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Effectiveness and acceptability of myo-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial

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Effectiveness and acceptability of *myo*-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial

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ABSTRACT

Introduction

Gestational diabetes increases maternal and offspring complications in pregnancy, and cardiovascular complications in the long term. The nutritional supplement *myo*-inositol may prevent gestational diabetes, however further evaluation is required, especially in multi-ethnic high-risk mothers. Our pilot trial on *myo*-inositol to prevent gestational diabetes will evaluate trial processes, assess acceptability to mothers, and obtain preliminary estimates of effect and cost data prior to a large full-scale trial.

Methods and analysis

EMmY is a multi-centre, placebo-controlled, double-blind pilot randomised trial, with qualitative evaluation. We will recruit pregnant women at 12-15^{+6} weeks gestation, with gestational diabetes risk factors, from five maternity units in England between 2018-2019. We will randomise 200 women to take either 2g of *myo*-inositol powder (intervention) or placebo, twice daily until delivery. We will assess rates of recruitment, randomisation, adherence to intervention, and follow-up. Gestational diabetes will be diagnosed at 24-28 weeks as per NICE (National Institute for Health and Care Excellence) criteria (fasting plasma glucose ≥ 5.6mmol/l, 2 hr plasma glucose ≥7.8 mmol/l). We will assess the effects of *myo*-inositol on glycaemic indices at 28 weeks, and on other maternal, fetal and neonatal outcomes at postnatal discharge. Qualitative evaluation will explore the acceptability of the trial and the intervention amongst women and healthcare professionals. Cost data and health related quality of life measures will be captured. We will summarise feasibility outcomes using standard methods for proportions and other descriptive statistics, and where appropriate, report point estimates of effect sizes (e.g. mean differences and relative risks) and associated 95% CIs.

Ethics and Dissemination

Ethical approval was obtained through the London Queen Square Research Ethics Committee (17/LO/1741). Study findings will be submitted for publication in peer-reviewed journals. Newsletters will be made available to participants, healthcare professionals and members of Katie's Team (a patient and public advisory group) to disseminate.

Trial registration number: International Standard Randomised Controlled Trial Number: ISRCTN48872100

Key words: Pregnancy, *myo*-inositol, gestational diabetes, pilot, randomised controlled trials, protocol

Protocol version and date: Version 4.0, 15th January 2018.

Strengths and limitations of this study

Strengths

- Pilot study on trial processes, clinical outcomes, and cost data to inform definitive trial.
- Qualitative evaluation on the acceptability of the trial and intervention.
- Pragmatically designed and reviewed by a patient and public involvement advisory group to allow for integration into current routine NHS clinical practice.

Limitations

- Trial applicable only to women with proficiency in English language.
- Intervention available over the counter and may be accessible to trial participants.

INTRODUCTION

Increasing rates of obesity worldwide, combined with sedentary lifestyle, has contributed to the rise in the number of women with gestational diabetes, a condition with high blood glucose levels diagnosed in pregnancy. The rates of gestational diabetes approach 24% in inner city maternity units in the UK.[1] This is likely to be due to the multi-ethnic populations in inner city areas with high levels of 'at-risk' populations, who are at greater risk of gestational diabetes. For instance, women of South Asian origin are 10 times more likely to develop gestational diabetes compared with Caucasian women.[2]

Gestational diabetes is associated with an increased risk of pregnancy complications including pre-eclampsia, macrosomia, caesarean section, postpartum haemorrhage, stillbirths and neonatal deaths.[3 4] Therefore, pregnant women who are considered to be at high risk are offered a screening test for gestational diabetes.[5] Pharmacological interventions such as metformin have not been shown to prevent gestational diabetes, and lifestyle interventions are challenging to implement, given their complexity. [6] *Myo*-inositol, a nutritional supplement has been reported to have beneficial effects in preventing gestational diabetes in some randomised trials.[6]

Existing randomised trials on *myo*-inositol are of poor quality, with small sample sizes, and involve homogeneous populations, mainly of Caucasian mothers from Italy. [7] The generalisability of these findings to the NHS setting is not known. Given the large sample size, and resources required to undertake a large-scale trial on the effects of *myo*-inositol on preventing gestational diabetes and its complications, there is a need to pilot trial procedures[8], ensure acceptability to participants and healthcare professionals, and obtain relevant preliminary data.

