	294	meet the eligibility criteria, and the number of women who did not give
15 16	295	consent to take part
17	296	Recruitment rate measured as the number of eligible participants who consent
19	297	to take part per month
20 21	298	Retention rate measured as the number of randomised participants who
22 23	299	complete the trial (those who attend the final visit) and the percentage of
24 25	300	participants who attend all 8 visits
26	301	Adherence to the dietary interventions assessed from self-reported adherence
27 28	302	to the potential low-calorie days between randomisation and delivery
29 30	303	 Completion of self-assessed glucose and ketone readings assessed as a
31 32 33 34 35	304	percentage of the required readings
	305	
	306	Safety outcomes:
36 37	307	 Percentage of women following ILED/best NHS care with
38 39 40 41 42	308	hypoglycaemia (episodes of blood glucose of <3.0mmol/mol) and
	309	hypoglycaemia requiring third-party assistance as measured by
	310	participants
43 44	311	 Percentage of women who develop significant ketonaemia in both
45 46	312	groups (defined as ≥1.0mmol/L) as measured by participants
47	313	 Percentage of neonatal hypoglycaemic episodes requiring intervention
48 49	314	(blood glucose checked 2- hours post-delivery and 2-hours thereafter
50 51	315	for 12 hours according to local protocol), neonatal birth weight,
52 53 54 55 56	316	gestational age at delivery, hyperbilirubinaemia/jaundice, and/or
	317	admission to Special Care Baby Unit or neonatal intensive care, and
	318	stillbirths
57 58	319	\circ The incidence and rate of other adverse events (e.g. headaches,
59 60	320	lethargy, constipation, or complications requiring hospital admission)

1 2	321	between the start of the trial intervention and delivery recorded as mild,
3 4	322	moderate and severe, as defined by Common Terminology Criteria for
5	323	Adverse Events version 5 (CTCAEv5)(34). Hospital admission for
6 7	324	routine labour and delivery will not be classified as an adverse event.
8 9	325	
10 11	326	Secondary outcomes
12	327	 Completeness of collection of trial endpoints including the percentage of
13 14	328	completed weight measurements, 4-day food diaries, and International
15 16	329	Physical Activity Questionnaire (IPAQ) scores
17	330	 Fidelity of delivery of the interventions will be measured through the number
19	331	and modality of completed planned patient contacts, electronic and paper
20 21	332	food diaries, and self-reported capillary glucose and ketone measurements
22 23	333	 Qualitative analysis of the acceptability and implementation of the
24 25	334	interventions will be explored amongst a subset of participants (~10 in each
25 26	335	group) and healthcare professionals through in-depth interviews
27 28	336	
29 30	337	Exploratory outcomes
31 32	338	The following outcomes will be explored without statistical inference.
32 33	339	1. Maternal outcomes:
34 35	340	 The percentage of women requiring metformin and/or insulin
36 37	341	Four-point capillary glucose profiles during third trimester (four times daily
38	342	until delivery)
39 40	343	 Change in fasting blood test results between baseline measurements, 36-
41 42	344	37 weeks' gestation, and 12 weeks post-delivery (including oral glucose
43 44	345	tolerance tests (OGTT)
45	346	 Mode of delivery, development of preeclampsia, polyhydramnios
40 47	347	(maximum liquor volume pool depth ≥8 cm)
48 49	348	 Quality of life and health status questionnaires (WHOQoL-BREF and SF-
50 51	349	36 questionnaires)(35,36)
52 52	350	2. Foetal outcomes:
53 54	351	Foetal weight
55 56	352	Gestational age at delivery
57 58	353	
59 60	354	

1 2	355	
3	356	
4 5	357	
6 7	358	
8	359	
9 10	360	Measurements
11 12	361	The full schedule of assessments can be found in figure 3.
13 14	362	
15	363	Physical measurements
16 17	364	Height weight and blood pressure will be measured using standardised calibrated
18 19	365	equipment in antenatal clinic
20	366	
21 22	367	Blood samples
23 24	368	Easting venous blood samples will be collected to assess maternal HbA1c, fasting
25	369	alucose insulin beta-bydroxybutyrate liver function tests free fatty acids thyroid
20 27	370	function tests, and full blood count. At the end of the study all samples will be
28 29	370	disposed of in accordance with the Human Tissue Act (2004)
30 31	371	disposed of in decordance with the Human Hissde Act (2004).
32	372	Questionnaires
33 34	374	Participants will be asked to complete four questionnaires at four time points
35 36	375	throughout the trial (self-reported). Quality of life and health status will be assessed
37	376	using the World Health Organisation Quality of Life Questionnaire (brief version) and
39	370	the 36-Item Short Form Survey respectively (35.36). Physical activity will be
40 41	378	measured using the International Physical Activity Questionnaire – Short Form, and
42 43	370	diet quality will be assessed using the LIK Diabetes and Diet Questionnaire (37.38)
44	280	These questionnaires are self-reported by participants and have been chosen as
45 46	201	they are widely used and validated tools
47 48	202	
49	202	Food Diarias
50 51	202	4 day distant records will be completed using Libre (Nutritice Mobile Application) or
52 53	384 205	a-day dietary records will be entered using Libro (Nutritics Mobile Application) of
54	385	paper lood diaries, which will be entered into Nutritics software (Nutritics, Dubini,
55 56	380	the huthe study distition. Disries will appride the assessed to an with information
57 58	387	unis by the study dietitian. Diaries will provide the research team with information
59 60	388	about the intake of energy, carbonydrate, fat, protein, fibre, glycaemic index, and the
00	389	timing or meals for participants in both groups. Participants will be asked what other

1 2 3 4 5	390	dietary modifications, if any, they have made at their fortnightly dietitian reviews to
	391	establish the adoption of any alternative dietary practices in the cohort.
	392	
6 7	393	Adverse Events
8 9	394	Participants in both groups will be asked about any adverse effects that they have
10 11	395	experienced at each visit. These will include, but are not limited to, the potential
12	396	effects of a low-energy diet, e.g. headache, lethargy, dizziness, constipation,
13 14	397	indigestion, poor concentration, and hunger. Adverse events will be graded as per
15 16	398	CTAEv5(34). Participants will be issued with a participation/emergency card with
17	399	emergency contact details for the research team to be carried at all times and to be
18 19	400	shown to the attending physician in case of emergency admission to hospital. All
20 21	401	participants will be issued with clear instructions as to how to manage a
22 23	402	hypoglycaemic and/or ketonaemic event (supplementary file 5).
24	403	
25 26	404	Data management
27 28	405	Participant data will be anonymised and will be stored in line with the Medicines for
29	406	Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act
30 31	407	(2018) and archived in line with the Medicines for Human Use (Clinical Trials)
32 33	408	Amended Regulations (2006) as defined in the MFT Clinical Trials Office Archiving
34 35	409	SOP (11; Retention of Data, Off-Site Archiving, and Destroying Documents).
36	410	Deidentified data will be stored in a study-specific Research Electronic Data Capture
37 38	411	(REDCap) database. The sponsor will periodically audit the site study file, a sample
39 40	412	of the case report form, consent forms, and source data, and check accuracy of the
41 42	413	study database to ensure satisfactory completion.
43	414	
44 45	415	Statistical methods
46 47	416	A statistical analysis plan specifying the full details of the primary and secondary
48	417	outcomes, other variables, and methods, will be produced prior to trial analysis. The
49 50	418	main analysis will be conducted via intention-to-treat population and will not
51 52	419	undertake any significance tests. Descriptive, graphical (summary), and basic
53 54	420	statistics (e.g. i. number, frequencies and percentages, ii. mean and standard
55	421	deviation, or iii. median and quartiles as appropriate) will be presented as
56 57	422	appropriate for each group respectively, for group difference jointly, and for each
58 59 60	423	stratum. Per-protocol analysis will be considered as a secondary analysis. Levels of
	424	missing data will be investigated and used to inform future studies. No imputation will

- 425 be used. The end of study questionnaire will be analysed using appropriate
- 426 descriptive statistics for closed questions and key themes will be extracted without
- 427 formal analysis from open questions to inform future research.
- **Progression Criterion**

- 430 The success of the feasibility trial will be defined by the progression criteria as
- ¹² 431 outlined in table 1. Any concerns regarding a low retention rate will be discussed with
 - the PPIE group. Interviews will include those who withdraw from the study to address

433 potential reasons for withdrawal with the aim to improve retention in future.

		F	
		Feasible with	
	Feasible (green)	modification of the	Not feasible (red)
		protocol (amber)	
Recruitment	≥4 patients/month	>2 patients/month	≤2 patients/month
Uptake to the	>15%	10 15%	<10%
feasibility study		10-13 /8	
Retention to the	>70%	50 70%	<50%
feasibility study	-10%	50-70 %	~50 %
Adherence to the	>50% of the low-	30-50% of the low-	<30% of the low-
ILED intervention	energy days	energy days	energy days
	completed (2/week	completed (2/week	completed (2/week
	between weeks 24-	between weeks 24-	between weeks 24-
	28 and delivery)	28 and delivery)	28 and delivery)

Table 1: Trial progression criterion

436 Qualitative sub-study

Participants will be invited to take part in an optional qualitative sub-study at 11-13
weeks post-partum. Healthcare professionals delivering the interventions will also be
invited to take part in this study.

51 440

We will undertake 11-12 semi-structured interviews with a subset of women from each group (ILED n=10 and best NHS Care n=10) at around 12 weeks post-delivery. The final sample size will be contingent on obtaining data saturation. We will also interview a sample of healthcare professionals (HCPs) involved in the delivery of care to study participants, including dieticians, obstetricians and midwives, including

1 2 3 4 5 6 7	446	those with leadership and clinical managerial roles. Sampling will be purposive,
	447	aiming to obtain women from a range of ethnic groups, ages, socioeconomic
	448	backgrounds, and self-reported engagement with the intervention. Participants and
	449	HCPs will be asked about their experiences and thoughts regarding the intervention,
8 9	450	including motivating factors, and facilitators/barriers to engagement. Interviews will
10	451	be conducted by a researcher from the University of Manchester/MFT who is
12	452	independent from the research staff involved in the delivery and assessment of the
13 14	453	programmes. Analysis will be conducted by two independent researchers at the
15 16	454	University of Manchester/MFT using Braun and Clarke's thematic analysis approach
17	455	to identify key issues around the acceptability, usefulness of the programmes, and
18 19	456	feasibility of a subsequent trial(40). Analysis will be inductive: open-ended,
20 21	457	exploratory, and driven by the data.
22 23	458	
23 24 25	459	All participants will also be asked to complete an optional and anonymous end of
25 26	460	study questionnaire developed by the study team at their post-partum visit
27 28	461	(supplementary file 6). This will give participants the opportunity to feedback on their
29 30	462	experience and will enable the study team to identify improvements to the design of
30 31 32 33 34 35 36 37 38 39 40	463	a possible follow-up study.
	464	
	465	Trial Steering Committee (TSC)
	466	The trial steering committee will include an independent consultant endocrinologist,
	467	obstetrician, dietitian, and the patient representative. The committee will oversee the
	468	trial to ensure that it is carried out to the expected standards. The TSC will liaise with
41 42	469	the CI to develop a schedule of meetings, proposed to occur every four months, with
43 44	470	meetings to occur no less than annually. Minutes will be taken at TSC meetings and
45	471	copies of the minutes will be filed in the Trial Master File; they will be shared with
46 47 48 49	472	relevant stakeholders as appropriate.
	473	
50 51	474	Patient and public involvement
51 52 53 54	475	Patient and public involvement was actively sought throughout the planning and
	476	design of this trial and continues to form a key part of the trial as it progresses. The
55 56	477	patient and public involvement and engagement (PPIE) group assisted in the
57	478	development of all participant materials and provided valuable insight into the
50 59	479	wording of participant information and acceptability of the proposed intervention. The

PPIE group will be updated as the trial progresses and a further focus group will be held to advise on the interview schedule and wording for the qualitative sub-study. The group will also be invited to aid in the development of summarising key findings for dissemination to relevant patient groups.

Ethics and dissemination

This study has been approved by the Cambridge East Research Ethics Committee and is sponsored by MFT. Findings will be disseminated via publication in peer-reviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists. Anonymised data will be available upon formal request once the principal results of the study have been published. Planned modifications to the protocol will be approved by the research ethics committee before they are adopted into the study. An audit trail of ethical amendments and documentation will allow monitoring by the research team and external regulatory bodies.

This is the first study to assess the feasibility and safety of an ILED in GDM as compared to best NHS care. Given the increasing incidence of GDM and associated health risks this research is both pertinent and important. The study is not powered to show differences between ILED and best NHS care, however the planned quantitative and qualitative assessments will inform the feasibility of the programme and a future definitive trial.

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3	516		
4 5 6 7 8	517		
	518		
	519	Full	References
9 10	520		
$\begin{array}{c} 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 56\\ 57\\ 58\\ 59\\ 60\\ \end{array}$	521 522 523	1.	The British Diabetic Association. Diabetes UK. [cited 2019 Nov 27]. What is gestational diabetes? Available from: https://www.diabetes.org.uk/diabetes-the-basics/gestational-diabetes
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30 31	647		
32 33	648	Autl	hors' contributions
34 35	649	Mich	nelle Harvie, Basil Issa and Elizabeth Dapre designed the study, wrote the
36	650	prote	ocol and secured funding. Brian McMillan designed and worded the qualitative
37 38	651	sub-	study Ting-Li Su developed the statistical analysis plan. Fahmy Hanna reviewed
39 40	652	and	advised on overall study design. Andrea Pilkington provided expert obstetric
41	652	anid	ance for the protocol design. Avni Vivas, Cheryl Lombardelli and Michelle Harvie
42 43	055	guiu	ducted dictotic reviews. Wembe Mubits beloed with recruitment and review of
44 45	054	CONC	in and a low of Votes and Degionalia France ware near and it is for any is at
46	655	parti	icipants. James Yates and Benjamin Evans were responsible for project
47 48	656	man	agement and data reporting. Sarah Mackie coordinated the clinical trial.
49	657	Eliza	abeth Dapre drafted the manuscript for publication, with input from Michelle
50 51	658	Har∖	vie, Basil Issa, Brian McMillan and Ting-Li Su. All authors have proofed and
52	659	cheo	cked the manuscript.
53 54 55	660		
56 57	661		
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8 9	667	the recruitment and follow up of participants throughout the trial.
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20	674	
22 23	675	Competing interests statement.
24 25	676	Michelle Harvie has co-authored three self-help books for the public to follow
26 27	677	intermittent diets. All author proceeds are paid directly to the charity Prevent Breast
28	678	Cancer (registered charity number 1109839) to fund breast cancer research.
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13 14	704	Appendix
15 16	705	1.0 Patient Information Sheet (supplementary document 1)
17	706	
18 19	707	2.0 Consent Form (supplementary document 2)
20 21	708	
22	709	3.0 Self-monitoring schedule for capillary glucose and ketone monitoring
23 24	710	(supplementary document 3)
25 26	711	
27 28	712	4.0 Intermittent Low Energy Diet Day Example (supplementary document 4)
29	713	
30 31	714	5.0 Medical Management Protocols (supplementary document 5)
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34 35	716	6.0 End of Study Questionnaire (supplementary document 6)
36	717	
37 38	718	
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46 47	723	 <image 1=""/>: Figure 1: Inclusion and exclusion criteria
48 49	724	 <image 2=""/>: Figure 2: Participant flow through trial
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inc	lusion Criteria			
AA A A	 > Pregnant women ≥18 years > BMI of ≥27.5kg/m2 or a BMI ≥25 kg/m² in high risk minority ethnic group (i.e. South Asian, Black African, African Caribbean) and <50 kg/m2 at booking appointment (8-12 weeks' gestation) > Newly diagnosed GDM according to local diagnostic criteria (fasting glucose ≥5.3mmol/l and/or 2-hour postprandial glucose ≥8.5mmol/l in a 75g OGTT) scheduled to receive first line diet and physical activity (best NHS care) > 24-30 weeks' pregnant at screening appointment 			
Ex	clusion Criteria			
AA AAA	Pregestational type 1 or type 2 diabetes. Fasting glucose of ≥7 or 2-hour postprandial of ≥11 on OGTT (immediate intervention with medication would be required in this group of women) Current multiple pregnancy Maturity Onset Diabetes of the Young (MODY) Significant comorbid disease that in PI's opinion would preclude participation in the study e.g. chronic kidney disease, significant cardiac disease, significant history of disordered eating or			

Figure 1: Inclusion and exclusion criteria

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Gestation (weeks)	~24-30	~24-30	~30-34	~32-36	~34-38	~36-40	delivery	11-13 post- partum
Eligibility confirmed	x							
Informed consent	x							
Randomisation	x							
Tailored dietitian review (face to face or remote)	x	x	x	x	x	x		x
Height	x							
Weight ^	x	x	x	x	х	x	х	x
Blood Pressure ^	x	x	x	x	х	х	x	x
Fasting blood sample *	x				x			x
Questionnaires #	x		x		x			x
4-day food diary		x			x			x
Foetal growth scan	x		x		x			
Review of glucose and ketone measurements		x	x	x	x	x		
Neonatal measurements §							x	
Oral glucose tolerance test								x
Exit interview / end of study questionnaires								x
Invitation to optional qualitative sub-study \$								x
A Frequency of assess Fasting bloods: urea hydroxybutyrate, free # Questionnaires: Wo Activity Questionnaire § Neonatal measuren § Sub-study involves :	sment will be a and electro fatty acids, orld Health O e (short form nents include semi-structu	e 2-4 weekly o olytes, liver fui full blood cou- inganisation Q n), UK Diabete e gestational red interview:	depending on nction tests, b mt, fasting glu (uality of Life es and Diet Qu age at deliver s exploring th	whether app cone profile, I ucose, insulin (brief version sestionnaire ry, mode of de noughts and e	ointment is fa ipids, thyroid), 36-Item Sh elivery, and ne xperiences of	ice-to-face or function tests ort Form Surv conatal weigh the trial	virtual due to s, HbA1c, beta rey, Internatio	o COVID-19 I ⁻ Inal Physical

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NHS Foundation Trust

Consultant Endocrinologist – Dr. Basil Issa Research Dietitian – Dr. Michelle Harvie Email: mft.middas.gdm@nhs.net Tel: 07815987910



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MIDDAS-GDM

<u>Manchester</u> Intermittent <u>Diet</u> in Gestational <u>D</u>iabetes <u>A</u>cceptability <u>S</u>tudy

Participant information sheet

We would like to invite you to take part in a research study that is testing two different diet programmes which aim to help people with gestational diabetes control their blood sugars.

If you decide to take part:

- You will be assigned to one of two diet programmes for the duration of your pregnancy. One involves following the standard NHS healthy diet recommendations for pregnancy, and the other follows the standard NHS healthy diet for 5 days/week plus two nonconsecutive calorie restricted days of 1,000 kcal per week (both groups will be encouraged to be physically active).
- You will be asked to attend your routine appointments at Wythenshawe or St Marys Hospital and will have fortnightly appointments until delivery of your baby (some appointments may be virtual depending on COVID-19 restrictions). You will be asked to attend the hospital for a blood test 12 weeks after having your baby.
- You will be supported by a diabetes specialist dietitian, midwife, consultant endocrinologist, and your obstetric team throughout the study to help manage your pregnancy and blood glucose safely.
- Throughout the study you will be asked to monitor your food intake via a smartphone/tablet app, or on paper if you prefer, and you will receive feedback on this during your dietary reviews. Comprehensive dietary advice and recipes will be provided.
- Throughout the study you will be asked to monitor your blood sugar using a blood sugar meter four times a day, and you will also be asked to monitor your ketone levels two times on two days of the week (ketones indicate how well your body is using sugar or fat as an energy source). You will be taught how to check your blood sugar and ketone levels.
- If you would like to take part, or you have any questions, then please contact mft.middas.gdm@nhs.uk





This study is being carried out by a team of trained dietitians, doctors, nurses, midwives and researchers under the supervision of Dr. Basil Issa and Dr. Michelle Harvie at Wythenshawe and St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what taking part would involve for you. Please take your time to read the following information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.