METHODS AND ANALYSIS

Study design

EMmY is a multi-centre, randomised, placebo controlled, double-blind, pilot trial with a nested qualitative evaluation.

Study aim and objectives

The aim of the EMmY trial is to pilot study procedures and assess acceptability prior to undertaking a full-scale trial on *myo*-inositol supplementation during pregnancy to prevent gestational diabetes in high risk women. Our primary objectives are to evaluate trial processes and procedures, obtain real time data on the study design, assess adherence and report any side effects. Our secondary objectives are to assess the acceptability of the study and the intervention to pregnant women and healthcare professionals, identify reasons for non-participation and non-retention, and identify barriers in recruitment and standardisation of care pathways for clinicians. Finally, we aim to obtain preliminary estimates on the effects of the intervention on glycaemic status, costs, and quality of life measures.

Study setting

The EMmY trial will be conducted in five inner city maternity units including Barts Health NHS Trust (The Royal London Hospital, Whipps Cross University Hospital and Newham University Hospital), St George's University Hospitals NHS Foundation Trust, and Manchester University Hospital NHS Foundation Trust (Manchester Royal Infirmary) over a period of 12 months (Feb 2018-Jan 2019).

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the EMmY trial are those with a singleton, viable pregnancy from 12^{+0} - 15^{+6} weeks gestation, able to provide written informed consent in English, and with at least one of the following risk factors: family history of diabetes in any one of their first degree relatives, gestational diabetes in a previous pregnancy, obesity (BMI ≥ 30 Kg/m2), minority ethnic family origin with a high prevalence of diabetes (such as South Asian and Black Caribbean/African), polycystic ovary syndrome, or previous macrosomic baby (birth weight > 4.5 kg). Women on corticosteroids, metformin or insulin treatment are not eligible for recruitment. Women with known pre-existing type 2 diabetes or diagnosed with pre-gestational diabetes in early pregnancy will not be randomised. This will be based on first trimester glycated haemoglobin (A1c) (HbA1c) levels and/or fasting and 2-hour postprandial Oral Glucose Tolerance Test (OGTT) depending on individual Trust policy.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Where possible, eligible participants will receive the EMmY Patient Information Sheet (PIS) at least twenty-four hours (24hrs) prior to their hospital booking visit or first trimester routine ultrasound scan depending on site policy. This is to make sure they have had ample time to consider the trial. The PIS will be accompanied by an invitation letter from the principal investigator (PI) informing patients that they may be approached by a member of the clinical research team, typically a research midwife to discuss participation in the trial at their hospital-booking visit or first trimester ultrasound scan. The PIS will be discussed with eligible women by a member of the research team, typically a research midwife. Potential participants will have the opportunity to ask any questions and to clarify the study processes. If women are keen to join the study after these discussions, informed written consent will be

obtained. Additional consent forms will be completed prospectively with regards to participating in qualitative interviews and the collection and storage of umbilical cord blood samples for future research. Women who do not wish to take part in the research interviews or consent to cord blood collection and storage, can still participate in the trial. The informed written consent form is submitted as supporting information. (See online supplementary file 1).

Following consent, participants with a history of gestational diabetes, will undergo an HbA1C and/or an OGTT test depending on individual trust policy before 16 weeks gestational age. These tests are conducted to rule out any potentially pre-existing but undiagnosed type 2 diabetes or early pre-gestational diabetes. Based on the NICE criteria, abnormal HbA1c results are defined as HbA1c levels > 48mmol/l and abnormal OGTT results defined as a fasting blood glucose level ≥ 5.6mmol/l and/or a 2-hour blood glucose level ≥7.8 mmol/l post 75g glucose load.[5]

Women with borderline HbA1c levels (41 – 47 mmol/l) at the booking visit will undergo first trimester OGTT. If the OGTT test shows an abnormal reading, these women will not be randomised. This process also allows us to assess the proportion of women with previous gestational diabetes, who enter subsequent pregnancies with potentially undiagnosed type 2 diabetes or pre-gestational diabetes. Participants eligible for randomisation will be randomly allocated to either the intervention group or the control group. The senior statistician will generate the allocation sequence. The randomisation and group allocation will be carried out through a secure online randomisation system. The randomisation scheme will be based on permuted blocks of random block size (sizes 4, 6 and 8), stratified by participating site. Research midwives will enrol and assign interventions to participants. Except for the senior statistician, study participants, care providers, data analysts and outcome assessors will be

blinded to the group allocation. The research team will be un-blinded only if necessary for the safety of the trial participant.