Please ring the research team at the number at the top of the first page, or e-mail mft.middas.gdm@nhs.net if there is anything that is not clear, or if you would like more information. You can attend an information session about the diets and the study before agreeing to take part if you would like to.

Your participation in the study is entirely voluntary; you do not have to take part if you do not want to and you can opt out of the study at any time without giving a reason. Thank you for reading this information. We hope this research will be of interest to you.

Why are we doing this research?

Around 1 in 8 pregnant women can develop gestational diabetes. This condition causes risks to mother and baby from high blood sugar, high blood pressure, induced labours, caesareansections, and larger babies. Women often need medication to control blood sugar despite following recommended NHS healthy eating plans for pregnancy. Intermittent low-calorie diets (two non-consecutive days over the course of the week) improve blood sugar control and reduce the need for medication in patients with type 2 diabetes. We want to find out whether intermittent low-calorie diets might also improve blood sugar control in gestational diabetes and reduce the need for medication as it is a similar condition to type 2 diabetes.

What is the purpose of this research?

This study aims to assess the acceptability (to you) and safety of an intermittent low-calorie diet compared to the usual recommended NHS healthy eating and lifestyle plan for gestational diabetes. A computer system will randomly allocate you to one of the two diets. We want to find out which diet is most acceptable to women, whether there is any difference in the two diets' effect on blood sugar control, and any side effects experienced by women. The findings of this study will inform a larger study which will be designed to more closely compare the effect of the two diets on blood sugar control in women with gestational diabetes.

Why have I been asked to take part?

You have been invited to take part in this study because you have been diagnosed with gestational diabetes. We hope to recruit around 48 people to take part in this study.

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What happens if you agree to take part?

If you agree to take part you will be randomly allocated via a computer system to one of two diet and lifestyle programmes for the remaining weeks of your pregnancy.

Best NHS Care Healthy Diet programme

You will receive personalised advice from a specialist dietician. Recommendations will include increased fruit/vegetable intake, low glycaemic index starchy foods (i.e starchy foods which are slowly absorbed and take a while to raise your blood sugar level), reducing refined sugar, and having regular mealtimes. You will be advised how to design your diet to include the right amount of protein, fats, carbohydrates, and fibre, and will be given meal plans and recipes. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week.

Intermittent Low-Calorie Diet programme

If you are allocated to this group you will receive personalised advice to follow a low-calorie diet of 1,000 kcal on two non-consecutive days of the week and the NHS healthy diet on the other five days of the week. The 1,000 kcal days include a set number of portions of protein, carbohydrates and fat foods, fruits, vegetables and dairy/dairy alternatives typically including \sim 210g (7 oz) of lean protein foods and 3-4 portions of wholegrain carbohydrates, 5 portions of vegetables, 2 of fruit, and 3 of dairy or dairy alternatives and a small amount of healthy fat. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week.

Monitoring

You will have all your usual routine antenatal appointments including checks on your weight, blood pressure, blood tests and ultrasound scans. Extra blood tests will be done as part of the study, and these will be added on to samples taken during your routine blood tests.

You will be asked to monitor your blood sugar at home four times a day until your baby is born which is usual care in the clinic. In addition, you will be asked to record ketone levels on two days of the week (you will be taught how to do this using a finger prick machine). The results will be recorded when you attend clinic.

When babies are born to mothers with gestational diabetes it is normal that their birth weight is recorded and that their blood sugar is monitored for 12 hours following delivery; these results will be recorded by the research team.

You will be asked to attend an additional glucose tolerance test at the hospital 12 weeks after delivery to assess whether you have any residual diabetes (95% of women do not) and also to assess how sensitive your body is to insulin (an important risk factor for the development of diabetes in the future). You will be asked to attend at 9:00am having fasted (no food or drink apart from water) from midnight. A blood sample (around 10 mL/2 teaspoons) will be taken for glucose and insulin and you will be asked to drink a sugary drink with 75 grams of glucose. A further blood sample will be taken after 2 hours for glucose and insulin. You will need to

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remain in hospital during this time. The reason for this is to help us to understand whether there could be any difference in the body's ability to process sugar between the two diet groups, and also to find out whether any women still have signs of diabetes after pregnancy.

Any blood samples taken as part of the study will be identifiable only using your study identification number and will have none of your personal details. Part of the sample will be sent for immediate analysis and any remaining will be stored securely, accessible only by the research team. At the end of the study any left over samples will be disposed of in accordance with the Human Tissue Act (2004).

You will be asked to record your food intake via the Libro smartphone/tablet app or in a paper diary for four days once a month throughout the study. You will also be asked to complete three questionnaires to assess your wellbeing and level of physical activity in these weeks, and a final end of study questionnaire at the final appointment.

Ongoing support from a specialist team of healthcare professionals

Your specialist team includes a Consultant Endocrinologist, Consultant Obstetrician, diabetes specialist dietitian, midwives, and a GP trainee with a special interest in women's health. The specialist team work closely with the usual obstetric teams involved in your care. Reviews with the team will be either face to face when you attend clinic or remotely using video calls.

Mobile Applications and Glucose Meters

You will be given the option of using a smartphone application called 'Libro' to record your dietary intake during the study. We will ask you to record 4 days of food and drink intake once a month across the study. Your diaries will be viewed by your allocated dietitian who will provide personalised dietary feedback via the app. You are also free to record more days of your diet should you wish, which some people find helpful. If you do not want to use the mobile app you can use paper instead. You will be supported to set up and use the Nutritics Libro App at your appointments. You do not have to use the application to be part of the study.

Your blood sugar will be monitored using a glucose monitoring device which checks your blood sugar using a 'fingerprick' blood test. You will be shown how to do this yourself. With your permission the research team will make a note of your glucose readings at every visit, either by checking your glucose monitoring device, or by uploading your glucose meter readings onto the computer if you are using a mobile application.

Intermittent low-ene	ergy diet monitoring	Best NHS care monitoring		
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose	
Fasting before breakfast the morning after each	Fasting (morning)	Fasting before breakfast on 2 non-consecutive	Fasting (morning)	
of the low-calorie days		days/weeks		
	1hr post breakfast		1hr post breakfast	
	1hr post lunch		1hr post lunch	

The self-monitoring schedule is as follows:

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1 hour post evening	1hr post dinner	1 hour post evening	1hr post dinner
meal on each of the low-		meal on 2 non-	
calorie days		consecutive days/week	

What should I do if my blood glucose or ketones are out of range?

Low Blood Sugar

It is unlikely that your blood sugar levels will drop too low as a result of being on the intermittent low calorie or the NHS standard diets. You are advised to take 15-20g of 'rapid acting' carbohydrate if your blood glucose is <4 mmol/L). Examples include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). You will need to repeat the treatment every 15 minutes until your blood glucose is ≥4 mmol/l.

The following table highlights when you need to consider an additional slower acting carbohvdrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g (eg half of one of the items below)
More than 2 hours before the next meal	15-20g (eg slice of toast, piece of fruit, small
	bowl of cereal, glass of milk)

Raised Ketones

It is unlikely that your ketone levels will rise significantly as a result of being on the intermittent low calorie or NHS standard diets.

If your ketone levels are \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If your ketone level has improved (<1.0mmol/L), no further action is required. •
- If your ketone level has increased or remains the same, repeat your ketone level after 2 hours.
- If your ketone level is persistently increased, consume 40g carbohydrates (eg one bagel, bowl of cereal and a banana, small jacket potato), and repeat in 2 hours.
- Continue to do this until your ketone levels are <1.0mmol/L.

Make Immediate Contact with the research team if:

Blood glucose	 Your blood glucose is <3.0 mmol/l or you have symptoms requiring medical attention which are thought to be due to low blood glucose, Your fasting blood glucose is >5.2 mmol/L on more than a quarter of your measurements on two days in a row, Your 1 hour post-meal blood glucose is >7.7 mmol/L on more than a quarter of your guarter of your measurements on two days in a row. 		
	quarter of your measurements on two days in a row		
MIDDAS-GDM IRAS 302762 Participant Information Sheet Version 4.0 22/09/2023			
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NHS Foundation Trust Ketones

Your blood ketones are >1.0 mmol/L

Will I need medications?

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If your blood sugars are found to be high despite following the recommended diet and lifestyle programmes you may be advised to start medication to help control your blood sugar. You will be advised on changes to your medications by a diabetes specialist nurse/diabetes midwife and also a Consultant Endocrinologist if required. This is usual practice regardless of whether you are taking part in the study.

What care will I receive after the study has stopped?

At the end of the study, you will be provided appropriate ongoing dietary advice from the study dietitian following your final glucose tolerance test to follow the NHS healthy eating and lifestyle plan. You will receive routine postnatal care from your GP, hospital team, and dietitian if required. You will be advised to see your GP for an annual blood test to check your blood sugar levels (this is routine care for women with gestational diabetes). Approximately 5% of women with gestational diabetes have residual diabetes after delivery. This will be identified from your glucose tolerance test/HbA1c; if this is the case you and your GP will be informed. Your GP will take over the management of your diabetes as per routine care outside the study.

Interview sub study

Women in this study may be invited to take part in an interview at the end of the study . You will be asked about your views and experiences on trying to follow your allocated diet programme. This interview can be arranged at a time that suits you, either at Wythenshawe or St Marys Hospital, at your home, or over the telephone. There is no obligation to take part in this interview study.

Frequently asked questions

Do I have to take part?

No, you do not have to take part if you do not wish to and your decision will not affect any standard of care you receive at Wythenshawe or St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

What happens if I change my mind?

It is OK if you agree to take part in the study but later change your mind. You do not need to give a reason and it will not affect the standard of care you receive. The study team may also choose to withdraw you if it is necessary for your health or safety due to unexpected findings during the study. If you decide to withdraw from the study, or the study is stopped for any reason, you will be asked whether or not you are happy for us to keep the data that may have already been collected. If you do withdraw from the study you will continue to be cared for by your usual specialist diabetes and obstetric teams for the duration of your pregnancy. You will still have the option of completing the end of study questionnaire and/or interview to provide feedback; this is very useful for the research team to help us understand potential reasons you may have chosen to withdraw from the study.

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You will also have the option that if you withdraw, researchers may still collect relevant information about your pregnancy and/or gestational diabetes from your medical records within the 18-month study duration. This will be an option on the consent form.

Are there any benefits from taking part?

You will receive frequent personalised advice and support to follow two diet and lifestyle programmes which may help to control your blood sugar levels throughout your pregnancy. The information gained from this study will also help inform the future NHS care of patients with gestational diabetes.

Are there any risks from taking part?

Research has found that diets consisting of two low-calorie days a week are very low risk. Pregnant women will develop slightly higher levels of ketones when following low calorie diets than women who are not pregnant. Ketones are produced naturally by the body when the body uses fat stores for energy (i.e. when we follow a low calorie diet or haven't eaten enough because we are ill).

Some research suggests that very high levels of ketones throughout pregnancy may cause a higher risk of babies being slightly smaller than average. It is very unlikely that you will develop high levels of ketones by following this diet. You will be provided with a ketone meter, and you will be asked to check your ketone levels after an evening meal on your low-calorie day, and the following morning, to make sure that your ketone levels are normal.

On your low-calorie days you may feel slightly more hungry, or you may experience other effects such as increased nausea, light headedness, or tiredness. It is important that you eat regularly throughout the day to reduce the risk of this happening. You will be asked to report any side effects of following the diet to the team at each appointment.

What happens if my baby or I become unwell during the study?

The safety of you and your baby are of utmost importance and remain our priority. In the instance that either of you become unwell your case will be reviewed by our specialist team and your suitability for continuing in the trial will be decided. Although it remains exceptionally rare, were you to experience the unexpected loss of your baby you will be withdrawn from the trial and supported by the dedicated specialist bereavement team at the hospital. Any information which has been collected as part of the trial will be stored securely and once we have finished the study we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What will happen to blood samples which are taken?

Some blood samples taken as part of the study will be sent to the laboratory immediately for analysis and any remaining will be stored securely for the duration of the study. Only your 'study ID' will be used – the samples will have none of your personal details on them. At the end of the study any remaining samples will be disposed of in accordance with the Human Tissue Act (2004).



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What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (**Dr. Basil Issa** or **Dr. Michelle Harvie – via the study office – via michelle.harvie@manchester.ac.uk or telephone 0161 291 4410**). If you remain unhappy and wish to complain formally, you can do so through the NHS complaints procedure. Details can be obtained from the NHS Patient and Liaison Service (PALS) on Tel: 0161 276 8686 or contact the team by email pals@mft.nhs.uk.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme. If something did go wrong and you were harmed or suffered deterioration in your health as a result of taking part in this study then you may have grounds for legal action or compensation.

Additional information about the study

Will my lifestyle be affected if I take part?

An essential aspect of this study is a change to your diet and physical activity patterns with support from a specialist team of healthcare professionals.

Payments

We are able to offer free parking at Wythenshawe/St Marys Hospitals for study visits and offer reimbursement for reasonable travel expenses (car, bus or tram) linked to visits for this study. There are no other payments for taking part.

Will my details be kept confidential?

Yes. The study team and any associated regulatory authorities follow strict ethical and legal guidance regarding participant confidentiality. Any information we have about you will be handled in confidence and will only be used for the purposes of this study. All data recorded will be coded and your name will remain anonymous.

During the study we will inform your GP via letter of your participation in the study and your ongoing results, including your weight, blood tests, any abnormal findings and any recommendations for treatment.

If you join the study, some relevant parts of your medical records may be looked at by authorised personnel at Wythenshawe or St Marys hospitals prior to starting the study. These records may also be looked at by an independent auditing body and regulatory authorities to check that the study is being carried out correctly. We will only access parts of your medical records that are relevant to this research and all information accessed will be kept strictly confidential.

How will we use information about you?

We will need to use information from you and from your medical records for this research project.

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- **NHS Foundation Trust**
 - This information will include the following:
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- · NHS number
- · Name
- Contact details
- Medical History including test results
- Demographic details

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Other researchers from outside the Trust may ask to see this data for the purposes of furthering their research. We will only share this upon written request to the Trust. The external researchers will be asked to sign a Confidentiality Agreement before any data is shared.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health during pregnancy from your hospital records. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
- by sending an email to mft.middas.gdm@nhs.net or
- by ringing us on **07815987910**

How will my details be used to access the Mobile Applications?

None of your personal details (other than email from which an application is downloaded) will be needed to access the nutritics mobile applications. You can opt to have a 'dummy' e-mail and password under a pseudonym (fake name). Only the research team will know the dummy e-mail address you have been assigned to, in order to be able to review your data. The application will not contain your identifiable data. If you choose to use a mobile application to monitor your blood sugar levels the relevant terms of service for the app and the app developers privacy policy will apply. It will be your responsibility to read and understand these prior to download.

Will my insurance be affected if I take part in this study?

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It is unlikely that your insurance premiums will be affected by participation in this study as the

study has the potential to improve your diabetic control and reduce your risk of ill health.

However, if you are at all concerned, then we advise that you contact your insurers and seek

Research in the NHS is looked at by an independent group of people called a Research Ethics

Committee (REC). The REC is made up of experts, non-experts and members of the general

public. Together they review research applications to ensure your safety, rights, wellbeing and

dignity are protected at all times. This study has been reviewed and given favourable opinion

It is intended that the results of this study will be presented at conferences and published in

medical journals so that we can explain to the medical community what our research results

have shown. To do this our study information is double-checked by other professionals in

research and healthcare. There is a possibility that the study and its results may be publicised

for example on radio, television, magazines, books and websites. You will not be identified

in any publicity, reports or publication arising from this study. If you would like a general

summary of the results of the study you can select this on the consent form or please contact



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Who is organising and funding the research?

What will happen to the study results?

Researchers from Wythenshawe hospital have designed this study and will be carrying out this research. This study has been funded by the National Institute of Health and Research.

Further information and contact details

Manchester University

Who has reviewed this study?

expert advice before agreeing to participate.

NHS Foundation Trust

by REC.

the research team.

For further information about this study, please contact mft.middas.gdm@nhs.net or 07815987910.

> Thank you for taking the time to read this information sheet. We hope it has been of interest to you.







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Please initial

box



Consultant Endocrinologist – Dr. Basil Issa Tel: 0161 291 7070 Research Dietitian – Dr. Michelle Harvie Tel: 07815987910 Email: <u>mft.middas.gdm@nhs.net</u>

Manchester University

NHS Foundation Trust

1st Floor Education and Research Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>

Participant Informed Consent Form

Participant Identification Number:

- 1. I confirm that I have read and understand the participant information sheet (version) for the above study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Manchester University NHS Foundation Trust and regulatory authorities, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records.
- 4. I consent to the collection of blood samples to be collected as described in the participant information sheet.
- 5. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.
- 6. I agree that my blood sugar readings can be recorded by the study team.
- 7. I agree to my GP being informed of my participation in this study and changes to my weight, body measurements, blood results, questionnaire results and medications as required
- 8. I understand that the information I provide to mobile applications as described in the Patient Information Sheet will be treated in line with the relevant terms of service and the app developers privacy policy at the time of downloading the application.

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9. I have informed the study team of any health issues, including those which may affect my ability to follow the diet, and I will inform the study team of any unusual symptoms that occur during the diet. I will inform the study team of changes to my health status during the study.

- 10. I have informed the study team of any health issues, including those which may affect my ability to exercise, and I will inform the study team of changes to my health status during the study.
- 11. I consent to the storage of personal information (including electronic) for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.
- 12. I agree to take part in the above study.
- 13. I agree that relevant information about my pregnancy and/or gestational diabetes can be obtained from my medical records within the 18-month study duration if I withdraw from the study early.
- 14. I am aware that my non-identifiable trial data may be shared with other researchers for the purposes of research.