Following randomisation, baseline information on demographic and clinical characteristics will be collected from participants' maternity notes. The European Quality of life 5-Dimensions 5-Level scale (EQ-5D-5L), a validated questionnaire, will be administered at baseline and at the end of the trial to capture QALYs (Quality-Adjusted Life-Years) in all participants. Participants in the intervention group will be provided with the *myo*-inositol powder supplement to be taken in a dose of 2g twice daily from 12^{+0} - 15^{+6} weeks gestational age until delivery. Participants in the control group will be provided with a placebo identical in colour, flavour and texture to the *myo*-inositol powder to be taken in the same dose and for the same duration of time. Information regarding supplement intake and dosage will be provided to prevent misinterpretation of instructions or ambiguity.

Adherence to the intervention

The participants will be provided with the intervention or placebo packs in two stages, with half of their supply being provided at **Visit 1** (recruitment and randomisation, at 12-15^{+6} gestational weeks), and the remaining half of their supply at **Visit 3** (approximately 28 gestational weeks). A paper based diary and/or a mobile application (depending on participant's preference) will be provided to participants to self-report on adherence, with reminder features which we anticipate will encourage adherence. Participants will also be asked to bring any remaining sachets to their 28 week visit, where they will receive the next batch of intervention or placebo. A count of unused sachets (supplements) will be recorded as an additional measure of adherence to the intervention. Urinary inositol levels will also be tested at **Visit 3** (approximately 28 gestational weeks) as an additional measure of adherence in both groups. Text messages or phone calls will be made by the research team, to remind

participants of their upcoming appointments during the study. A participant will be deemed non-adherent if she has used 75% or less of her trial sachets. **Figure 1** below provides details of trial processes and procedures.

Sample size calculation

We expect that 1500 women will be booked for antenatal care each month at the participating hospitals, and at least 300 of those will be eligible. Assuming 1000 eligible women were approached, we expect about 25% (250/1000) to be consented. We expect that 20% (50) of women who consent to the study will have a previous history of gestational diabetes. These women will undergo an early HbA1C and/ or an OGTT test before 16 weeks gestational age to rule out any potentially pre-existing but undiagnosed type 2 diabetes or early pre-gestational diabetes. Any of these women with abnormal HbA1C (> 48mmol/l) and/ or OGTT (fasting blood glucose ≥ 5.6mmol/l and/or a 2-hour 75g blood glucose level ≥7.8 mmol/l) results and hence a diagnosis of early gestational diabetes will be excluded from the study. This will result in 200 women being randomised to either the *myo*-inositol or placebo arm. With an estimated attrition rate of 20%, we expect that 160 (160/200) women will remain in the study. Amongst these 160 women, we expect 80% of them (128/160) to be adherent to the study processes. These numbers will allow for estimation of the 95% confidence intervals for trial feasibility outcomes with amplitudes of around 10%.

Primary and secondary outcome measures and outcome assessment

The primary outcomes are the proportion of eligible, consented, and randomised participants. The secondary outcomes include the acceptability of the study and the intervention as well as the proportion of outcome measures obtained in the trial. Laboratory outcomes will be assessed at 28 weeks gestation including plasma glucose levels and the diagnosis of

gestational diabetes. This will be achieved through fasting and 2-hour postprandial 75 g oral glucose tolerance test (OGTT). Gestational diabetes will be diagnosed according to the 2015 National Institute for Health and Care Excellence (NICE) criteria (fasting glucose ≥ 5.6mmol/l, 2 hr ≥7.8 mmol/l). Other laboratory outcomes include insulin levels, leptin and adiponectin levels, c-peptide levels at fasting and 2hrs post-glucose load, HOMA-IR and urinary inositol levels.

Maternal, fetal and neonatal outcomes will also be assessed at delivery and/or discharge. Maternal outcomes include pre-eclampsia, gestational age at delivery, postpartum haemorrhage, mode of delivery, preterm delivery before 34 and 37 weeks, perineal trauma, admission to high dependency unit (HDU) or intensive care unit (ITU), maternal death and maternal infection. Fetal and neonatal outcomes include, birth weight, macrosomia (birth weight>4.5Kg), admission to neonatal intensive care unit (NICU), shoulder dystocia, neonatal death, respiratory distress syndrome, septicaemia, stillbirth, small for gestational age ($< 10^{th}$, $< 5^{th}$, $< 3^{rd}$) as per population-based centile, hypoglycaemia, hypocalcaemia, Apgar at 10 minutes, birth trauma such as shoulder dystocia fracture, and hyperbilirubinaemia.
Cord blood will be collected and tested for c-peptide levels in the neonate. In addition, cost data and health related quality of life measures will be captured. Cost data include the cost of *myo*-inositol and placebo administration, cost of routine tests, additional laboratory tests and other investigations in both groups, cost of clinic visits, hospital admissions, type of delivery, cost to treat adverse events, antenatal costs, postnatal costs, and neonatal costs.
A schedule of assessments is shown below in **Table 1**.

Visit number		0	1	2	3	4	5
Gestational Weeks		**<16w**	**12-15^{+6}w**	**~20w**	**~ 28w**	**~ 36w**	**Delivery**
Tasks	Consent	**x**					
	Participant demographic data	**x**					
	OGTT/HbA1c pre-randomisation (if previous GDM history)	**x**					
	Randomisation		**x**				
	Delivery of intervention		**x**	**x**	**x**	**x**	
	OGTT to diagnose GDM				**x**		
	Assess Adherence (App / Diary)			**x**	**x**	**x**	**x**
	Maternal, fetal and neonatal outcomes						**x**
	Qualitative data collection (interviews)			**x**		**x**	
* Assessments will be completed as near to the scheduled date as possible, depending on participant's appointment date.							

Table 1 shows the schedule of assessments for the EMmY study

Qualitative evaluation

The qualitative evaluation will explore the acceptability of the trial and the intervention amongst participating women and healthcare professionals. This will be achieved through direct observation of recruitment, and semi-structured interviews as outlined below.

Recruitment observation

A sample of recruitment appointments (approximately 3-4 participants at each site) will be observed, in order to gain detailed knowledge of women's specific needs or concerns, as well

as factors in the recruitment setting/environment that may impact on the recruitment process and outcomes.

Brief interview/open ended questionnaire with those who decline recruitment

Women who decline to participate in the pilot trial will be invited to complete an open-ended questionnaire (either verbally or in writing) on (i) their reasons for declining to participate and (ii) their feedback on the recruitment process. Responses will inform recruitment procedures both for the pilot trial and the potential future full-scale trial. This model has been recently used in a pilot trial of group antenatal care at Barts Health NHS Trust (Pregnancy Circles study) and was found to work well as a means of identifying barriers to trial participation. [9]

Interviews with randomised participants

Following consent, semi-structured interviews will be conducted with a purposive sample of approximately 15-20 women at different points in the trial. Interviews will be conducted approximately two months after randomisation (20-24 weeks of pregnancy) and towards the end of pregnancy (36-38 weeks) to capture women's experiences throughout pregnancy. The first interview will explore participants' experience of their pregnancy so far, their understanding, beliefs and perception of gestational diabetes, perceived acceptability of the study procedures and intervention, and other factors that can influence adherence. The second phase of interviews will purposively include 10 participants from the first interview phase who found intervention compliance and adherence particularly difficult or easy in the early stages of the study. This will be to address any further difficulties and supports for managing adherence to the intervention, and any further experiences with study participation, data

collection methods, and follow up procedures. We will also endeavour to interview a sample of women who drop out of the trial.

All interviews will be audio-recorded with consent, and participants will also be offered a £10 voucher for each interview.

Interviews and/or focus groups with healthcare professionals

Semi-structured interviews or focus groups, will be conducted with a cross-section of key healthcare professionals (approximately10-15 consisting of obstetricians, diabetologists, and midwives) who are involved in delivering the intervention, and/ or who have expertise in the area of gestational diabetes. Here, we will explore various approaches to managing/preventing GDM in multi-ethnic populations in the NHS setting. We will obtain their views on barriers to recruitment, compliance, retention, and any suggestions on how these could be overcome. Informed consent will be gained and a prepared interview guide will include questions arranged in topics.