Optional (delete as appropriate)

- 15. I agree to be approached to take part in sub-study 1 (interview study), and understand that I will be approached to take part in the sub-study regardless of whether I withdraw from the main study YES/NO 16. I would like to receive a summary of the final study results YES/NO
- 17. I agree to be contacted regarding future research opportunities YES/NO

My preferred contact (please tick and include email if preferred)

Do not contact

Post

Email

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Signatures		
Name of participant	Date	Signature
Name of person taking consent	Date	Signature
When completed: 1 for participa	nt; 1 for patient file; 1 for m file	nedical notes;; 1 (original) for site

Self-monitoring schedule for capillary glucose and ketone monitoring

ILE	D	Best Nł	IS Care
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)
the morning after each of		on 2 non-consecutive	
the low-energy days		days / week	
1 hour post evening meal	1hr post breakfast	1 hour post evening	1hr post breakfast
on each of the low-energy		meal on 2 non-	
days		consecutive days / week	
	1hr post lunch		1hr post lunch
	1hr post dinner		1hr post dinner

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Example of 1 day meal plan for Diet Day

The diet days aim to limit the calories to 1000 calories per day. You are aiming to include 2 (not consecutive) diet days each week. The other 5 days, follow the Mediterranean diet as described earlier. To keep the calories to 1000, the diet day will look like this:

Mixed diet		Vegetarian/ vegan diet
4	Carbohydrate portions	3
6	Protein portions	7
5	Vegetable portions	5
2	Fruit portions	2
3	Dairy portions	3
	Fat portions	1

Below are some examples of meals that can be used to help you follow a 1000 calorie diet... There are options for a mixed diet or vegan or vegetarian options, if you feel you wanted to try meat free days. Filling up on vegetables will make you feel less hungry

Mixed diet options

Breakfast	Portion	Dairy	Protein	Carb	Veg	Fruit	Fat
Grilled lean bacon	1 rasher	0	1	0	0	0	0
Grilled tomatoes	7 cherry tomatoes	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning	Ť						
Diet or natural yogurt	1 small carton	1	0	0	0	0	0
Lunch							
Wholegrain bread	2 medium slices	0	0	2	0	0	0
Tuna	⅓ of a 120g can	0	1	0	0	0	0
Green salad	Cereal bowl full / 80 g with oil-free dressing	0	0	0	1	0	0
Satsumas	2	0	0	0	0	1	0
Mid afternoon							
Low fat cheese	30g / match box size	1	0	0	0	0	0
Apple slices	I medium apple	0	0	0	0	1	0
Tea/ coffee		0	0	0	0	0	0
Evening							
Vegetable rice	4 tablespoons cooked rice 160g of mix vegetables	0	0	2	2	0	0
Chicken curry	90g /average chicken breast (no skin) & ½ can tomatoes, 1 desertspoon oil	0	3	0	1	0	1
Bedtime							
Low fat houmous	1 level tablespoon	0	1	0	0	0	0
Pepper sticks	1/2 red pepper	0	0	0	1	0	0
Milk	1 small glass	1	0	0	0	0	0
Total portions	a day	3 portions	6 portions	4 portions	5 portions	2 portions	1 portio

Vegetarian option

Breakfast		Dairy	Protein	Carb	Veg	Fruit	Fat
Egg	2 poached	0	2	0	0	0	0
Mushrooms	2 cupped handfuls / 80g	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Cheddar cheese	1 match box size / 30g	1	0	0	0	0	0
Cucumber	Sliced handful	0	0	0	1	0	0
Lunch							
Baked beans	2 tablespoons	0	1	0	0	0	0
Seeded bread toasted	1 medium sliced	0	0	1	0	0	0
Blueberries	1 handful	0	0	0	0	1	0
Mid afternoon							
Meat free ham	2 slice small	0	1	0	0	0	0
Pepper	1/2 sliced	0	0	0	1	0	0
Avocado	1/4	0	0	0	0	0	1
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening	Ŭ						
Vegetarian sausage casserole Jacket potato (100g)	1 grilled sausage 2 cereal bowls vegetables 1 ½ egg sized (100 g)	0	2	1	2	0	0
Bedtime							
Pear	1 medium	0	0	0	0	1	0
Low fat cream cheese	1 tablespoon	1	0	0	0	0	0
Whole wheat cracker	2 biscuits	0	0	1	0	0	0
Milk	1 small glass	1	1	0	0	0	0
Total portions	s a day	3 portions	7 portions	3 portions	5 portions	2 portions	1 portions

Vegan options

Breakfast		Dairy equivalent	Protein	Carb	Veg	Fruit	Fat
Branflakes	3 tablespoons	0	0	1	0	0	0
Milk- sova	200 ml	1	0	0	0	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Soya yogurt	3 tablespoons	1	0	0	0	0	0
Lunch							
Kidney bean & Vegetable chilli Wholemeal pitta	3 tablespoons of beans 60g with 1 cereal bowl mixed vegetables & 1/2 can chopped tomatoes 1/2 pitta	0	2	1	2	0	0
Banana	1 medium	0	0	0	0	1	0
Mid		_			-		
afternoon							
Low fat hummus	2 level tablespoon	0	2	0	0	0	0
1 carrot	I medium carrot (80g)	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Quinoa	2 tablespoon cooked	0	0	21	0	0	0
Tofu	4 matchbox	0	2	0	0	0	0
Mixed salad with edamame beans	2 x Cereal bowl full with oil free dressing & 1 tablespoons of edamame	0	1	0	2	0	0
Bedtime							
Peanut butter	1 heaped teaspoon	0	0	0	0	0	1
Apple	1 medium sliced	0	0	0	0	1	0
Milk	1 small glass	1	0	0	0	0	0
Total portion	s a day	3 portions	7	2	5	2	1
			portions	portions	portions	portions	portions

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59 60 To help with estimation of portions the following tables outline weight and measures of the different food groups. Where possible household measures are given to make things a little easier. Use these to help you plan your 2 days in the week of 1000 calories.

Carbohydrate 4 portions - mixed diet 3 portions - vegan/vegetarian	Equal to
Wholewheat or oat breakfast cereal, e.g. wholewheat biscuit, malted wholewheat squares, Grapenuts, bran flakes, fruit & fibre	24g or 3 tablespoons or 1 whole wheat biscuit
Porridge oats or no-added sugar muesli	20g or 1 heaped tablespoon
Wholegrain, wholemeal, rye, granary bread	36g or medium slice of bread (other than rye), 1½ slices of rye, or ½ roll
Wholemeal or multigrain pitta bread or tortilla wrap, chapatti made without fat	60g or 1x 8" tortilla or 1 standard pitta or small thin chapatti
Rye crispbread, crackers, oak cakes	22g or 2 crispbreads/ 2 oatcakes
Wholegrain rice cake	16g or 2 rice cakes
Wholewheat pasta or rice - cooked amount	1 tablespoon uncooked 2 tablespoons cooked
Cous cous, Duigar wheat, Quinoa, r ear baney	30g- raw weight or 60g cooked
Lasagne (wholemeal if possible)	20g raw weight or 1 large sheet or 1½ smaller sheets
Noodles (wholemeal if possible)	25g raw weight or ½ block/nest
Baked or boiled potato (in skin), cassava, sweet potato	1½ egg sized potatoes or 100g raw weight
Wholemeal pizza base (topping is from other food groups)	35g or $^{1}/_{6}$ of thin 10" pizza base
Unsweetened popcorn	20g or 2 handfuls

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Protein 6 portions – mixed diet 7 portions – vegan/vegetarian	Equal to
Fresh or smoked white fish (e.g. haddock or cod)	60g or 2oz 2 fish finger size
Seafood, e.g. prawns, mussels, crab	45g or 1½oz
Canned tuna or salmon in brine or spring water	45g or 1½oz ⅓ standard tin (120g)
Oily fish (fresh or tinned in tomato sauce or olive oil - drained), e.g. mackerel, sardines, salmon, fresh tuna, kippers, smoked salmon or trout	30g or 1oz or ¼ standard tin (120g) or ¼ fillet of salmon
Chicken, turkey, duck, pheasant (cooked without skin) Lean beef, pork, lamb, rabbit, venison, offal (fat removed) Quorn fillets, steak, mince or pieces Vegetarian mince frozen	30g or 1oz or 1 slice size of playing card
Lean grilled bacon Quorn ham	25g or ¾oz or 1 rasher
Lean ham Quorn bacon rashers (not slices)	30g or 1oz or 1 medium, 2 small or 4 wafer thin slices
Eggs	60 g or 2 oz or 1 egg
Tofu	50g or $1^2/_3$ oz or Size of 2 match boxes
Tempeh	25 g or 1 oz or Size of 1 match box
Baked beans (reduced sugar)	60 g or 2 oz or 2 tablespoons
Lentils, chickpeas and kidney beans, mung beans, black (eye beans, puy lentils, toor dahl, urad dahl, Raw weight	20g or ⅔ oz or 1 tablespoon raw
Cooked or tinned weight	65g or 2oz or 1 ¹ / ₂ tablespoons cooked /tinned or 1 cupped handful
Soya beans (frozen or cooked) or edamame beans	30g or 1oz or 1 tablespoon
Vegetarian sausage	25g or ¾ oz or ½ sausage
Textured vegetable protein (TVP)	10g or ⅓ oz uncooked or 1 heaped tablespoon uncooked
Low fat hummus	30g or 1oz or 1 level tablespoon

Cottage cheese

Cream cheese (light or extra light)

Bavarian smoked, feta, ricotta, mozzarella, reduced fat

halloumi, paneer made from semi-skimmed milk

Lower fat hard cheeses e.g.:

Reduced fat cheddar, Edam,

Vegetables – min 5 portions 1 portion = 80g or 2⅔oz	1 portion is equal to
Asparagus, Aubergines, Broccoli, Brussel sprouts, Carrots, Cabbage, Cauliflower, Chinese leaves, Courgettes, Cucumber, Curly kale, Green beans, Lettuce (mixed leaves), Mange tout, Methi, Mushrooms, Okra, Pak choi, Peas, Sugar snap, Spinach, Spring greens cooked, Sweetcorn, Tomatoes, Watercress fresh	80g or 2 ² / ₃ oz or 2 spears of broccoli, 8 cauliflower florets. 3 heaped tablespoons of vegetables or large cereal bowl of salad.
Fruit - 2 portions. 1 portion = 80g or 22/30z (30g or 1oz dried fruits)	1 portion is equal to
Berries (e.g. blackberries, blueberries, redcurrants, raspberries, strawberries) Cherries or grapes	80g or 2⅔oz 1 handful
Grapefruit, guava and mango	80g or 2⅔oz or ½ a whole fruit
Large fruit (e.g. melon, pineapple, papaya)	80g or 2⅔oz or 1 medium slice
Medium fruits (e.g. apple, pear, nectarine, orange, peach, banana, pomegranate)	80g or 2⅔oz 1 fruit
Small fruit (e.g. fresh apricots, kiwi, clementine, passion fruit, plums)	80g or 2⅔oz or 2 fruits
Any stewed fruit—unsweetened or with calorie-free sweetener e.g. apple, rhubarb	80g or 2⅔oz or 3 tablespoons
Kumquats, lychees, physalis	5 fruits
Dried fruits (raisins, currants, apricots)	30g or 1oz or 1 tablespoon
Milk and dairy foods - 3 portions	Equal to
Milk (semi-skimmed or skimmed) Alternative 'milks' with added calcium, e.g. soya **	¹ ⁄₃ pint or 200ml or 1 small glass
Diet yoghurts, Low fat/fat-free Greek or Greek Style or natural yoghurts, fromage frais or plain soya yoghurt, high protein yogurt	120-150g or 4-5oz or 1 small pot or 3 tablespoons
Whole milk natural yogurt	80g or 1 ⅔ oz or 2 tablespoons
	75g or 11⁄20z or

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** we recommend soya milk as coconut, oat and almond milks are lower in protein and calcium

1/4 pot, 2 tablespoons

30g or 1oz or Matchbox size

No more than 180g or 6oz a

30g or 1oz or

1 tablespoon

week

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Equal to
8g or 1 teaspoon 1 dessertspoon of oil
7g or 1 dessertspoon
7g or 1 dessertspoon 3 walnut halves, 3 Brazil, 4 almonds, 8 peanuts, 10 cashews or pistachios
50g or 10 olives
15g or ½ oz or 1 tablespoon
11g or ⅓ oz or 1 heaped teaspoon
12 g or ⅓ oz or 2 heaped teaspoons
40g or 1⅓ oz or 1/4 of an average pear
40g or 1 ¹ / ₃ oz or 2 tablespoons

Medical Management Protocols

Hypoglycaemia

Participants will be advised to take 15-20g of rapid acting carbohydrate in the event of hypoglycaemia, (defined as blood glucose <4 mmol/L) which is anticipated to raise blood glucose by 3 mmol/L. Examples of rapid acting carbohydrate include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). Participants will be advised to repeat the treatment every 15 minutes until blood glucose is ≥4 mmol/l. The following table highlights when participants should consider taking additional follow-up slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g
More than 2 hours before the next meal	15-20g

Ketonaemia

Ketone levels ≥1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If ketone level has improved (<1.0mmol/L), no further action required.
- If ketone level has increased or remains the same, repeat ketone level after 2 hours.
- If ketone level is persistently increased, consume 40g carbohydrates and repeat in 2 hours.
- Continue to do this until ketone levels <1.0mmol/L.

If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed.

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Guidance for the introduction of diabetes medication (week 24-delivery)

Diabetes medication will be introduced according to the following protocol:

- If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated.
- If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l,
- and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence prandial fast acting insulin analogue (Humalog or Novorapid)
 2-4 units with the relevant meal. Uptitrate the dose by 2 units every 3 days aiming for a 1 hour postprandial glucose of ≤7 mmol/l.
- Medication adjustment will be made in accordance with the above guidance.

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MIDDAS-GDM End of Study Questionnaire

Thank you for taking part in the MIDDAS-GDM Study.

This is one of the first studies of its kind. We hope to learn as much as possible from this study, in particular the views of people who have taken part. We are inviting you to provide your views on different aspects of the study and following the diet, and how we can improve our programmes and research studies in future.

Please complete the following questions and return this questionnaire to the MIDDAS-GDM study team in the envelope provided. If there is anything else you would like to say about your experiences of the study, please use the section at the end. Your answers to the questions below will remain anonymous.

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			•••••	•••••					
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2. How sa	tisfied v	were you	with stu	idy overall	(recruit	ment,	appointin) : (0//0/
2. How sa	tisfied v	were you 3	4	5	6	ment, a	8	9 9): (cii ci 1
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2. How sa 1 Not at all satisfied Comments	2	3 Slig satis	4 htly sfied	5 Quit satisfi	6 e ed	7 s:	8 Very atisfied	9	1 Extre sati

3. You were asked to attend additional face to face appointments at the hospital by the study team (please fill in the number)

4. You were asked to attend additional virtual (i.e. video call or telephone)



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appointments by the study team (please fill in the number)	
5. How do you feel about the number of additional appointments you were asked to attend? (tick)	
□ I was happy with the number of appointments	
I would have preferred fewer face to face appointments	
I would have preferred more face to face appointments	
I would have preferred fewer virtual appointments	
I would have preferred more virtual appointments	
Comments:	••
6. How do you feel about virtual (i.e. video call or telephone) appointments?	
□ I prefer virtual appointments to face to face appointments (please explain why below)	
□ I prefer face to face appointments to virtual appointments (please explain why below)	
Comments:	••
	••
	•
Diet	
7 Which diet were you asked to follow? (please tick)	
7. Which diet were you asked to follow: (please lick)	
Best NHS Care (i.e. increased fruit/vegetable intake, low-GI foods, reduction in free sugar	s,
regular meals)	
□ Intermittent low energy diet (5 days of the best NHS care diet plus 2 non-consecutive days of	
1000 kcal each week)	
8. Was the diet easy to follow?	
IZ345676910Not at allSlightlyModeratelyVeryExtremely	



Comments:				
9. Did you enjoy	following the diet	plan?	7 0	0 10
Not at all	3 4 Slightly	b 6 Moderately	ہ Very	9 10 Extreme
Comments:				
10. Would you ma	ake any changes to	the written infor	mation (i.e. diet b	ooklets, recipes)
were given on	how to follow the	diet plan?	-	
□ Yes				
□ No				
If ves what chang	es would vou make	2		
in yes, what onding				
Comments:				
			2	••••••
11. How was you	first appointment	with the distition	2 (tick all that apply	40
11. How was your	r first appointment	with the dietitian	? (tick all that apply	/)?
11. How was your	r first appointment of information I rece	with the dietitian eived was OK	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece	with the dietitian eived was OK eived was too little	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece of information I rece	with the dietitian eived was OK eived was too little eived was too muc	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u> □ I was happy	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec	with the dietitian eived was OK eived was too little eived was too muc ceived	? (tick all that apply	/)?
 11. How was your □ The amount □ The amount □ The amount □ The amount □ I was happy □ The advice I 	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/)?
11. How was your The <u>amount</u> The <u>amount</u> The <u>amount</u> I was happy The <u>advice</u> I Comments:	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/)?

Page 54 of 78 **Manchester University**

	diatitian a			smanay 2			•	, .
	dietitian c	auring yo	ur pre	gnancy ?				
⊔ Yes								
□ No								
Comments:								
13. How use	ful was ye	our final a	appoir	ntment with the die	titian at 1	2 weeks	s post-c	delivery?
			••		_		•	
1 Not at all	2	3 Slightly	4 ′	5 6 Quite	7 Ver	8 Y	9	10 Extreme
Comments:			\sim					
			<u> </u>					
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14. Dia you i	leer conne		ercise	e whilst on the diet	i pian r			
1	2	3	4	5 6	7	8	0	10
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Not at all confident		Slightly confider	it	Quite confident	' Very confide	nt	9	Extremely confident
Not at all confident		Slightly confider	it	Quite confident	' Very confide	nt	9	Extremely confident
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Not at all confident Comments:		Slightly confider		Quite confident	' Very confide	nt		Extremely confident
Not at all confident Comments:		Slightly confider		Quite confident Additional suppor	' Very confide	nt		Extremely confident
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Not at all confident Comments:	ny of the f	Slightly confider	t have Ye s	Quite confident Additional suppor been useful & if so Preferred meth contact	very confide <u>t</u> how ofte	nt n?		Extremely confident
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				NHS Foundation Trus
Additional support from			Face to face / phone	
the doctors in the clinic				
More contact with other			Face to face / phone	
women in the study				
following the diets				
Other, please specify:				
		4		
16. Did you receive any si	uppor	t outs	ide of the study team help	o to keep you on track as you
progressed through th	ne stu	dy?		
🗆 No				
□ Yes				
If ves, what support did voi	ı recei	ve?		
in yoo, milat ouppoint and you	. 1000			
		•••••		
			<u>Record keeping</u>	
17. How did you find the	finge	r pric	k testing requirements or	n the study? (tick all those that
apply)				
Challenging but on the construction of the	ne who	ole <u>ac</u> ł	nievable	
□ Challenging and <u>not</u>	achiev	able		
Not challenging at all				
□ I felt it was <u>necessary</u>	<u>/</u> to te	st this	often to ensure my safety	
□ I felt it was <u>unnecess</u>	<u>ary</u> to	test th	nis often to ensure my safety	/
Comments:				
18 How did you find the	koton	o tost	ing requirements on the s	tudy? (tick all those that and
io. now ala you fina the	NELUII		ing requirements on the s	ing an mose mar appi
	I		i	
	ie who	bie <u>act</u>	nevable	
Challenging and not a	achiev	able		


2	NHS Foundation Trust
3 4	□ Not challenging at all
5 6	□ I felt it was <u>necessary</u> to test this often to ensure my safety
7	I felt it was <u>unnecessary</u> to test this often to ensure my safety
9	
10 11	Comments:
12 13 14	
15 16	19. How did you find using Diasend software?
17 18	□ Straightforward
19	□ Challenging but on the whole <u>achievable</u>
20 21	□ Challenging and <u>not achievable</u>
22 23	I felt uncomfortable using computer software to keep track of my medical details
24 25	I felt comfortable using computer software to keep track of my medical details
26	
28	Comments:
29 30 31	
32 33	20. How did you find completing the food diary during the study? (tick all those that apply)
34 35	Challenging but on the whole <u>achievable</u>
36 37	□ Challenging and <u>not achievable</u>
38	□ Not challenging at all
39 40	
41 42	Comments:
43 44	
45	
40 47 48	21. How did you find the physical activity questionnaires on the study? (tick all those that apply)
49 50	□ Challenging but on the whole achievable
51 52	□ Challenging and <u>not achievable</u>
53 54	□ Not challenging at all
55	
50 57	Comments:
58 59	
60	

		Manches	NHS Foundation
22. How did you find the quality of life	fe questionnaires	on the study? (ticl	k all those that a
Challenging but on the whole <u>a</u>	<u>chievable</u>		
□ Challenging and not achievable			
□ Not challenging at all	-		
Comments:			
	Libro® app		
23. Did you use the Libro® app?			
□ Yes			
\square No (please move to question 25)			
24. Did you find the App helpful?			
1 2 3 4 Not at all Slightly	5 6 Moderately	7 8 Very	9 10 Extrem
Comments	14.		
25 What did you like about the App?			
		4	
26 What did you dialika about the Ar	an and could be im	aproved?	
20. What did you dislike about the Ap	op and could be in	iproved ?	
27 If you didn't use the ann what	were the reasons	for this? (tick all th	at apply)

NILC

Manchester University

							NHS FO	undation in
🗆 Don	't like usin	ng apps in gene	eral	□ Not use	r friendly			
🗆 Labo	our intens	ive / time cons	uming	□ Prefer to	o use pen	and pap	er	
□ Find	mobile d	evices challen	ging					
🗆 Lack	of regula	ar internet acce	ess					
Othe	ər (provide	e details below)					
			Dias	send Softwa	re			
28. Did you fi	nd the Di	iasend softwa	re helpf	ful?				
1 Not at all	2	3 4 Slightly	5 M	6 Ioderately	7 	8	9	10 Extremely
NOT at all		Silghuy		loueratery	vei	у		LAttemety
0								
Comments								
Comments								
Comments								
				<u> </u>				
29. What did	you like a	about the Dias	send so	ftware?				
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29. What did	you like a	about the Dias	send so	ftware?				
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29. What did	you like a you dislil	about the Dias ke about the D y most about	send so Diasend <u>Study I</u> the stuc	ftware? software ar <u>mprovemen</u> dy?	nd could k	be impro	oved?	



	NHS Foundation Trust
22 What did you an	iou least shout the study and sould be improved?
32. What did you en	joy least about the study and could be improved?
••••••	
•••••	
	Any other comments about the study
	\sim
Thar	nk you for completing this questionnaire, please return to:
	MIDDAS-GDM Study Team Nightingale Centre
	Muthershows Hearital Manchester M22.01 T
	wythenshawe Hospital, Manchester, M23 921

MeSH Descriptors

Infant, newborn Pregnancy Glucose Intolerance Diabetes, Gestational Insulin Hyperglycaemia Prediabetic state Metformin **Glycated Hemoglobin** Overweight Obesity Diabetes Mellitus, Type 2 Diet, Healthy **Feasibility Studies Mobile Applications Body Weight** Hypoglycaemic agents Fasting Intermittent Fasting

SPIRIT CHECKLIST

Section/Item	ltem no	
Title	1	
Trial Registration	2a	
	2b	
Protocol Version	3	
Funding	4	
Roles and responsibilities	5a]
	5b]
	5c	
	5d	
Introduction		
Background and rationale	6a	C
	6b	
Objectives	7	
Trial Design	8	3
Methods: Participants, interventions, a	nd outcomes	
Study setting	9	
Eligibility criteria	10	



	11b	
	11c	
	11d	
Outcomes	12	
Participant Timeline	13	
Sample Size	14	
Recruitment	15	O.
Methods: Assignment of interventions (fo	or controlled tri	1
Sequence generation	16a	071
Allocation concealment mechanism	16b	
Implementation	16c	

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		1
Blinding (masking)	17a	
	17b	
Methods: Data collection, management, a	nd analysis	
Data collection methods	18a	
	18b	
Data management	19	ie
Statistical methods	20a	20
	20b	1
	20c	
Methods: Monitoring		
Data monitoring	21a	

	21b	
Harms	22	
Auditing	23	
Ethics and dissemination		
Research ethics approval	24	
Protocol amendments	25	
Consent or assent	26a	
	26b	
Confidentiality	27	20
Declaration of interests	28	2/
Access to data	29	
Ancillary and post-trial care	30	
Dissemination policy	31a	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendices

Informed consent materials

Biological specimens

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For peer terien ont

31b

31c

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Description	Location
Descriptive title identifying the study design, population,	1
interventions, and, if applicable, trial acronym	-
Trial identifier and registry name. If not yet registered, name of intended registry	3
All items from the World Health Organization Trial Registration Data Set	throughout
Date and version identifier	n/a
Sources and types of financial, material, and other support	23
Names, affiliations, and roles of protocol contributors	1
Name and contact information for the trial sponsor	name only, 23
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	23
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)	18
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
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 Explanation for choice of comparators	4-5
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 Explanation for choice of comparators Specific objectives or hypotheses	4-5 4-5 13-14
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 Explanation for choice of comparators Specific objectives or hypotheses Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5 4-5 13-14 6
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 Explanation for choice of comparators Specific objectives or hypotheses Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5 4-5 13-14 6
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Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	13-14
Time schedule of enrolment, interventions (including any run- ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Strategies for achieving adequate participant enrolment to reach target sample size	n/a
ils)	
Method of generating the allocation sequence (eg, computer-	0
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	8
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 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	8

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Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
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	9-15
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	supplementary PIS
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	16
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	16
Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
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	18

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
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 16
Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	n/a
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)	19
Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, supplementary conser
Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	16
Financial and other competing interests for principal investigators for the overall trial and each study site	23
Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	supplementary PIS
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	19

Authorship eligibility guidelines and any intended use of	
professional writers	n/a
Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	19
Model consent form and other related documentation given to participants and authorised surrogates	supplementary mate
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	15



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T DieR Template for Intervention

BMJ Open The TIDieR (Template for Intervention Description and Repliced tion) Checklist*:

Information to include when describing an intervention and the location and the location

Description	and Replication Information to include when describing an intervention and the location	E E E		mormation	
Item	Item	ing	ň 1	Where lo	ocated **
number		for L	B rim	ary paper	Other † (details)
		Ens	e Goage	e or appendix	
		rela	2 Ngumb	per)	
		eme ted t	024.		
	BRIEF NAME	io te	Dov		
1.	Provide the name or a phrase that describes the intervention.	upe xt a			
	WHY	rieur (nd dat	aded f		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	a mi	6 <u>4</u> −5		
		ning.	http		
	WHAT	9, ≥			
3	Materials: Describe any physical or informational materials used in the intervention, including those	traji		15	annendix
0.	provided to participants or used in intervention delivery or in training of intervention, meldeling these	ning	P 1 2 ,	10	
		, an	<u>ă</u> .		
	Provide information on where the materials can be accessed (e.g. online appendix, URL).	d sir	Som		
		nilar	on /		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention,	. tec	<u>F</u> 6-1	2	
	including any enabling or support activities.	hno	e 12		
		logie	20		
	WHO PROVIDED	S.	25 a		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their		 Ag1, 7	-12, 17-18	
	expertise, background and any specific training given.		ence		
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TIDieR che	cklist For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtm	I	e de		1

of 78	BMJ Open	open-2	
6.	<u>ع</u> Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or	9 96-18	
	telephone) of the intervention and whether it was provided individually or in a group.	78264 o	
	WHERE	n 10	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary	Fe 06-18	
	infrastructure or relevant features.	ny 20	
	WHEN and HOW MUCH	024. E	
8.	Describe the number of times the intervention was delivered and over what period of time including $\frac{2}{2}$	ŏ ≸6-18	
	the number of sessions, their schedule, and their duration, intensity or dose.	loaded f	
		rom	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why,	6-18	
	when, and how.	/bmjope	
	MODIFICATIONS	n.br	
10. [‡]	If the intervention was modified during the course of the study, describe the changes (what, why,	<u>e</u> N/A	
	when, and how).	h/ on Ju	
	HOW WELL	ne 12	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any	8 13-14	
	strategies were used to maintain or improve fidelity, describe them.	5 at Age	
12. [‡]	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	N/A	
	intervention was delivered as planned.	3ibliogr	
		aphiqu	
TIDieR ch	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	e de	

- BMJ Open ** Authors use N/A if an item is not applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. sufficiently reported. sufficiently reported.
- or other published papers (provide citation details) or a website (provide the URL). + If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.
- * We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains an elaboration and elaboration for each item.
- * The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study ether elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist $\mathbf{\hat{P}}_{\mathbf{\hat{k}}}$ a randomised trial is being reported, the Lit-statem, in conjunction with th, i.e.R can be used in conjunction w TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of the CONSORT 2010 Statement. When a clinical trial protocol is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement a statement Statement (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropria to that study design (see from h (ABES) ata mini www.equator-network.org).

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Manchester Intermittent Diet in Gestational Diabetes Acceptability Study (MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater Manchester

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-078264.R4
Article Type:	Protocol
Date Submitted by the Author:	11-Jan-2024
Complete List of Authors:	Dapre, Elizabeth; Wythenshawe Hospital Issa, Basil; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Harvie, Michelle; University Hospital of South Manchester NHS Foundation Trust, Genesis prevention centre Su, Ting-Li; University of Manchester, Dentistry McMillan, Brian; The University of Manchester, Centre for Primary Care and Health Services Research Pilkington, A.; Wythenshawe Hospital Hanna, F.; University Hospitals of North Midlands NHS Trust Vyas, Avni; Manchester Metropolitan University Faculty of Health Psychology and Social Care, Health Professionals Mackie, S.; Wythenshawe Hospital Yates, James; Manchester University NHS Foundation Trust Evans, Benjamin; Manchester University NHS Foundation Trust Mubita, Womba; Manchester University NHS Foundation Trust, Department of Endocrinology and Diabetes Lombardelli, Cheryl; Manchester University NHS Foundation Trust
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Obstetrics and gynaecology, Reproductive medicine
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, DIABETES & ENDOCRINOLOGY, Obesity, NUTRITION & DIETETICS, Feasibility Studies, Maternal medicine < OBSTETRICS
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BMJ Open

	Manchester Intermittent Diet in Gestational Diabetes Acceptability Study	
(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent		
Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater		
Manchester		
uthors: Dapre E Issa	B Harvie M Su T McMillan B Hanna F Pilkington	
Vvas. A Yates. J N	Aackie, S., Evans, B., Mubita, W., Lombardelli, C.	
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1 2	18	
3	19	<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>
5	20	(MIDDAS-GDM): A Two-Arm Randomised Feasibility Protocol Trial of an Intermittent
6 7	21	Low-Energy Diet (ILED) in women with Gestational Diabetes and Obesity in Greater
8 9	22	Manchester
10	23	
12	24	Authors: Dapre, E., Issa, B., Harvie, M., Su, T., McMillan, B., Hanna, F., Pilkington,
13 14	25	A., Vyas, A., Yates, J., Mackie, S., Evans, B., Mubita, W., Lombardelli, C.
15 16	26	
17	27	Corresponding Author: elizabeth.dapre@nhs.net
18 19	28	
20 21	29	Abstract (word count 298)
22 23	30	Introduction: The prevalence of gestational diabetes mellitus (GDM) is rising in the
24	31	UK and is associated with maternal and neonatal complications. National Institute for
25 26	32	Health and Care Excellence (NICE) guidance advises first line management with
27 28	33	healthy eating and physical activity which is only moderately effective for achieving
29 30	34	glycaemic targets. Approximately 30% of women require medication with metformin
31	35	and/or insulin. There is currently no strong evidence base for any particular dietary
32 33	36	regimen to improve outcomes in GDM. Intermittent low-energy diets (ILEDs) are
34 35	37	associated with improved glycaemic control and reduced insulin resistance in type 2
36 37	38	diabetes (T2DM) and could be a viable option in the management of GDM. This
38	39	study aims to test the safety, feasibility and acceptability of an ILED intervention
39 40	40	amongst women with GDM compared to best National Health Service (NHS) care.
41 42	41	
43	42	Method and analysis: We aim to recruit 48 women with GDM diagnosed between 24-
44	43	28 weeks gestation from antenatal clinics at Wythenshawe and St Mary's hospitals,
46 47	44	Manchester Foundation Trust, over 13 months starting in November 2022.
48 49	45	Participants will be randomised (1:1) to ILED (2 low-energy diet days/week of
50	46	1000kcal and 5 days/week of the best NHS care healthy diet and physical activity
52	47	advice) or best NHS care 7 days/week until delivery of their baby. Primary outcomes
53 54	48	include uptake and retention of participants to the trial, and adherence to both dietary
55 56	49	interventions. Safety outcomes will include birthweight, gestational age at delivery,
57	50	neonatal hypoglycaemic episodes requiring intervention, neonatal
58 59	51	hyperbilirubinaemia, admission to special care baby unit or neonatal intensive care
60	52	unit, stillbirths, the percentage of women with hypoglycaemic episodes requiring

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1 2	53	third-party assistance, and significant maternal ketonaemia (defined as ≥1.0mmol/L)
3	54	Secondary outcomes will assess the fidelity of delivery of the interventions, and
4 5	55	qualitative analysis of participant and healthcare professionals' experiences of the
6 7	56	diet. Exploratory outcomes include the number of women requiring metformin and/or
8 9	57	insulin.
10	58	
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13 14	60	
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36 37	73	
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48 49	80	
50 51	81	Ethics and dissemination: Ethical approval has been granted by the Cambridge
52	82 83	publication in peer-reviewed journals, conference presentations, and shared with
53 54	84	diabetes charitable bodies and organisations in the UK, such as Diabetes UK and
55 56	85	the Association of British Clinical Diabetologists.
57 58	86	
59	87	
60	88	Irial Registration Number: NC105344066

1 2	89	
3		Strengths and limitations of this study
4 5		Strengths
6		This mixed methods feasibility study includes both quantitative and qualitative
7 8		• This mixed methods leasibility study includes both quantitative and quantative
9 10 11		evaluation of the acceptability of the dietary intervention
		This study has been informed by an experienced patient and public involvement
12 13		and engagement group
13 14 15 16 17 18 19 20 21 22 23 24 25 26		Limitations
		This study involves a small sample size and is not powered to show efficacy of
		the intervention
		Women joining this study are likely to be highly motivated and adherence may
		not reflect that seen in the wider general population
	90	
	91	INTRODUCTION (word count: 3539)
	92	Background
27 28	93	In the UK up to 16% of pregnant women develop gestational diabetes (GDM) and
29 30	94	the incidence is rising, in part due to increasing rates of obesity and maternal
30 31 22	95	age(1,2). GDM is associated with maternal and neonatal complications (the risk
33	96	increases with poor glycaemic control), including macrosomia, shoulder dystocia,
34 35	97	caesarean-sections, neonatal hypoglycaemia and/or hyperbilirubinaemia, preterm
36 37	98	delivery, preeclampsia, and stillbirth(2). Women who have had GDM have an
38	99	estimated seven to ten-fold risk of developing type 2 diabetes (T2DM) later in life,
40	100	and their children have a higher risk of developing adult obesity and T2DM(2–4).
41 42	101	
43 44	102	Excessive weight gain in pregnancy is a particular problem for women with GDM(5).
45	103	Harper et al demonstrated that, in women with GDM, every additional 1lb/week
46 47 48 49 50 51	104	gained following diagnosis of GDM resulted in a 36-83% increased risk of pre-
	105	eclampsia, caesarean-section, macrosomia, and large for gestational age babies(5).
	106	Such studies highlight the importance of adequate weight control throughout
52	107	pregnancy in women with GDM in order to reduce both maternal and neonatal
53 54	108	complications.
55 56	109	
50 57	110	First-line therapy for GDM is diet and physical activity. National Institute for Health
58 59	111	and Care Excellence (NICE) guidance encourages a healthy diet with increased fruit
60		

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- and vegetables, low-glycaemic index (GI) foods, reduced refined sugars, regular mealtimes and regular physical activity(6,7). These dietary measures fail to achieve glycaemic targets in ~30% of women who require medication with metformin and/or insulin(8). A range of dietary approaches have been studied including daily diets promoting low-GI diets (limiting refined and promoting complex carbohydrates), continuous modest energy-restriction (1800 Kcal/day), and low carbohydrate diets(9). There is currently no strong evidence base for any particular dietary regimen to improve outcomes in GDM. Intermittent Low-Energy Diets (ILED) The pathogenesis of GDM is strongly linked to obesity and chronic insulin resistance with many clinicians viewing GDM as a form of evolving T2DM. ILEDs typically include several days of a food based or meal replacement (e.g. drinks/bars) low-energy diet (650-1000kcal) diet, with a standard healthy (non-restrictive) diet recommended on the remaining days of the week. These diets are associated with significant reductions in weight, insulin resistance and hyperglycaemia in patients with prediabetes (HbA1c between 42-47mmol/mol, impaired glucose tolerance, or impaired fasting glycaemia), those with T2DM, and otherwise healthy subjects with overweight/obesity(10–17). These changes are equivalent to, or greater than, those achieved with standard daily energy restriction. A popular intermittent diet involves 2 consecutive or non-consecutive days/week of a low-energy diet (650-1000kcal) and 5 days of normal eating/week, known as the 5:2 diet. The Manchester Intermittent
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- participants in the ILED group completed the study and achieved a 6% reduction of their baseline body weight. Forty two percent achieved an HbA1c of <48 mmol/mol(18). Given the strong overlap between GDM and T2DM, an ILED may be a promising dietary intervention for those with GDM. A successful dietary approach to glycaemic control could empower women to take charge of the management of their GDM. Women with GDM are motivated to modify their diet driven by a desire to improve foetal outcomes(19-21).

vs. Daily Diabetes App Study (MIDDAS), a study comparing an ILED and a

continuous low-energy diet in T2D conducted in our unit, has shown the feasibility

including those using insulin(18). At the end of the study approximately 70% of

and safety of an ILED (800kcal for 2 days/week) in patients with T2DM and obesity.

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1 2	147	Our Patient and Public Involvement and Engagement (PPIE) work indicates that
3	148	women find the current National Institute for Health and Care Excellence (NICE)
4 5	149	healthy eating guidance(6,7) confusing and vague. Our PPIE work has indicated that
6 7	150	women are keen to try alternative dietary approaches, particularly if alternative diets
8 9	151	are more effective in preventing the need to progress to medications such as
10	152	metformin and insulin.
12	153	
13 14	154	Aim
15 16	155	The aim of this trial is to test the safety, feasibility, and acceptability of an ILED in
17	156	GDM to inform a future large-scale RCT.
18 19	157	
20 21	158	METHODS
22 23	159	Trial Design
24	160	The study is a 28-week feasibility two-arm RCT in one NHS trust performed in
25 26	161	patients with GDM and BMI ≥27.5 kg/m², or ≥25 kg/m² in high-risk minority ethnic
27 28	162	groups (i.e. South Asian, Black African, African Caribbean) in Greater Manchester,
20 29 30 31	163	between December 2022 and July 2024(22,23). There will be an embedded
	164	qualitative sub-study for participants and healthcare professionals. Due to the nature
32 33	165	of the intervention, it will not be possible to blind the participants, clinicians, or study
34 35	166	team to the treatment allocation after randomisation (the statistician and laboratory
36	167	technicians will remain blinded).
37 38	168	
39 40	169	Trial Setting and Recruitment
41 42	170	Participants will be recruited from antenatal clinics at Wythenshawe and St Mary's
43	171	Hospitals, Manchester Foundation Trust (MFT) between November 2022 and
44 45	172	December 2023. This is an urban area within Greater Manchester, and MFT serves
46 47	173	patients from a wide range of minority ethnic and socio-demographic backgrounds.
48 49	174	Women may self-refer to the antenatal clinic or be referred by their primary care
50	175	team. Assessments will be carried out at MFT, or remotely if required by COVID-19
51 52	176	restrictions. The qualitative sub-study will be carried out at MFT, remotely, or at a
53 54	177	location of the participant's choosing. We aim to recruit eligible participants over a
55	178	period of 13 months. Potential participants will be given written information about the
56 57	179	study and the opportunity to ask questions about the study prior to providing written
58 59	180	consent (supplementary files 1 and 2).
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1 2	182	Eligibility Criteria
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5	184	<image exclusion="" figure1="" inclusion="" jpg="" one;=""/>
6 7	185	
8 9	186	
10	187	Participant Flow
12	188	Participants who fulfil the broad eligibility criteria will be notified about the trial by the
13 14	189	GDM nurse/midwife at the time of their diagnosis. Those who are interested will be
15 16	190	provided with a comprehensive patient information sheet (supplementary file 1) and
17	191	more detailed eligibility screening questions. They will be asked to attend their first
18 19	192	appointment having fasted for at least 6 hours and complete a four-day food diary (in
20 21 22 23 24 25 26 27 28 29 30 31	193	line with our department's usual care). On attending their first routine clinic
	194	appointment, interested participants will receive further information from the research
	195	team. They will have the opportunity to ask questions, have their eligibility confirmed,
	196	and will be asked for their written consent to take part. Baseline assessments will be
	197	taken and participants will be randomised to their allocated treatment group using an
	198	online randomisation platform. Participant flow through the study is demonstrated in
	199	figure 2.
32 33	200	
34 35	201	Sample Size
32 33 34 35 36 37 38	202	We plan to recruit 24 participants per study arm (n=48) which, when considering an
	203	estimated attrition rate of 15%, will provide complete outcome data on 40
39 40	204	participants(24–26). It has been estimated that 24 participants per group will be
41 42	205	sufficient to determine study outcomes, in line with sample size recommendations for
42	206	feasibility studies(27–29).
44 45	207	
46 47	208	This number will allow us to enable estimation of recruitment/retention parameters
48	209	with sufficient precision. For example, based on 40 completed participants, it will
49 50	210	enable recruitment rates in the region of 25% to be estimated with an error of +/-
51 52	211	13.42% at most; retention of 85% will be estimated with error of +/-11.07% at most. It
53 54	212	is also sufficient for estimation of variability (e.g. standard deviation) in gestational
55	213	weight gain and capillary glucose concentrations (proposed outcomes for the future
56 57	214	definitive trial) with negligible bias (30).
58 59	215	
60	216	