Patient and public involvement

Prior to the grant application, the development of the EMmY research question was informed by patients' priorities and preferences. In our survey of pregnant women (n=71) within the Barts Health NHS Foundation Trust, 83% (59/71) agreed that there was a need to prevent gestational diabetes. More women indicated that they would be inclined to take *myo*-inositol (79%, 56/71) than follow a complex lifestyle intervention (60%, 43/71); and 8 out of 10 informed that they may or would definitely join a trial on *myo*-inositol. Additionally, two-thirds of healthcare professionals surveyed (66%, 58/88) were keen to participate in a trial on *myo*-inositol.

We have collaborated with "Katie's Team", a women's health and childbirth specific patient and public involvement advisory group [10] to inform several elements of the EMmY pilot trial. Katie's Team members contributed to the development of the study design, reviewed the trial documents such as the patient information sheets and informed consent forms and developed the interview schedule. Patients and public representatives are not involved in recruitment or the conduct of the study

We will submit study findings for publication in published in peer-reviewed journals. Study results will be circulated to participants, healthcare professionals and members of Katie's Team through newsletters, who in turn will further disseminate through traditional means and social media platforms.

Data analysis

Statistical analysis

Data will be analysed using descriptive statistics in order to inform trial feasibility and process. We cannot reliably assess the effect of the intervention on outcomes, given the pilot sample size. However, where appropriate, we will present point estimates of effect sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals. The primary analysis will also involve the estimation of the proportions of the primary outcomes (i.e. eligible women recruited into the trial, recruited women who complete the trial and adhere to the intervention treatment until delivery). We will also test if the proportions of the primary outcomes differ between the treatment group and the control group. We will explore the effect of mother's ethnicity, history of previous gestational diabetes, and maternity unit attended, on recruitment, adherence and attrition. All analysis will be performed using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Economic analysis

A cost-utility analysis will be undertaken using a short term time horizon (the 'within trial' period) to obtain preliminary estimates of the cost-effectiveness of *myo*-inositol supplementation versus placebo in the prevention of gestational diabetes, which will inform the full-scale trial. The cost utility measures in the short-run will be the incremental cost per unit of change per Quality-Adjusted Life-Year (QALY) gained. Unit costs will be collected and assessed from the perspective of the NHS and personal social services via standard sources. QALYs will be calculated based on the health related quality of life (HRQL) collected during the trial from the EQ-5D-5L questionnaires. The QALYs experienced from baseline to end of trial will be calculated as the area underneath this profile. Cost-utility will be calculated as the mean cost difference between the intervention and control group divided by the mean difference in outcomes to give the incremental cost-effectiveness ratio (ICER). Cost-effectiveness acceptability curves will be constructed and we will subject the results to extensive deterministic sensitivity analysis.

Qualitative data analysis

Interview data will be subjected to thematic analysis. Transcripts will be coded for themes and concepts relating to women's and health professionals' experiences and perceptions of this intervention and the study. In this way we will develop an analytical framework to identify key themes and how these inter-relate. Where possible, we will use constant comparison techniques and examine deviant cases to refine our analysis.

Clinical management

Besides *myo*-inositol and placebo, EMmY does not involve any other intervention. All aspects of antenatal care will be at the discretion of local clinicians. Further management of women diagnosed with gestational diabetes will be as per local guidelines for management of gestational diabetes.

Participant withdrawal

After consent, a participant can decide to self-withdraw from the trial. Clear distinctions will be made if the participant is only withdrawing from the trial but allowing further follow-up or withdrawing from both the trial and follow-up. A participant can also be withdrawn from the trial treatment if based on the opinion of the clinical carers and the investigators, it is medically necessary to do so. However, with any post randomisation exclusions, the research team will endeavour to obtain and record the reasons for withdrawal and any adverse events in the case report form. Where appropriate, efforts will be made to follow up women who withdraw for all safety and efficacy outcomes.