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1 2	217	Randomisation
3 1	218	The randomisation schedule will be independently set up and known only by the trial
5	219	statistician. The trial statistician will be blinded to the participant's identity using
6 7	220	"sealed envelope" software (https://www.sealedenvelope.com/). Randomisation will
8 9	221	be carried out by generating an online pseudo-random list with random permuted
10	222	blocks of varying size, known only to the statistician, and will be stratified for two
12	223	variables:
13 14	224	- Age (18-35, >35 years)
15 16	225	- BMI (27.5-34.99kg/m ² and >35kg/m2, >25-32.49kg/m ² and >32.5kg/m ² for
17	226	high-risk minority ethnic groups (i.e. South Asian, Black African, African
18 19	227	Caribbean)
20 21	228	These stratification variables have been chosen to reduce potential bias as we
22 23	229	expect varying severity of GDM with increasing age and BMI, and possible
24	230	differences in diet adherence(31).
25 26	231	
27 28	232	Treatment to intervention and control groups will be allocated in a 1:1 ratio. A
29	233	member of the research team who will be unaware of the randomisation algorithm
31	234	(principal investigator, clinical research nurse, clinical research fellow or project
32 33	235	manager) will trigger the randomisation procedure onsite; participants and clinicians
34 35	236	will then be informed of the allocated treatment group. Clinicians will not be blinded
36	237	due to the need to remain astute to safety, adherence, and side effects, requiring
37 38	238	open and honest discussions with patients at each appointment. The statistician will
39 40	239	remain blinded to treatment allocation until all outcome measures for all subjects
41 42	240	have been collected.
43	241	
44 45	242	Interventions
46 47	243	Study Arm 1: Best NHS Care Diet
48	244	All dietetic advice will be face to face or via video calls or the telephone. Participants
50	245	will receive one to one personalised written and verbal advice from a dietitian to
51 52	246	follow NICE diet and physical activity recommendations(6,7). Dietitians and midwives
53 54	247	will receive training to ensure standardised delivery of information in clinic, and
55	248	standardised patient information leaflets will be supplied to include information about
56 57	249	increased fruit/vegetable intake, low-glycaemic index foods, and a reduction in free
58 59	250	sugars. Information will include advice about the importance of regular meals; dietary
60	251	advice aims to ensure that participants include at least 70g protein/28g fibre, and

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1 2	252	predominantly mono- and polyunsaturated fats as per American Diabetes
3	253	Association recommendations(32). Participants will be advised to be physically
5	254	active, for example walking for 30 minutes after a meal. Participants will receive
6 7	255	ongoing dietetic education and support every 2 weeks until delivery. This level of
8 9	256	support is higher than typically provided in NHS GDM antenatal clinics due to limited
10	257	resources but has been utilised to reflect best NHS care. They will receive suggested
12	258	menus and recipes to follow the NICE recommended healthy diet for GDM.
13 14	259	Participants will be asked to measure their capillary glucose four times each day and
15 16	260	their ketones on two random (recorded) days of the week of their choosing
17	261	(supplementary file 3).
18 19	262	
20 21	263	Study Arm 2: Intermittent Low-Energy Diet (ILED)
22 23	264	Participants will receive the same level of dietetic support as the best NHS care
24	265	group. They will be given advice on adopting an ILED which involves 2 non-
25 26	266	consecutive low-energy diet days/week (1000kcal to include 100g low-GI
27 28	267	carbohydrate and 70g of protein) and 5 days/week of the NICE healthy eating low-GI
29 30	268	diet and physical activity recommended for the best NHS care group. The low-
31	269	energy days involve women selecting a set number of portions of protein,
32 33	270	carbohydrate, fat, fruit, vegetables, and dairy/dairy alternatives as described in
34 35	271	previous studies(33). Each low-energy day includes ~210g of lean protein foods, 3-4
36 37	272	portions of wholegrain carbohydrates, 1x7g portion of fat, 5 portions of vegetables, 2
38	273	of fruit, and 3 of dairy/dairy alternatives. Food and drink will be self-selected and not
39 40	274	provided by the study team. Participants will be provided with comprehensive food
41 42	275	lists, advice on portion sizes for the low-energy days and suggested menus and
43 44	276	recipes to follow for both the low-energy and NICE recommended healthy diet days
45	277	(supplementary file 4). Both diets can be successfully adapted for people of different
46 47	278	ethnicities and those following omnivorous, vegetarian and vegan diets. Participants
48 49	279	will be asked to measure their capillary glucose four times each day and their
50	280	ketones on (and the morning after) the two low-energy days (supplementary file 3).
52	281	
53 54	282	
55 56	283	<image 2="" 2:="" figure="" flow="" jpg=""/>
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58 59	200	<image 2="" 2:="" assessments="" figure="" ing="" schod=""/>
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2	287	
3 4	288	
5	289	
6 7	290	Outcomes
8 9	291	Primary outcomes
10 11	292	Uptake rate measured as a percentage of eligible participants who consent to
12	293	take part, including the proportion of women who were screened who did not
13 14	294	meet the eligibility criteria, and the number of women who did not give
15 16	295	consent to take part
17 18 19	296	Recruitment rate measured as the number of eligible participants who consent
	297	to take part per month
20 21	298	Retention rate measured as the number of randomised participants who
22 23 24 25 26 27 28 29 30 31 32 33 34 35	299	complete the trial (those who attend the final visit) and the percentage of
	300	participants who attend all 8 visits
	301	Adherence to the dietary interventions assessed from self-reported adherence
	302	to the potential low-calorie days between randomisation and delivery
	303	 Completion of self-assessed glucose and ketone readings assessed as a
	304	percentage of the required readings
	305	
	306	Safety outcomes:
36 37	307	 Percentage of women following ILED/best NHS care with
38 39 40	308	hypoglycaemia (episodes of blood glucose of <3.0mmol/mol) and
	309	hypoglycaemia requiring third-party assistance as measured by
41 42	310	participants
43 44	311	 Percentage of women who develop significant ketonaemia in both
45 46	312	groups (defined as ≥1.0mmol/L) as measured by participants
47	313	 Percentage of neonatal hypoglycaemic episodes requiring intervention
48 49	314	(blood glucose checked 2- hours post-delivery and 2-hours thereafter
50 51	315	for 12 hours according to local protocol), neonatal birth weight,
52	316	gestational age at delivery, hyperbilirubinaemia/jaundice, and/or
53 54	317	admission to Special Care Baby Unit or neonatal intensive care, and
55 56	318	stillbirths
57 58	319	\circ The incidence and rate of other adverse events (e.g. headaches,
59 60	320	lethargy, constipation, or complications requiring hospital admission)

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1 2	321	between the start of the trial intervention and delivery recorded as mild,
3 4	322	moderate and severe, as defined by Common Terminology Criteria for
5	323	Adverse Events version 5 (CTCAEv5)(34). Hospital admission for
6 7	324	routine labour and delivery will not be classified as an adverse event.
8 9	325	
10 11	326	Secondary outcomes
12	327	 Completeness of collection of trial endpoints including the percentage of
13 14	328	completed weight measurements, 4-day food diaries, and International
15 16	329	Physical Activity Questionnaire (IPAQ) scores
17	330	 Fidelity of delivery of the interventions will be measured through the number
18 19	331	and modality of completed planned patient contacts, electronic and paper
20 21	332	food diaries, and self-reported capillary glucose and ketone measurements
22 23	333	 Qualitative analysis of the acceptability and implementation of the
24	334	interventions will be explored amongst a subset of participants (~10 in each
25 26	335	group) and healthcare professionals through in-depth interviews
27 28	336	
29 30	337	Exploratory outcomes
31	338	The following outcomes will be explored without statistical inference.
32 33	339	1. Maternal outcomes:
34 35	340	 The percentage of women requiring metformin and/or insulin
36 37	341	Four-point capillary glucose profiles during third trimester (four times daily
38	342	until delivery)
39 40	343	 Change in fasting blood test results between baseline measurements, 36-
41 42	344	37 weeks' gestation, and 12 weeks post-delivery (including oral glucose
43 44	345	tolerance tests (OGTT)
45	346	 Mode of delivery, development of preeclampsia, polyhydramnios
46 47	347	(maximum liquor volume pool depth ≥8 cm)
48 49	348	 Quality of life and health status questionnaires (WHOQoL-BREF and SF-
50 51	349	36 questionnaires)(35,36)
52	350	2. Foetal outcomes:
53 54	351	Foetal weight
55 56	352	Gestational age at delivery
57 58	353	
59 60	354	

1 2	355	
3	356	
4 5	357	
6 7	358	
8	359	
9 10	360	Measurements
11 12	361	The full schedule of assessments can be found in figure 3.
13 14	362	
14	363	Physical measurements
16 17	364	Height weight and blood pressure will be measured using standardised calibrated
18 19	365	equipment in antenatal clinic
20	366	
21 22	367	Blood samples
23 24	368	Easting venous blood samples will be collected to assess maternal HbA1c, fasting
25	369	alucose insulin beta-bydroxybutyrate liver function tests free fatty acids thyroid
20 27	370	function tests, and full blood count. At the end of the study all samples will be
28 29	371	disposed of in accordance with the Human Tissue Act (2004)
30 31	371	disposed of in decordance with the Human Hissue Act (2004).
32	372	Questionnaires
33 34	374	Participants will be asked to complete four questionnaires at four time points
35 36	375	throughout the trial (self-reported). Quality of life and health status will be assessed
37	376	using the World Health Organisation Quality of Life Questionnaire (brief version) and
38 39	277	the 36-Item Short Form Survey respectively (35.36). Physical activity will be
40 41	270	measured using the International Physical Activity Questionnaire – Short Form, and
42 43	270	diet quality will be assessed using the LIK Diabetes and Diet Questionnaire (37.38)
44	200	These questionnaires are self reported by participants and have been chosen as
45 46	201	they are widely used and validated tools
47 48	202	they are widely used and validated tools.
49	382	Food Diarias
50 51	383	<u>Food Diaries</u>
52 53	384	4-day dietary records will be completed using Libro (Nutritics Mobile Application) or
54	385	paper food diaries, which will be entered into Nutritics software (Nutritics, Dublin,
55 56	386	Ireland)(39). Participants who wish to use Libro will receive one to one training to use
57 58	387	this by the study dietitian. Diaries will provide the research team with information
59	388	about the intake of energy, carbohydrate, fat, protein, fibre, glycaemic index, and the
00	389	timing of meals for participants in both groups. Participants will be asked what other
1 2 3 4 5	390	dietary modifications, if any, they have made at their fortnightly dietitian reviews to
----------------------------	-----	---
	391	establish the adoption of any alternative dietary practices in the cohort.
	392	
6 7	393	Adverse Events
8 9	394	Participants in both groups will be asked about any adverse effects that they have
10 11	395	experienced at each visit. These will include, but are not limited to, the potential
12	396	effects of a low-energy diet, e.g. headache, lethargy, dizziness, constipation,
13 14	397	indigestion, poor concentration, and hunger. Adverse events will be graded as per
15 16	398	CTAEv5(34). Participants will be issued with a participation/emergency card with
17	399	emergency contact details for the research team to be carried at all times and to be
18 19	400	shown to the attending physician in case of emergency admission to hospital. All
20 21	401	participants will be issued with clear instructions as to how to manage a
22 23	402	hypoglycaemic and/or ketonaemic event (supplementary file 5).
24	403	
25 26	404	Data management
27 28	405	Participant data will be anonymised and will be stored in line with the Medicines for
29	406	Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act
30 31	407	(2018) and archived in line with the Medicines for Human Use (Clinical Trials)
32 33	408	Amended Regulations (2006) as defined in the MFT Clinical Trials Office Archiving
34 35	409	SOP (11; Retention of Data, Off-Site Archiving, and Destroying Documents).
36	410	Deidentified data will be stored in a study-specific Research Electronic Data Capture
37 38	411	(REDCap) database. The sponsor will periodically audit the site study file, a sample
39 40	412	of the case report form, consent forms, and source data, and check accuracy of the
41 42	413	study database to ensure satisfactory completion.
43	414	
44 45	415	Statistical methods
46 47	416	A statistical analysis plan specifying the full details of the primary and secondary
48	417	outcomes, other variables, and methods, will be produced prior to trial analysis. The
49 50	418	main analysis will be conducted via intention-to-treat population and will not
51 52	419	undertake any significance tests. Descriptive, graphical (summary), and basic
53 54	420	statistics (e.g. i. number, frequencies and percentages, ii. mean and standard
55	421	deviation, or iii. median and quartiles as appropriate) will be presented as
56 57 58 59 60	422	appropriate for each group respectively, for group difference jointly, and for each
	423	stratum. Per-protocol analysis will be considered as a secondary analysis. Levels of
	424	missing data will be investigated and used to inform future studies. No imputation will

- 425 be used. The end of study questionnaire will be analysed using appropriate
- 426 descriptive statistics for closed questions and key themes will be extracted without
- 427 formal analysis from open questions to inform future research.
- **Progression Criterion**

- 430 The success of the feasibility trial will be defined by the progression criteria as
- ¹² 431 outlined in table 1. Any concerns regarding a low retention rate will be discussed with
 - the PPIE group. Interviews will include those who withdraw from the study to address

433 potential reasons for withdrawal with the aim to improve retention in future.

		F	
		Feasible with	
	Feasible (green)	modification of the	Not feasible (red)
		protocol (amber)	
Recruitment	≥4 patients/month	>2 patients/month	≤2 patients/month
Uptake to the	>15%	10 15%	<10%
feasibility study		10-13 /8	
Retention to the	>70%	50 70%	<50%
feasibility study	-10%	50-70 %	~50 %
Adherence to the	>50% of the low-	30-50% of the low-	<30% of the low-
ILED intervention	energy days	energy days	energy days
	completed (2/week	completed (2/week	completed (2/week
	between weeks 24-	between weeks 24-	between weeks 24-
	28 and delivery)	28 and delivery)	28 and delivery)

Table 1: Trial progression criterion

436 Qualitative sub-study

Participants will be invited to take part in an optional qualitative sub-study at 11-13
weeks post-partum. Healthcare professionals delivering the interventions will also be
invited to take part in this study.

51 440

We will undertake 11-12 semi-structured interviews with a subset of women from each group (ILED n=10 and best NHS Care n=10) at around 12 weeks post-delivery. The final sample size will be contingent on obtaining data saturation. We will also interview a sample of healthcare professionals (HCPs) involved in the delivery of care to study participants, including dieticians, obstetricians and midwives, including

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1 2 3 4 5	446	those with leadership and clinical managerial roles. Sampling will be purposive,
	447	aiming to obtain women from a range of ethnic groups, ages, socioeconomic
	448	backgrounds, and self-reported engagement with the intervention. Participants and
6 7	449	HCPs will be asked about their experiences and thoughts regarding the intervention,
8 9	450	including motivating factors, and facilitators/barriers to engagement. Interviews will
9 10 11 12	451	be conducted by a researcher from the University of Manchester/MFT who is
	452	independent from the research staff involved in the delivery and assessment of the
13 14	453	programmes. Analysis will be conducted by two independent researchers at the
15 16	454	University of Manchester/MFT using Braun and Clarke's thematic analysis approach
17	455	to identify key issues around the acceptability, usefulness of the programmes, and
18 19	456	feasibility of a subsequent trial(40). Analysis will be inductive: open-ended,
20 21	457	exploratory, and driven by the data.
22 23	458	
23 24 25	459	All participants will also be asked to complete an optional and anonymous end of
25 26	460	study questionnaire developed by the study team at their post-partum visit
27 28	461	(supplementary file 6). This will give participants the opportunity to feedback on their
29 30	462	experience and will enable the study team to identify improvements to the design of
31	463	a possible follow-up study.
32 33 34 35 36 37 38 39 40	464	
	465	Trial Steering Committee (TSC)
	466	The trial steering committee will include an independent consultant endocrinologist,
	467	obstetrician, dietitian, and the patient representative. The committee will oversee the
	468	trial to ensure that it is carried out to the expected standards. The TSC will liaise with
41 42	469	the CI to develop a schedule of meetings, proposed to occur every four months, with
43 44	470	meetings to occur no less than annually. Minutes will be taken at TSC meetings and
45	471	copies of the minutes will be filed in the Trial Master File; they will be shared with
46 47 48 49	472	relevant stakeholders as appropriate.
	473	
50 51	474	Patient and public involvement
51 52 53 54	475	Patient and public involvement was actively sought throughout the planning and
	476	design of this trial and continues to form a key part of the trial as it progresses. The
55 56	477	patient and public involvement and engagement (PPIE) group assisted in the
57	478	development of all participant materials and provided valuable insight into the
50 59	479	wording of participant information and acceptability of the proposed intervention. The

PPIE group will be updated as the trial progresses and a further focus group will be held to advise on the interview schedule and wording for the qualitative sub-study. The group will also be invited to aid in the development of summarising key findings for dissemination to relevant patient groups.

Ethics and dissemination

This study has been approved by the Cambridge East Research Ethics Committee and is sponsored by MFT. Findings will be disseminated via publication in peer-reviewed journals, conference presentations, and shared with diabetes charitable bodies and organisations in the UK, such as Diabetes UK and the Association of British Clinical Diabetologists. Anonymised data will be available upon formal request once the principal results of the study have been published. Planned modifications to the protocol will be approved by the research ethics committee before they are adopted into the study. An audit trail of ethical amendments and documentation will allow monitoring by the research team and external regulatory bodies.

This is the first study to assess the feasibility and safety of an ILED in GDM as compared to best NHS care. Given the increasing incidence of GDM and associated health risks this research is both pertinent and important. The study is not powered to show differences between ILED and best NHS care, however the planned quantitative and qualitative assessments will inform the feasibility of the programme and a future definitive trial.

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30 31	647		
32 33	648	Autl	hors' contributions
34 35	649	Mich	nelle Harvie, Basil Issa and Elizabeth Dapre designed the study, wrote the
36	650	prote	ocol and secured funding. Brian McMillan designed and worded the qualitative
37 38	651	sub-	study Ting-Li Su developed the statistical analysis plan. Fahmy Hanna reviewed
39 40	652	and	advised on overall study design. Andrea Pilkington provided expert obstetric
41	652	anid	ance for the protocol design. Avni Vivas, Cheryl Lombardelli and Michelle Harvie
42 43	055	guiu	ducted dictotic reviews. Wembe Mubits beloed with recruitment and review of
44 45	054	CONC	in and a low of Votes and Degionalia France ware near and it is for any is at
46	655	parti	icipants. James Yates and Benjamin Evans were responsible for project
47 48	656	man	agement and data reporting. Sarah Mackie coordinated the clinical trial.
49	657	Eliza	abeth Dapre drafted the manuscript for publication, with input from Michelle
50 51	658	Har∖	vie, Basil Issa, Brian McMillan and Ting-Li Su. All authors have proofed and
52	659	cheo	cked the manuscript.
53 54 55	660		
56 57	661		
58 59 60	662	Ack	nowledgments

1 2	663	With thanks to Mrs Rebecca Lumsden, our patient expert, whose insight has been
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8 9	667	the recruitment and follow up of participants throughout the trial.
10 11	668	
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13 14	670	This trial is funded by the National Institute for Health Research (NIHR201944) and
15 16	671	sponsored by Manchester University NHS Foundation Trust (MFT). The funders of
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19 20 21 22 23 24	673	NIHR sponsored GP academic clinical fellow.
	674	
22 23	675	Competing interests statement.
24 25 26 27 28 29 30 31 32 33 34	676	Michelle Harvie has co-authored three self-help books for the public to follow
	677	intermittent diets. All author proceeds are paid directly to the charity Prevent Breast
	678	Cancer (registered charity number 1109839) to fund breast cancer research.
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13 14	704	Appendix
15 16	705	1.0 Patient Information Sheet (supplementary document 1)
17	706	
18 19	707	2.0 Consent Form (supplementary document 2)
20 21	708	
22	709	3.0 Self-monitoring schedule for capillary glucose and ketone monitoring
23 24	710	(supplementary document 3)
25 26	711	
27 28	712	4.0 Intermittent Low Energy Diet Day Example (supplementary document 4)
29	713	
30 31	714	5.0 Medical Management Protocols (supplementary document 5)
32 33	715	
34 35	716	6.0 End of Study Questionnaire (supplementary document 6)
36	717	
37 38	718	
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43 44	721	
45	722	LEGENDS
46 47	723	 <image 1=""/>: Figure 1: Inclusion and exclusion criteria
48 49	724	 <image 2=""/>: Figure 2: Participant flow through trial
50 51	725	 <image 3=""/>: Figure 3: Schedule of assessments
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inc	lusion Criteria
AA A A	Pregnant women ≥18 years BMI of ≥27.5kg/m2 or a BMI ≥25 kg/m ² in high risk minority ethnic group (i.e. South Asian, Black African, African Caribbean) and <50 kg/m2 at booking appointment (8-12 weeks' gestation) Newly diagnosed GDM according to local diagnostic criteria (fasting glucose ≥5.3mmol/l and/or 2-hour postprandial glucose ≥8.5mmol/l in a 75g OGTT) scheduled to receive first line diet and physical activity (best NHS care) 24-30 weeks' pregnant at screening appointment
Ex	clusion Criteria
AA AAA	Pregestational type 1 or type 2 diabetes. Fasting glucose of ≥7 or 2-hour postprandial of ≥11 on OGTT (immediate intervention with medication would be required in this group of women) Current multiple pregnancy Maturity Onset Diabetes of the Young (MODY) Significant comorbid disease that in PI's opinion would preclude participation in the study e.g. chronic kidney disease, significant cardiac disease, significant history of disordered eating or

Figure 1: Inclusion and exclusion criteria

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154x245mm (220 x 220 DPI)

Study Visit

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Gestation (weeks)	~24-30	~24-30	~30-34	~32-36	~34-38	~36-40	delivery	11-13 post- partum
Eligibility confirmed	x							
Informed consent	x							
Randomisation	x							
Tailored dietitian review (face to face or remote)	x	x	x	x	x	x		x
Height	x							
Weight ^	x	x	x	x	x	x	х	x
Blood Pressure ^	x	x	x	x	х	х	x	x
Fasting blood sample *	x				x			x
Questionnaires #	x		x		x			x
4-day food diary		x			x			x
Foetal growth scan	x		x		x			
Review of glucose and ketone measurements		x	x	x	x	x		
Neonatal measurements §							x	
Oral glucose tolerance test								x
Exit interview / end of study questionnaires								x
Invitation to optional qualitative sub-study \$	myitation to optional qualitative X sub-study \$							
⁵ Frequency of assessment will be 2-4 weekly depending on whether appointment is face-to-face or virtual due to COVID-19 ⁶ Fasting bloods: urea and electrolytes, liver function tests, bone profile, lipids, thyroid function tests, HbA1c, beta- hydroxybutyrate, free fatty acids, full blood count, fasting glucose, insulin # Questionnaires: World Health Organisation Quality of Life (brief version), 36-Item Short Form Survey, International Physical Activity Questionnaire (short form), UK Diabetes and Diet Questionnaire § Neonatal measurements include gestational age at delivery, mode of delivery, and neonatal weight § Sub-study involves semi-structured interviews exploring thoughts and experiences of the trial								

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Consultant Endocrinologist – Dr. Basil Issa Research Dietitian – Dr. Michelle Harvie Email: mft.middas.gdm@nhs.net Tel: 07815987910



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MIDDAS-GDM

<u>Manchester</u> Intermittent <u>Diet</u> in Gestational <u>D</u>iabetes <u>A</u>cceptability <u>S</u>tudy

Participant information sheet

We would like to invite you to take part in a research study that is testing two different diet programmes which aim to help people with gestational diabetes control their blood sugars.

If you decide to take part:

- You will be assigned to one of two diet programmes for the duration of your pregnancy. One involves following the standard NHS healthy diet recommendations for pregnancy, and the other follows the standard NHS healthy diet for 5 days/week plus two nonconsecutive calorie restricted days of 1,000 kcal per week (both groups will be encouraged to be physically active).
- You will be asked to attend your routine appointments at Wythenshawe or St Marys Hospital and will have fortnightly appointments until delivery of your baby (some appointments may be virtual depending on COVID-19 restrictions). You will be asked to attend the hospital for a blood test 12 weeks after having your baby.
- You will be supported by a diabetes specialist dietitian, midwife, consultant endocrinologist, and your obstetric team throughout the study to help manage your pregnancy and blood glucose safely.
- Throughout the study you will be asked to monitor your food intake via a smartphone/tablet app, or on paper if you prefer, and you will receive feedback on this during your dietary reviews. Comprehensive dietary advice and recipes will be provided.
- Throughout the study you will be asked to monitor your blood sugar using a blood sugar meter four times a day, and you will also be asked to monitor your ketone levels two times on two days of the week (ketones indicate how well your body is using sugar or fat as an energy source). You will be taught how to check your blood sugar and ketone levels.
- If you would like to take part, or you have any questions, then please contact mft.middas.gdm@nhs.uk





This study is being carried out by a team of trained dietitians, doctors, nurses, midwives and researchers under the supervision of Dr. Basil Issa and Dr. Michelle Harvie at Wythenshawe and St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what taking part would involve for you. Please take your time to read the following information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.

Please ring the research team at the number at the top of the first page, or e-mail mft.middas.gdm@nhs.net if there is anything that is not clear, or if you would like more information. You can attend an information session about the diets and the study before agreeing to take part if you would like to.

Your participation in the study is entirely voluntary; you do not have to take part if you do not want to and you can opt out of the study at any time without giving a reason. Thank you for reading this information. We hope this research will be of interest to you.

Why are we doing this research?

Around 1 in 8 pregnant women can develop gestational diabetes. This condition causes risks to mother and baby from high blood sugar, high blood pressure, induced labours, caesareansections, and larger babies. Women often need medication to control blood sugar despite following recommended NHS healthy eating plans for pregnancy. Intermittent low-calorie diets (two non-consecutive days over the course of the week) improve blood sugar control and reduce the need for medication in patients with type 2 diabetes. We want to find out whether intermittent low-calorie diets might also improve blood sugar control in gestational diabetes and reduce the need for medication as it is a similar condition to type 2 diabetes.

What is the purpose of this research?

This study aims to assess the acceptability (to you) and safety of an intermittent low-calorie diet compared to the usual recommended NHS healthy eating and lifestyle plan for gestational diabetes. A computer system will randomly allocate you to one of the two diets. We want to find out which diet is most acceptable to women, whether there is any difference in the two diets' effect on blood sugar control, and any side effects experienced by women. The findings of this study will inform a larger study which will be designed to more closely compare the effect of the two diets on blood sugar control in women with gestational diabetes.

Why have I been asked to take part?

You have been invited to take part in this study because you have been diagnosed with gestational diabetes. We hope to recruit around 48 people to take part in this study.

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What happens if you agree to take part?

If you agree to take part you will be randomly allocated via a computer system to one of two diet and lifestyle programmes for the remaining weeks of your pregnancy.

Best NHS Care Healthy Diet programme

You will receive personalised advice from a specialist dietician. Recommendations will include increased fruit/vegetable intake, low glycaemic index starchy foods (i.e starchy foods which are slowly absorbed and take a while to raise your blood sugar level), reducing refined sugar, and having regular mealtimes. You will be advised how to design your diet to include the right amount of protein, fats, carbohydrates, and fibre, and will be given meal plans and recipes. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week.

Intermittent Low-Calorie Diet programme

If you are allocated to this group you will receive personalised advice to follow a low-calorie diet of 1,000 kcal on two non-consecutive days of the week and the NHS healthy diet on the other five days of the week. The 1,000 kcal days include a set number of portions of protein, carbohydrates and fat foods, fruits, vegetables and dairy/dairy alternatives typically including \sim 210g (7 oz) of lean protein foods and 3-4 portions of wholegrain carbohydrates, 5 portions of vegetables, 2 of fruit, and 3 of dairy or dairy alternatives and a small amount of healthy fat. You will also be advised to try to complete 150 minutes of moderate intensity exercise a week.

Monitoring

You will have all your usual routine antenatal appointments including checks on your weight, blood pressure, blood tests and ultrasound scans. Extra blood tests will be done as part of the study, and these will be added on to samples taken during your routine blood tests.

You will be asked to monitor your blood sugar at home four times a day until your baby is born which is usual care in the clinic. In addition, you will be asked to record ketone levels on two days of the week (you will be taught how to do this using a finger prick machine). The results will be recorded when you attend clinic.

When babies are born to mothers with gestational diabetes it is normal that their birth weight is recorded and that their blood sugar is monitored for 12 hours following delivery; these results will be recorded by the research team.

You will be asked to attend an additional glucose tolerance test at the hospital 12 weeks after delivery to assess whether you have any residual diabetes (95% of women do not) and also to assess how sensitive your body is to insulin (an important risk factor for the development of diabetes in the future). You will be asked to attend at 9:00am having fasted (no food or drink apart from water) from midnight. A blood sample (around 10 mL/2 teaspoons) will be taken for glucose and insulin and you will be asked to drink a sugary drink with 75 grams of glucose. A further blood sample will be taken after 2 hours for glucose and insulin. You will need to

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remain in hospital during this time. The reason for this is to help us to understand whether there could be any difference in the body's ability to process sugar between the two diet groups, and also to find out whether any women still have signs of diabetes after pregnancy.

Any blood samples taken as part of the study will be identifiable only using your study identification number and will have none of your personal details. Part of the sample will be sent for immediate analysis and any remaining will be stored securely, accessible only by the research team. At the end of the study any left over samples will be disposed of in accordance with the Human Tissue Act (2004).

You will be asked to record your food intake via the Libro smartphone/tablet app or in a paper diary for four days once a month throughout the study. You will also be asked to complete three questionnaires to assess your wellbeing and level of physical activity in these weeks, and a final end of study questionnaire at the final appointment.

Ongoing support from a specialist team of healthcare professionals

Your specialist team includes a Consultant Endocrinologist, Consultant Obstetrician, diabetes specialist dietitian, midwives, and a GP trainee with a special interest in women's health. The specialist team work closely with the usual obstetric teams involved in your care. Reviews with the team will be either face to face when you attend clinic or remotely using video calls.

Mobile Applications and Glucose Meters

You will be given the option of using a smartphone application called 'Libro' to record your dietary intake during the study. We will ask you to record 4 days of food and drink intake once a month across the study. Your diaries will be viewed by your allocated dietitian who will provide personalised dietary feedback via the app. You are also free to record more days of your diet should you wish, which some people find helpful. If you do not want to use the mobile app you can use paper instead. You will be supported to set up and use the Nutritics Libro App at your appointments. You do not have to use the application to be part of the study.

Your blood sugar will be monitored using a glucose monitoring device which checks your blood sugar using a 'fingerprick' blood test. You will be shown how to do this yourself. With your permission the research team will make a note of your glucose readings at every visit, either by checking your glucose monitoring device, or by uploading your glucose meter readings onto the computer if you are using a mobile application.

Intermittent low-ene	ergy diet monitoring	Best NHS care monitoring		
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose	
Fasting before breakfast the morning after each	Fasting (morning)	Fasting before breakfast on 2 non-consecutive	Fasting (morning)	
of the low-calorie days		days/weeks		
	1hr post breakfast		1hr post breakfast	
	1hr post lunch		1hr post lunch	

The self-monitoring schedule is as follows:

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1 hour post evening	1hr post dinner	1 hour post evening	1hr post dinner
meal on each of the low-		meal on 2 non-	
calorie days		consecutive days/week	

What should I do if my blood glucose or ketones are out of range?

Low Blood Sugar

It is unlikely that your blood sugar levels will drop too low as a result of being on the intermittent low calorie or the NHS standard diets. You are advised to take 15-20g of 'rapid acting' carbohydrate if your blood glucose is <4 mmol/L). Examples include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). You will need to repeat the treatment every 15 minutes until your blood glucose is ≥4 mmol/l.

The following table highlights when you need to consider an additional slower acting carbohvdrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g (eg half of one of the items below)
More than 2 hours before the next meal	15-20g (eg slice of toast, piece of fruit, small
	bowl of cereal, glass of milk)

Raised Ketones

It is unlikely that your ketone levels will rise significantly as a result of being on the intermittent low calorie or NHS standard diets.

If your ketone levels are \geq 1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If your ketone level has improved (<1.0mmol/L), no further action is required. •
- If your ketone level has increased or remains the same, repeat your ketone level after 2 hours.
- If your ketone level is persistently increased, consume 40g carbohydrates (eg one bagel, bowl of cereal and a banana, small jacket potato), and repeat in 2 hours.
- Continue to do this until your ketone levels are <1.0mmol/L.

Make Immediate Contact with the research team if:

Blood glucose	 Your blood glucose is <3.0 mmol/l or you have symptoms requiring medical attention which are thought to be due to low blood glucose, Your fasting blood glucose is >5.2 mmol/L on more than a quarter of your measurements on two days in a row, Your 1 hour post-meal blood glucose is >7.7 mmol/L on more than a quarter of your guarter of your measurements on two days in a row.
	quarter of your measurements on two days in a row
MIDDAS-G	DM IRAS 302762 Participant Information Sheet Version 4.0 22/09/2023
F	Page 5 of 11 or peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



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Your blood ketones are >1.0 mmol/L

Will I need medications?

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If your blood sugars are found to be high despite following the recommended diet and lifestyle programmes you may be advised to start medication to help control your blood sugar. You will be advised on changes to your medications by a diabetes specialist nurse/diabetes midwife and also a Consultant Endocrinologist if required. This is usual practice regardless of whether you are taking part in the study.

What care will I receive after the study has stopped?

At the end of the study, you will be provided appropriate ongoing dietary advice from the study dietitian following your final glucose tolerance test to follow the NHS healthy eating and lifestyle plan. You will receive routine postnatal care from your GP, hospital team, and dietitian if required. You will be advised to see your GP for an annual blood test to check your blood sugar levels (this is routine care for women with gestational diabetes). Approximately 5% of women with gestational diabetes have residual diabetes after delivery. This will be identified from your glucose tolerance test/HbA1c; if this is the case you and your GP will be informed. Your GP will take over the management of your diabetes as per routine care outside the study.

Interview sub study

Women in this study may be invited to take part in an interview at the end of the study . You will be asked about your views and experiences on trying to follow your allocated diet programme. This interview can be arranged at a time that suits you, either at Wythenshawe or St Marys Hospital, at your home, or over the telephone. There is no obligation to take part in this interview study.

Frequently asked questions

Do I have to take part?

No, you do not have to take part if you do not wish to and your decision will not affect any standard of care you receive at Wythenshawe or St Marys hospitals (Manchester University NHS Foundation Trust, MFT).

What happens if I change my mind?

It is OK if you agree to take part in the study but later change your mind. You do not need to give a reason and it will not affect the standard of care you receive. The study team may also choose to withdraw you if it is necessary for your health or safety due to unexpected findings during the study. If you decide to withdraw from the study, or the study is stopped for any reason, you will be asked whether or not you are happy for us to keep the data that may have already been collected. If you do withdraw from the study you will continue to be cared for by your usual specialist diabetes and obstetric teams for the duration of your pregnancy. You will still have the option of completing the end of study questionnaire and/or interview to provide feedback; this is very useful for the research team to help us understand potential reasons you may have chosen to withdraw from the study.

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You will also have the option that if you withdraw, researchers may still collect relevant information about your pregnancy and/or gestational diabetes from your medical records within the 18-month study duration. This will be an option on the consent form.

Are there any benefits from taking part?

You will receive frequent personalised advice and support to follow two diet and lifestyle programmes which may help to control your blood sugar levels throughout your pregnancy. The information gained from this study will also help inform the future NHS care of patients with gestational diabetes.

Are there any risks from taking part?

Research has found that diets consisting of two low-calorie days a week are very low risk. Pregnant women will develop slightly higher levels of ketones when following low calorie diets than women who are not pregnant. Ketones are produced naturally by the body when the body uses fat stores for energy (i.e. when we follow a low calorie diet or haven't eaten enough because we are ill).

Some research suggests that very high levels of ketones throughout pregnancy may cause a higher risk of babies being slightly smaller than average. It is very unlikely that you will develop high levels of ketones by following this diet. You will be provided with a ketone meter, and you will be asked to check your ketone levels after an evening meal on your low-calorie day, and the following morning, to make sure that your ketone levels are normal.

On your low-calorie days you may feel slightly more hungry, or you may experience other effects such as increased nausea, light headedness, or tiredness. It is important that you eat regularly throughout the day to reduce the risk of this happening. You will be asked to report any side effects of following the diet to the team at each appointment.

What happens if my baby or I become unwell during the study?

The safety of you and your baby are of utmost importance and remain our priority. In the instance that either of you become unwell your case will be reviewed by our specialist team and your suitability for continuing in the trial will be decided. Although it remains exceptionally rare, were you to experience the unexpected loss of your baby you will be withdrawn from the trial and supported by the dedicated specialist bereavement team at the hospital. Any information which has been collected as part of the trial will be stored securely and once we have finished the study we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What will happen to blood samples which are taken?

Some blood samples taken as part of the study will be sent to the laboratory immediately for analysis and any remaining will be stored securely for the duration of the study. Only your 'study ID' will be used – the samples will have none of your personal details on them. At the end of the study any remaining samples will be disposed of in accordance with the Human Tissue Act (2004).



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What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (**Dr. Basil Issa** or **Dr. Michelle Harvie – via the study office – via michelle.harvie@manchester.ac.uk or telephone 0161 291 4410**). If you remain unhappy and wish to complain formally, you can do so through the NHS complaints procedure. Details can be obtained from the NHS Patient and Liaison Service (PALS) on Tel: 0161 276 8686 or contact the team by email pals@mft.nhs.uk.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme. If something did go wrong and you were harmed or suffered deterioration in your health as a result of taking part in this study then you may have grounds for legal action or compensation.

Additional information about the study

Will my lifestyle be affected if I take part?

An essential aspect of this study is a change to your diet and physical activity patterns with support from a specialist team of healthcare professionals.

Payments

We are able to offer free parking at Wythenshawe/St Marys Hospitals for study visits and offer reimbursement for reasonable travel expenses (car, bus or tram) linked to visits for this study. There are no other payments for taking part.

Will my details be kept confidential?

Yes. The study team and any associated regulatory authorities follow strict ethical and legal guidance regarding participant confidentiality. Any information we have about you will be handled in confidence and will only be used for the purposes of this study. All data recorded will be coded and your name will remain anonymous.

During the study we will inform your GP via letter of your participation in the study and your ongoing results, including your weight, blood tests, any abnormal findings and any recommendations for treatment.

If you join the study, some relevant parts of your medical records may be looked at by authorised personnel at Wythenshawe or St Marys hospitals prior to starting the study. These records may also be looked at by an independent auditing body and regulatory authorities to check that the study is being carried out correctly. We will only access parts of your medical records that are relevant to this research and all information accessed will be kept strictly confidential.

How will we use information about you?

We will need to use information from you and from your medical records for this research project.

MANCHESTER

The University of Manchester

NIHR National Institute for Health Research



- **NHS Foundation Trust**
 - This information will include the following:
- · Initials

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- · NHS number
- · Name
- Contact details
- Medical History including test results
- Demographic details

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Other researchers from outside the Trust may ask to see this data for the purposes of furthering their research. We will only share this upon written request to the Trust. The external researchers will be asked to sign a Confidentiality Agreement before any data is shared.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health during pregnancy from your hospital records. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
- by sending an email to mft.middas.gdm@nhs.net or
- by ringing us on **07815987910**

How will my details be used to access the Mobile Applications?

None of your personal details (other than email from which an application is downloaded) will be needed to access the nutritics mobile applications. You can opt to have a 'dummy' e-mail and password under a pseudonym (fake name). Only the research team will know the dummy e-mail address you have been assigned to, in order to be able to review your data. The application will not contain your identifiable data. If you choose to use a mobile application to monitor your blood sugar levels the relevant terms of service for the app and the app developers privacy policy will apply. It will be your responsibility to read and understand these prior to download.

Will my insurance be affected if I take part in this study?

MIDDAS-GDM | IRAS 302762 | Participant Information Sheet | Version 4.0 | 22/09/2023 Page 9 of 11 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

It is unlikely that your insurance premiums will be affected by participation in this study as the

study has the potential to improve your diabetic control and reduce your risk of ill health.

However, if you are at all concerned, then we advise that you contact your insurers and seek

Research in the NHS is looked at by an independent group of people called a Research Ethics

Committee (REC). The REC is made up of experts, non-experts and members of the general

public. Together they review research applications to ensure your safety, rights, wellbeing and

dignity are protected at all times. This study has been reviewed and given favourable opinion

It is intended that the results of this study will be presented at conferences and published in

medical journals so that we can explain to the medical community what our research results

have shown. To do this our study information is double-checked by other professionals in

research and healthcare. There is a possibility that the study and its results may be publicised

for example on radio, television, magazines, books and websites. You will not be identified

in any publicity, reports or publication arising from this study. If you would like a general

summary of the results of the study you can select this on the consent form or please contact



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Who is organising and funding the research?

What will happen to the study results?

Researchers from Wythenshawe hospital have designed this study and will be carrying out this research. This study has been funded by the National Institute of Health and Research.

Further information and contact details

Manchester University

Who has reviewed this study?

expert advice before agreeing to participate.

NHS Foundation Trust

by REC.

the research team.

For further information about this study, please contact mft.middas.gdm@nhs.net or 07815987910.

> Thank you for taking the time to read this information sheet. We hope it has been of interest to you.







 MANCHESTER



Please initial

box



Consultant Endocrinologist – Dr. Basil Issa Tel: 0161 291 7070 Research Dietitian – Dr. Michelle Harvie Tel: 07815987910 Email: <u>mft.middas.gdm@nhs.net</u>

Manchester University

NHS Foundation Trust

1st Floor Education and Research Centre Manchester University NHS Foundation Trust Wythenshawe Hospital Manchester M23 9LT

MIDDAS-GDM

<u>Manchester Intermittent Diet in Gestational Diabetes Acceptability Study</u>

Participant Informed Consent Form

Participant Identification Number:

- 1. I confirm that I have read and understand the participant information sheet (version) for the above study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Manchester University NHS Foundation Trust and regulatory authorities, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records.
- 4. I consent to the collection of blood samples to be collected as described in the participant information sheet.
- 5. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.
- 6. I agree that my blood sugar readings can be recorded by the study team.
- 7. I agree to my GP being informed of my participation in this study and changes to my weight, body measurements, blood results, questionnaire results and medications as required
- 8. I understand that the information I provide to mobile applications as described in the Patient Information Sheet will be treated in line with the relevant terms of service and the app developers privacy policy at the time of downloading the application.

Manchester University **NHS Foundation Trust**

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9. I have informed the study team of any health issues, including those which may affect my ability to follow the diet, and I will inform the study team of any unusual symptoms that occur during the diet. I will inform the study team of changes to my health status during the study.

- 10. I have informed the study team of any health issues, including those which may affect my ability to exercise, and I will inform the study team of changes to my health status during the study.
- 11. I consent to the storage of personal information (including electronic) for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.
- 12. I agree to take part in the above study.
- 13. I agree that relevant information about my pregnancy and/or gestational diabetes can be obtained from my medical records within the 18-month study duration if I withdraw from the study early.
- 14. I am aware that my non-identifiable trial data may be shared with other researchers for the purposes of research.

Optional (delete as appropriate)

- 15. I agree to be approached to take part in sub-study 1 (interview study), and understand that I will be approached to take part in the sub-study regardless of whether I withdraw from the main study YES/NO 16. I would like to receive a summary of the final study results YES/NO
- 17. I agree to be contacted regarding future research opportunities YES/NO

My preferred contact (please tick and include email if preferred)

Do not contact

Post

Email

MANCHESTER The University of Manchester

for Health Research

NIHR National Institute

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Signatures		
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Name of person taking consent	Date	Signature
When completed: 1 for participa	nt; 1 for patient file; 1 for m file	nedical notes;; 1 (original) for site

Self-monitoring schedule for capillary glucose and ketone monitoring

ILE	D	Best Nł	IS Care
Ketones (low kcal days)	Glucose	Ketones (2 days/wk)	Glucose
Fasting before breakfast	Fasting (morning)	Fasting before breakfast	Fasting (morning)
the morning after each of		on 2 non-consecutive	
the low-energy days		days / week	
1 hour post evening meal	1hr post breakfast	1 hour post evening	1hr post breakfast
on each of the low-energy		meal on 2 non-	
days		consecutive days / week	
	1hr post lunch		1hr post lunch
	1hr post dinner		1hr post dinner

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Example of 1 day meal plan for Diet Day

The diet days aim to limit the calories to 1000 calories per day. You are aiming to include 2 (not consecutive) diet days each week. The other 5 days, follow the Mediterranean diet as described earlier. To keep the calories to 1000, the diet day will look like this:

Mixed diet		Vegetarian/ vegan diet
4	Carbohydrate portions	3
6	Protein portions	7
5	Vegetable portions	5
2	Fruit portions	2
3	Dairy portions	3
	Fat portions	1

Below are some examples of meals that can be used to help you follow a 1000 calorie diet... There are options for a mixed diet or vegan or vegetarian options, if you feel you wanted to try meat free days. Filling up on vegetables will make you feel less hungry

Mixed diet options

Breakfast	Portion	Dairy	Protein	Carb	Veg	Fruit	Fat
Grilled lean bacon	1 rasher	0	1	0	0	0	0
Grilled tomatoes	7 cherry tomatoes	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning	Ť						
Diet or natural yogurt	1 small carton	1	0	0	0	0	0
Lunch							
Wholegrain bread	2 medium slices	0	0	2	0	0	0
Tuna	⅓ of a 120g can	0	1	0	0	0	0
Green salad	Cereal bowl full / 80 g with oil-free dressing	0	0	0	1	0	0
Satsumas	2	0	0	0	0	1	0
Mid afternoon							
Low fat cheese	30g / match box size	1	0	0	0	0	0
Apple slices	I medium apple	0	0	0	0	1	0
Tea/ coffee		0	0	0	0	0	0
Evening							
Vegetable rice	4 tablespoons cooked rice 160g of mix vegetables	0	0	2	2	0	0
Chicken curry	90g /average chicken breast (no skin) & ½ can tomatoes, 1 desertspoon oil	0	3	0	1	0	1
Bedtime							
Low fat houmous	1 level tablespoon	0	1	0	0	0	0
Pepper sticks	1/2 red pepper	0	0	0	1	0	0
Milk	1 small glass	1	0	0	0	0	0
Total portions	a day	3 portions	6 portions	4 portions	5 portions	2 portions	1 portio

Vegetarian option

Breakfast		Dairy	Protein	Carb	Veg	Fruit	Fat
Egg	2 poached	0	2	0	0	0	0
Mushrooms	2 cupped handfuls / 80g	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Cheddar cheese	1 match box size / 30g	1	0	0	0	0	0
Cucumber	Sliced handful	0	0	0	1	0	0
Lunch							
Baked beans	2 tablespoons	0	1	0	0	0	0
Seeded bread toasted	1 medium sliced	0	0	1	0	0	0
Blueberries	1 handful	0	0	0	0	1	0
Mid afternoon							
Meat free ham	2 slice small	0	1	0	0	0	0
Pepper	1/2 sliced	0	0	0	1	0	0
Avocado	1/4	0	0	0	0	0	1
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Vegetarian sausage casserole Jacket potato (100g)	1 grilled sausage 2 cereal bowls vegetables 1 ½ egg sized (100 g)	0	2	1	2	0	0
Bedtime							
Pear	1 medium	0	0	0	0	1	0
Low fat cream cheese	1 tablespoon	1	0	0	0	0	0
Whole wheat cracker	2 biscuits	0	0	1	0	0	0
Milk	1 small glass	1	1	0	0	0	0
Total portions	a day	3 nortions	7	3	5 portions	2	1 nortions

Vegan options

Breakfast		Dairy equivalent	Protein	Carb	Veg	Fruit	Fat
Branflakes	3 tablespoons	0	0	1	0	0	0
Milk- sova	200 ml	1	0	0	0	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Midmorning							
Soya yogurt	3 tablespoons	1	0	0	0	0	0
Lunch							
Kidney bean & Vegetable chilli Wholemeal pitta	3 tablespoons of beans 60g with 1 cereal bowl mixed vegetables & 1/2 can chopped tomatoes 1/2 pitta	0	2	1	2	0	0
Banana	1 medium	0	0	0	0	1	0
Mid				-	-	-	
afternoon							
Low fat hummus	2 level tablespoon	0	2	0	0	0	0
1 carrot	I medium carrot (80g)	0	0	0	1	0	0
Tea/ coffee	1 mug	0	0	0	0	0	0
Evening							
Quinoa	2 tablespoon cooked	0	0	21	0	0	0
Tofu	4 matchbox	0	2	0	0	0	0
Mixed salad with edamame beans	2 x Cereal bowl full with oil free dressing & 1 tablespoons of edamame	0	1	0	2	0	0
Bedtime							
Peanut butter	1 heaped teaspoon	0	0	0	0	0	1
Apple	1 medium sliced	0	0	0	0	1	0
Milk	1 small glass	1	0	0	0	0	0
Total portion	s a day	3 portions	7	2	5	2	1
			portions	portions	portions	portions	portions

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59 60 To help with estimation of portions the following tables outline weight and measures of the different food groups. Where possible household measures are given to make things a little easier. Use these to help you plan your 2 days in the week of 1000 calories.

Carbohydrate 4 portions - mixed diet 3 portions - vegan/vegetarian	Equal to
Wholewheat or oat breakfast cereal, e.g. wholewheat biscuit, malted wholewheat squares, Grapenuts, bran flakes, fruit & fibre	24g or 3 tablespoons or 1 whole wheat biscuit
Porridge oats or no-added sugar muesli	20g or 1 heaped tablespoon
Wholegrain, wholemeal, rye, granary bread	36g or medium slice of bread (other than rye), 1½ slices of rye, or ½ roll
Wholemeal or multigrain pitta bread or tortilla wrap, chapatti made without fat	60g or 1x 8" tortilla or 1 standard pitta or small thin chapatti
Rye crispbread, crackers, oak cakes	22g or 2 crispbreads/ 2 oatcakes
Wholegrain rice cake	16g or 2 rice cakes
Wholewheat pasta or rice - cooked amount	1 tablespoon uncooked 2 tablespoons cooked
Cous cous, bulgar wheat, Quinoa, r earl baney	30g- raw weight or 60g cooked
Lasagne (wholemeal if possible)	20g raw weight or 1 large sheet or 1½ smaller sheets
Noodles (wholemeal if possible)	25g raw weight or ½ block/nest
Baked or boiled potato (in skin), cassava, sweet potato	1½ egg sized potatoes or 100g raw weight
Wholemeal pizza base (topping is from other food groups)	35g or $^{1}/_{6}$ of thin 10" pizza base
Unsweetened popcorn	20g or 2 handfuls

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Protein 6 portions – mixed diet 7 portions – vegan/vegetarian	Equal to
Fresh or smoked white fish (e.g. haddock or cod)	60g or 2oz 2 fish finger size
Seafood, e.g. prawns, mussels, crab	45g or 1½oz
Canned tuna or salmon in brine or spring water	45g or 1½oz ⅓ standard tin (120g)
Oily fish (fresh or tinned in tomato sauce or olive oil - drained), e.g. mackerel, sardines, salmon, fresh tuna, kippers, smoked salmon or trout	30g or 1oz or ¼ standard tin (120g) or ¼ fillet of salmon
Chicken, turkey, duck, pheasant (cooked without skin) Lean beef, pork, lamb, rabbit, venison, offal (fat removed) Quorn fillets, steak, mince or pieces Vegetarian mince frozen	30g or 1oz or 1 slice size of playing card
Lean grilled bacon Quorn ham	25g or ¾oz or 1 rasher
Lean ham Quorn bacon rashers (not slices)	30g or 1oz or 1 medium, 2 small or 4 wafer thin slices
Eggs	60 g or 2 oz or 1 egg
Tofu	50g or $1^2/_3$ oz or Size of 2 match boxes
Tempeh	25 g or 1 oz or Size of 1 match box
Baked beans (reduced sugar)	60 g or 2 oz or 2 tablespoons
Lentils, chickpeas and kidney beans, mung beans, black (eye beans, puy lentils, toor dahl, urad dahl, Raw weight	20g or ⅔ oz or 1 tablespoon raw
Cooked or tinned weight	65g or 2oz or 1 ¹ / ₂ tablespoons cooked /tinned or 1 cupped handful
Soya beans (frozen or cooked) or edamame beans	30g or 1oz or 1 tablespoon
Vegetarian sausage	25g or ¾ oz or ½ sausage
Textured vegetable protein (TVP)	10g or ⅓ oz uncooked or 1 heaped tablespoon uncooked
Low fat hummus	30g or 1oz or 1 level tablespoon

Cottage cheese

Cream cheese (light or extra light)

Bavarian smoked, feta, ricotta, mozzarella, reduced fat

halloumi, paneer made from semi-skimmed milk

Lower fat hard cheeses e.g.:

Reduced fat cheddar, Edam,

Vegetables – min 5 portions 1 portion = 80g or 2⅔oz	1 portion is equal to
Asparagus, Aubergines, Broccoli, Brussel sprouts, Carrots, Cabbage, Cauliflower, Chinese leaves, Courgettes, Cucumber, Curly kale, Green beans, Lettuce (mixed leaves), Mange tout, Methi, Mushrooms, Okra, Pak choi, Peas, Sugar snap, Spinach, Spring greens cooked, Sweetcorn, Tomatoes, Watercress fresh	80g or 2 ² / ₃ oz or 2 spears of broccoli, 8 cauliflower florets. 3 heaped tablespoons of vegetables or large cereal bowl of salad.
Fruit - 2 portions. 1 portion = 80g or 22/30z (30g or 1oz dried fruits)	1 portion is equal to
Berries (e.g. blackberries, blueberries, redcurrants, raspberries, strawberries) Cherries or grapes	80g or 2⅔oz 1 handful
Grapefruit, guava and mango	80g or 2⅔oz or ½ a whole fruit
Large fruit (e.g. melon, pineapple, papaya)	80g or 2⅔oz or 1 medium slice
Medium fruits (e.g. apple, pear, nectarine, orange, peach, banana, pomegranate)	80g or 2⅔oz 1 fruit
Small fruit (e.g. fresh apricots, kiwi, clementine, passion fruit, plums)	80g or 2⅔oz or 2 fruits
Any stewed fruit—unsweetened or with calorie-free sweetener e.g. apple, rhubarb	80g or 2⅔oz or 3 tablespoons
Kumquats, lychees, physalis	5 fruits
Dried fruits (raisins, currants, apricots)	30g or 1oz or 1 tablespoon
Milk and dairy foods - 3 portions	Equal to
Milk (semi-skimmed or skimmed) Alternative 'milks' with added calcium, e.g. soya **	¹ ⁄₃ pint or 200ml or 1 small glass
Diet yoghurts, Low fat/fat-free Greek or Greek Style or natural yoghurts, fromage frais or plain soya yoghurt, high protein yogurt	120-150g or 4-5oz or 1 small pot or 3 tablespoons
Whole milk natural yogurt	80g or 1 ⅔ oz or 2 tablespoons
	75g or 11⁄20z or

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** we recommend soya milk as coconut, oat and almond milks are lower in protein and calcium

1/4 pot, 2 tablespoons

30g or 1oz or Matchbox size

No more than 180g or 6oz a

30g or 1oz or

1 tablespoon

week

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Equal to
8g or 1 teaspoon 1 dessertspoon of oil
7g or 1 dessertspoon
7g or 1 dessertspoon 3 walnut halves, 3 Brazil, 4 almonds, 8 peanuts, 10 cashews or pistachios
50g or 10 olives
15g or ½ oz or 1 tablespoon
11g or ⅓ oz or 1 heaped teaspoon
12 g or ⅓ oz or 2 heaped teaspoons
40g or 1⅓ oz or 1/4 of an average pear
40g or 1 ¹ / ₃ oz or 2 tablespoons
Medical Management Protocols

Hypoglycaemia

Participants will be advised to take 15-20g of rapid acting carbohydrate in the event of hypoglycaemia, (defined as blood glucose <4 mmol/L) which is anticipated to raise blood glucose by 3 mmol/L. Examples of rapid acting carbohydrate include 170-225ml Lucozade Original (not Lucozade Sport), a small carton of fruit juice, 5-6 glucose tablets, 4/5 jelly babies, or a small tin of cola (150-200ml). Participants will be advised to repeat the treatment every 15 minutes until blood glucose is ≥4 mmol/l. The following table highlights when participants should consider taking additional follow-up slower acting carbohydrate:

Situation	Acceptable slow acting carbohydrate
Less than 1 hour before the next meal	Try and avoid
1-2 hour before the next meal	10g
More than 2 hours before the next meal	15-20g

Ketonaemia

Ketone levels ≥1.0 mmol/L on a fasting sample:

- Drink 1L fluids and repeat ketone levels after 4 hours.
- If ketone level has improved (<1.0mmol/L), no further action required.
- If ketone level has increased or remains the same, repeat ketone level after 2 hours.
- If ketone level is persistently increased, consume 40g carbohydrates and repeat in 2 hours.
- Continue to do this until ketone levels <1.0mmol/L.

If a participant experiences >2 episodes of the above throughout the course of the study their notes will be reviewed by the PI and their suitability for remaining in the trial will be assessed.

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Guidance for the introduction of diabetes medication (week 24-delivery)

Diabetes medication will be introduced according to the following protocol:

- If ≥25% fasting blood glucose readings are >5 mmol/l and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence Metformin MR 500 mg daily to be increased every 3 days by 500 mg to 1 gram BD if tolerated.
- If after reaching optimal or maximum tolerated dose Metformin ≥25% fasting blood glucose readings are >5 mmol/l in a 7-day period: commence bedtime isophane insulin 4 units and uptitrate the dose by 2 units every 3 days aiming for a fasting glucose of ≤5 mmol/l,
- and/or ≥25% of 1 hour postprandial glucose readings are >7 mmol/l in a 7 day period: commence prandial fast acting insulin analogue (Humalog or Novorapid)
 2-4 units with the relevant meal. Uptitrate the dose by 2 units every 3 days aiming for a 1 hour postprandial glucose of ≤7 mmol/l.
- Medication adjustment will be made in accordance with the above guidance.

BMJ Open



MIDDAS-GDM End of Study Questionnaire

Thank you for taking part in the MIDDAS-GDM Study.

This is one of the first studies of its kind. We hope to learn as much as possible from this study, in particular the views of people who have taken part. We are inviting you to provide your views on different aspects of the study and following the diet, and how we can improve our programmes and research studies in future.

Please complete the following questions and return this questionnaire to the MIDDAS-GDM study team in the envelope provided. If there is anything else you would like to say about your experiences of the study, please use the section at the end. Your answers to the questions below will remain anonymous.

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2. How sa 1 Not at all satisfied Comments	2	3 Sligh satis	4 htly fied	i dy overall 5 Quit satisfi	6 e ed	rent, s	8 Very atisfied	9 	1 Extro sati
2. How sa 1 Not at all satisfied Comments	2	3 Sligh satis	4 htly fied	idy overall 5 Quit satisfi	6 e ed	ment, 7 	8 Very atisfied	9 	1 Extro sati
2. How sa 1 Not at all satisfied Comments	2	3 Sligh satis	4 htly fied	i dy overall 5 Quit satisfi	6 e ed	ment, 7 	8 Very atisfied	9 	1 Extra sati

3. You were asked to attend additional face to face appointments at the hospital by the study team (please fill in the number)

4. You were asked to attend additional virtual (i.e. video call or telephone)



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appointments by the study team (please fill in the number)	
5. How do you feel about the number of additional appointments you attend? (tick)	u were asked to
I was happy with the number of appointments	
I would have preferred fewer face to face appointments	
I would have preferred more face to face appointments	
I would have preferred fewer virtual appointments	
I would have preferred more virtual appointments	
Comments:	
6. How do you feel about virtual (i.e. video call or telephone) appoint	tments?
□ I prefer virtual appointments to face to face appointments (please expla	in why below)
□ I prefer face to face appointments to virtual appointments (please expla	in why below)
Comments:	
<u>Diet</u>	
7. Which diet were you asked to follow? (<i>please tick</i>)	
	and a time in factor and a
Best NHS Care (i.e. increased fruit/vegetable intake, low-GI foods, r	reduction in free sugars,
regular meals)	a second
L Intermittent low energy diet (5 days of the best NHS care diet plus 2 not	n-consecutive days of
1000 kcal each week)	
v. was the diet easy to follow?	9 10
Not at all Slightly Moderately Very	Extremely



Comments:				
9. Did you enjoy	following the diet	plan?	7 0	0 10
Not at all	3 4 Slightly	b 6 Moderately	ہ Very	9 10 Extreme
Comments:				
10. Would you ma	ake any changes to	the written infor	mation (i.e. diet b	ooklets, recipes)
were given on	how to follow the	diet plan?	-	
□ Yes				
□ No				
If ves what chang	es would vou make	2		
in yes, what onding				
Commonts:				
			2	••••••
				•••••
11. How was you	first appointment	with the distition	2 (tick all that apply	40
11. How was your	r first appointment	with the dietitian	? (tick all that apply	/)?
11. How was your	r first appointment of information I rece	with the dietitian eived was OK	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece	with the dietitian eived was OK eived was too little	? (tick all that apply	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u>	r first appointment of information I rece of information I rece of information I rece	with the dietitian eived was OK eived was too little eived was too muc	? <i>(tick all that appl</i> y	/)?
11. How was your □ The <u>amount</u> □ The <u>amount</u> □ The <u>amount</u> □ I was happy	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec	with the dietitian eived was OK eived was too little eived was too muc ceived	? (tick all that apply	/)?
 11. How was your □ The amount □ The amount □ The amount □ I was happy □ The advice I 	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/) ?
11. How was your The <u>amount</u> The <u>amount</u> The <u>amount</u> I was happy The <u>advice</u> I Comments:	r first appointment of information I rece of information I rece of information I rece with the <u>advice</u> I rec received could be i	with the dietitian eived was OK eived was too little eived was too muc ceived mproved (specify b	? (tick all that apply h below)	/)?

Page 54 of 78 **Manchester University**

	diatitian a							
	dietitian c	auring yo	ur pre	gnancy ?				
⊔ Yes								
□ No								
Comments:								
13. How use	ful was yo	our final a	appoin	tment with the die	titian at 1	2 week	s post-c	delivery?
			•••		_		•	
1 Not at all	2	3 Slightly	4	5 6 Quite	7 Ver	8 У	9	10 Extreme
Comments:			2					
14. Did you f	feel confid	dent to ex	ercise	e whilst on the diet	plan?			
-	0	2	4	E C C		o		10
	2	.)	/1				~ ~ ~	
Not at all	-	Slightly	4	5 0 Quite	/ Very	0	9	Extremely
Not at all confident	-	Slightly confiden	t	Quite confident	/ Very confide	ent	9	Extremely confident
Not at all confident	_	Slightly confiden	t	Quite confident	/ Very confide	ent	9	Extremely confident
Not at all confident	-	Slightly confiden	t	Quite confident	/ Very confide	ent	g	Extremely confident
Not at all confident Comments:	-	Slightly confiden	+ t	S G Quite confident	7 Very confide	ent	9	Extremely confident
Not at all confident Comments:	-	Slightly confiden	+ t	S O Quite confident	Very confide	•nt	9 	Extremely confident
Not at all confident Comments:	- 	Slightly confiden	+ t	S G Quite confident	7 Very confide	o nt	9	Extremely confident
Not at all confident Comments:	_ 	Slightly confiden	+ t	S G Quite confident	7 Very confide	o nt	9 	Extremely confident
Not at all confident Comments:		Slightly confiden	+ t	Additional suppor	very confide	o Int	9 	Extremely confident
Not at all confident Comments:	ny of the f	Slightly confiden	t have	Additional suppor	t how ofte	ent	9	Extremely confident
Not at all confident Comments:	ny of the f	Slightly confiden	+ t have Ye	Additional suppor been useful & if so	t bod of	ent	9 	Extremely confident
Not at all confident	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	•nt •nt • n ?	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	ent	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s	ny of the f	following	+ t have Ye s	Additional suppor been useful & if so Preferred metho contact	very confide	o nt 	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s dietitian	ny of the f	Slightly confiden	+ t have Ye s	Additional suppor been useful & if so Preferred metho contact Face to face / p	very confide	•nt	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s dietitian	upport from	Slightly confiden	+ t have Ye s □	Additional suppor been useful & if so Preferred metho contact Face to face / p	very confide	nt •nt •n?	9 	Extremely confident
Not at all confident Comments: 15. Would ar Additional s dietitian	ny of the f	Slightly confiden	t have Ye s	Additional suppor been useful & if so Preferred metho contact Face to face / p	very confide	o nt 	9 	Extremely confident



				NHS Foundation Trus
Additional support from			Face to face / phone	
the doctors in the clinic				
More contact with other			Face to face / phone	
women in the study				
following the diets				
Other, please specify:				
		4		
16. Did you receive any si	uppor	t outs	ide of the study team help	o to keep you on track as you
progressed through th	ne stu	dy?		
🗆 No				
□ Yes				
If ves, what support did you	ı recei	ve?		
in yoo, milat ouppoint and you	. 1000			
		•••••		
			Record keeping	
17. How did you find the	finge	r pric	k testing requirements on	the study? (tick all those that
apply)				
Challenging but on the contract of the cont	ne who	ole <u>ac</u> ł	nievable	
□ Challenging and <u>not</u>	achiev	<u>able</u>		
Not challenging at all				
□ I felt it was <u>necessary</u>	<u>/</u> to te	st this	often to ensure my safety	
□ I felt it was <u>unnecess</u>	<u>ary</u> to	test th	nis often to ensure my safety	/
Comments:				
18 How did you find the	katan	a tast	ing requirements on the s	tudy? (tick all those that and
io. now ala you fina the	NELUII		ing requirements on the s	i uon an uiose uiaι appi
	ie who	bie <u>act</u>	nevable	
Challenging and not a	achiev	able		



2	NHS Foundation Trust
3 4	□ Not challenging at all
5 6	□ I felt it was <u>necessary</u> to test this often to ensure my safety
7	I felt it was <u>unnecessary</u> to test this often to ensure my safety
9	
10 11	Comments:
12 13 14	
15 16	19. How did you find using Diasend software?
17 18	□ Straightforward
19	□ Challenging but on the whole <u>achievable</u>
20 21	□ Challenging and <u>not achievable</u>
22 23	I felt uncomfortable using computer software to keep track of my medical details
24 25	I felt comfortable using computer software to keep track of my medical details
26	
28	Comments:
29 30 31	
32 33	20. How did you find completing the food diary during the study? (tick all those that apply)
34 35	Challenging but on the whole <u>achievable</u>
36 37	□ Challenging and <u>not achievable</u>
38	□ Not challenging at all
39 40	
41 42	Comments:
43 44	
45	
40 47 48	21. How did you find the physical activity questionnaires on the study? (tick all those that apply)
49 50	□ Challenging but on the whole achievable
51 52	□ Challenging and <u>not achievable</u>
53 54	□ Not challenging at all
55	
50 57	Comments:
58 59	
60	

		Manches	NHS Foundation
22. How did you find the quality of life	fe questionnaires	on the study? (ticl	k all those that a
Challenging but on the whole <u>a</u>	<u>chievable</u>		
□ Challenging and not achievable			
□ Not challenging at all	-		
Comments:			
	Libro® app		
23. Did you use the Libro® app?			
□ Yes			
\square No (please move to question 25)			
24. Did you find the App helpful?			
1 2 3 4 Not at all Slightly	5 6 Moderately	7 8 Very	9 10 Extrem
Comments	1		
25 What did you like about the App?			
		4	
26 What did you dialika about the Ar	an and could be im	aproved?	
20. What did you dislike about the Ap	op and could be in	iproved ?	
27 If you didn't use the ann what	were the reasons	for this? (tick all th	at apply)

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Manchester University

							NHS FO	undation in
🗆 Don	't like usin	ng apps in gene	eral	□ Not use	r friendly			
🗆 Labo	our intens	ive / time cons	uming	Prefer to use pen and paper				
□ Find	mobile d	evices challen	ging					
🗆 Lack	of regula	ar internet acce	ess					
Othe	ər (provide	e details below)					
			Dias	send Softwa	re			
28. Did you fi	nd the Di	iasend softwa	re helpf	ful?				
1 Not at all	2	3 4 Slightly	5 M	6 Ioderately	7 	8	9	10 Extremely
NOT at all		Silghuy		loueratery	vei	у		Lynemery
0								
Comments								
Comments								
Comments								
				<u> </u>				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias	send so	ftware?				
29. What did	you like a	about the Dias ke about the [send so Diasend	ftware? software ar	nd could t	be impro	oved?	
29. What did	you like a	about the Dias	send sor	ftware? software ar	nd could k	be impro	oved?	
29. What did	you like a	about the Dias ke about the D	send so Diasend	ftware? software ar	nd could k	be impro	oved?	
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29. What did	you like a	about the Dias	send so Diasend	ftware? software ar	nd could k	be impro	oved?	
29. What did	you like a you dislil	about the Dias ke about the D	send so Diasend <u>Study I</u>	ftware? software ar <u>mprovemen</u> dy?	nd could k	be impro	oved?	
29. What did	you like a you dislil you enjoy	about the Dias ke about the D	send so Diasend <u>Study I</u>	ftware? software ar <u>mprovemen</u> dy?	nd could t	be impro	oved?	
29. What did	you like a you dislil	about the Dias ke about the D	send so Diasend <u>Study I</u>	ftware? software ar <u>mprovemer</u> dy?	nd could b	be impro	oved?	
29. What did	you like a you dislil	about the Dias ke about the D	send so Diasend <u>Study I</u> the stud	ftware? software ar <u>mprovemen</u> dy?	nd could k	be impro	oved?	
29. What did	you like a you dislil	about the Dias ke about the D	send so Diasend <u>Study I</u> the stuc	ftware? software ar <u>mprovemen</u> dy?	nd could k	be impro	oved?	
29. What did	you like a you dislil	about the Dias ke about the D y most about	send so Diasend <u>Study I</u> the stuc	ftware? software ar <u>mprovemen</u> dy?	nd could k	be impro	oved?	



	NHS Foundation Trust
22 What did you an	iou least shout the study and sould be improved?
32. What did you en	joy least about the study and could be improved?
••••••	
•••••	
	Any other comments about the study
	\sim
Thar	nk you for completing this questionnaire, please return to:
	MIDDAS-GDM Study Team Nightingale Centre
	Muthershows Hearital Manchester M22.01 T
	wythenshawe Hospital, Manchester, M23 921

SPIRIT CHECKLIST

Section/Item	ltem no	
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Trial Registration	2a	
	2b	
Protocol Version	3	
Funding	4	
Roles and responsibilities	5a	
	5c	
	5d	
Introduction		
Background and rationale	6a	C
	6b	
Objectives	7	0,
Trial Design	8	2
Methods: Participants, interventions, and	d outcomes	
Study setting	9	
Eligibility criteria	10	
Interventions	11a	
		l i i i i i i i i i i i i i i i i i i i



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	11b	
	11c	
	11d	
Outcomes	12	
Participant Timeline	13	
Sample Size	14	
Recruitment	15	0
Methods: Assignment of interventions (fo	r controlled tri	
Allocation		
Sequence generation	16a	
Allocation concealment mechanism	16b	
Implementation	16c	



		i de la constante de
Blinding (masking)	17a	
	17b	
Methods: Data collection, management, a	ind analysis	
Data collection methods	18a	
	18b	
Data management	19	·C.
Statistical methods	20a	20
	20b	1
	20c	
Methods: Monitoring		
Data monitoring	21a	

	21b	
Harms	22	
Auditing	23	
Ethics and dissemination		
Research ethics approval	24	
Protocol amendments	25	
Consent or assent	26a	
	26b	.e
Confidentiality	27	· 2 0,
Declaration of interests	28	2/
Access to data	29	
Ancillary and post-trial care	30	
Dissemination policy	31a	

	31b
	31c
Appendices	
Informed consent materials	32
Biological specimens	33

Description	Location
Descriptive title identifying the study design, population,	1
interventions, and, if applicable, trial acronym	
Trial identifier and registry name. If not yet registered, name	2
of intended registry	3
All items from the World Health Organization Trial	throughout
Registration Data Set	Inroughout
Date and version identifier	n/a
Sources and types of financial, material, and other support	23
Names, affiliations, and roles of protocol contributors	1
Name and contact information for the trial sponsor	name only, 23
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	23
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)	18
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Explanation for choice of comparators	4-5
Specific objectives or hypotheses	13-14
Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
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	6
Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions for each group with sufficient detail to allow	9

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	n/a
disease)	
Strategies to improve adherence to intervention protocols,	
and any procedures for monitoring adherence (eg, drug tablet	13
return, laboratory tests)	
Relevant concomitant care and interventions that are	-
permitted or prohibited during the trial	/
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	13-14
time point for each outcome. Explanation of the clinical	
relevance of chosen officery and have subscreep in the set	
relevance of chosen enicacy and narm outcomes is strongly	
recommended	
Time schedule of enrolment, interventions (including any run-	
ins and washouts), assessments, and visits for participants. A	11-12
schematic diagram is highly recommended (see Figure)	
seremente diagram is highly recommended (see Figure)	
Estimated number of participants needed to achieve study	
objectives and how it was determined including clinical and	
	8
statistical assumptions supporting any sample size	
calculations	
Strategies for achieving adequate participant enrolment to	
reach target sample size	n/a
als)	
Method of generating the allocation sequence (eg, computer-	
generated random numbers) and list of any factors for	
stratification. To reduce predictability of a rendem converse.	
stratification. To reduce predictability of a random sequence,	8
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	
Mechanism of implementing the allocation sequence (eg	
control tolophonou convertibly numbered provide cost-	
central telephone, sequentially numbered, opaque, sealed	8
envelopes), describing any steps to conceal the sequence	
until interventions are assigned	
Who will generate the allocation sequence, who will enrol	7 0
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
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	9-15
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	supplementary PIS
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 wher details of data management procedures can be found, if not in the protocol	e 16
Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistica analysis plan can be found, if not in the protocol	16
Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Composition of data monitoring committee (DMC); summar	,

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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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 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) Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	n/a 13, 16 16 n/a 19
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 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) Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Iten 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	13, 16 16 n/a 19
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Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Iten 32) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	
Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies if applicable 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 Financial and other competing interests for principal	7, supplementary consei
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 Financial and other competing interests for principal	n/a
Financial and other competing interests for principal	16
investigators for the overall trial and each study site	23
Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	supplementary PIS
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	

Authorship eligibility guidelines and any intended use of professional writers	n/a
Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	19
Model consent form and other related documentation given to participants and authorised surrogates	supplementary materials
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	15

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6 Infant, newborn	
⁷ Pregnancy	
Glucose Intolerance	
10 Diabetes, Gestational	
¹¹ Insulin	
12 13 Hyperglycaemia	
14 Prediabetic state	
¹⁵ Metformin	
16 Glycated Hemoglobin	
17 Overweight	
19 Obesity	
20 Diabetes Mellitus Type 2	
21 Diabetes Mellitus, Type 2	
22 Diel, rieditry 23 Eessibility Studies	
²⁴ Mobile Applications	
25 Iniobile Applications	
26 Body Weight	
²⁷ Hypoglycaemic agents	
29 Fasting	
30 Intermittent Fasting	
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T DieR Template for Intervention

BMJ Open The TIDieR (Template for Intervention Description and Repliced tion) Checklist*:

Information to include when describing an intervention and the location and the location

Description	and Replication Information to include when describing an intervention and the location	E E E		mormation		
Item	Item			Where located **		
number		for L	B rim	ary paper	Other † (details)	
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		rela	2 Ngumb	per)		
		eme ted t	024.			
	BRIEF NAME	io te	Dov			
1.	Provide the name or a phrase that describes the intervention.	upe xt a				
	WHY	rieur (nd dat	aded f			
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	a mi	6 <u>4</u> −5			
		ning.	http			
	WHAT	9, ≥				
3	Materials: Describe any physical or informational materials used in the intervention, including those	traji		15	annendix	
0.	provided to participants or used in intervention delivery or in training of intervention, meldeling these	ning	P 1 2 ,	10		
		, an	<u>ă</u> .			
	Provide information on where the materials can be accessed (e.g. online appendix, URL).	d sir	ŝ			
		nilar	on /			
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention,	. tec	<u>F</u> 6-1	2		
	including any enabling or support activities.	hno	e 12			
		logie	20			
	WHO PROVIDED	S.	25 a			
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their		 Ag1, 7	-12, 17-18		
	expertise, background and any specific training given.		ence			
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TIDieR che	cklist For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtm	I	e de		1	

of 78	BMJ Open	open-2	
6.	<u>کے</u> Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or	<u>8</u> 46-18	
	telephone) of the intervention and whether it was provided individually or in a group.	78264 o	
	WHERE	n 10	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary	February	
	WHEN and HOW MUCH	2024.	
8.	ع 2 Describe the number of times the intervention was delivered and over what period of time including	6 ≰6-18	
	the number of sessions, their schedule, and their duration, intensity or dose.	nloaded	
		from	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why,	6-18	
	when, and how.	//bmjop	
	MODIFICATIONS	en.bn	
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why,		
	when, and how).	n/ on Ju	
	HOW WELL	ne 12	
11.	مع Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any	2 2 2 13-14	
	م strategies were used to maintain or improve fidelity, describe them.	5 at Ag	
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	N/A	
	intervention was delivered as planned.	3ibliogr	
		aphique	
TIDieR cł	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	de	

- BMJ Open ** Authors use N/A if an item is not applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. Reviewers use '?' if information applicable for the intervention being described. sufficiently reported. sufficiently reported.
- or other published papers (provide citation details) or a website (provide the URL). + If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.
- * We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains an elaboration and elaboration for each item.
- * The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study ether elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist $\mathbf{\hat{P}}_{\mathbf{\hat{k}}}$ a randomised trial is being reported, the Lit-statem, in conjunction with th, i.e.R can be used in conjunction w TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of the CONSORT 2010 Statement. When a clinical trial protocol is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement a statement Statement (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropria to that study design (see from h (ABES) ata mini www.equator-network.org).

ttp://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique

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