If a participant explicitly withdraws consent to any further data collection, her decision will be respected, noted in the final study form and no further data will be collected from that participant. The participant will continue with NHS standard practice for follow-up care.

Data management

All participants in the EMmY trial will be given a unique trial number and will be identified to their local sites by their NHS hospital number. The Chief Investigator has a responsibility to ensure that participant anonymity is protected, maintained and associated participant information kept confidential and managed in accordance with the Data Protection Act (1998-UK), the sponsor's data management Standard Operating Procedures (SOPs), The

Research Governance Framework for Health and Social Care, The Research Ethics Committee Approval and the NHS Caldicott Guardian. All data will be monitored centrally and locally at the trials coordinating centre- Barts Research Centre for Women's Health (BARC) for consistency, viability and quality using bespoke data management systems. All participants' data obtained for the trial, including personal information, will be anonymised, held securely and treated as strictly confidential. The data will be entered onto a secure computer database, either by a member of the research team or directly via a secure internet connection. All staff at each participating site and at the trials unit, share a responsibility of care to prevent unauthorised disclosure of personal information. No identifiable individual data will be published. In accordance to the MRC guidelines on data retention, participants' data collected will be kept for 20 years following the end of trial to allow for verification and further data sharing via an individual patient data meta-analysis for instance.

Monitoring and auditing

The study sites will perform remote trial monitoring according to the agreed trial monitoring plan and self-monitoring template, at the trials coordinating centre, Barts Research Centre for Women's Health (BARC). Trial monitoring will include source data verification, checks on all informed consent forms (ICF) and eligibility for randomisation log, and a sample set of case report forms (CRFs). Any major discrepancies with respect to trial regulatory matters and study protocol found at a site visit will trigger an audit of trial data by the coordinating team at the site involved, independently of the sponsor and investigators. The Chief Investigator (CI) will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements, including, but not limited to, the Trust and Research Office policies and

procedures, the Research Governance Framework, guidelines for good clinical practice (GCP) and any subsequent amendments. Any form of non-compliance will be captured through communications and updates, monitoring visits, CRFs and other sources. In order to identify and verify any developing trends, the sponsor will maintain a log of any non-compliances, assess them and action a timeframe in which they need to be dealt with. In the event of any safety information which may require significant changes to the risk/benefit analysis of the study, the protocol, the ICF and the PIS will be amended and submitted to REC for revision and approval. All participants of the EMmY study will be duly informed and provided with a revised copy of the PIS and the ICF to confirm their wish to continue where possible.

Sample handling, labelling and logging

Participants' samples collected will be processed by either NHS laboratory services, or by Affinity Biomarker Labs (Imperial College London, W12 0BZ). Samples will be labelled with the date of collection and participant's unique trial number. Upon arrival at the laboratories, samples will be handled as per routine clinical practice and local policies. Samples will be stored, processed and analysed by laboratory staff as defined by study standard operating procedures (SOPs), with any inconsistencies referred back to the research team or the clinical team. All samples received and processed in the NHS Labs will be logged onto the NHS database, and samples received and processed by the Affinity Biomarker Labs will be logged onto the trial specific secure database.

Trial organisation

EMmY has a Project Steering Committee (PSC) that provides independent supervision of the trial, providing advice to the Chief and Co-Investigators and the Sponsor on all aspects of the

trial and affording protection for patients by ensuring the trial is conducted according to the principles of Good Clinical Practice in Clinical Trials**.** The trial will also be overseen by a Trial Management Group (TMG), who will meet regularly up until the end of the trial to evaluate trial progress and resolve any potential challenges. The TMG consists of the lead investigators, research midwives, and the project team at BARC.

EMmY is a pilot study with a low risk intervention and therefore no major safety concerns. In addition, EMmY aims to primarily assess the feasibility of conducting a potential full-scale trial rather than the effectiveness of the intervention and therefore does not require a data monitoring committee (DMC).

Safety assessment

Adverse events (AEs), are defined as any untoward medical occurrences in a participant which are not necessarily related to the intervention administered. AEs will be recorded by the principal investigator in the CRF and the participant's medical notes. Participants experiencing AEs will be followed up by the research team. Serious adverse events (SAEs) are defined as any untoward occurrences that results in death, that is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, that results in persistent or significant disability or incapacity, or is otherwise considered medically significant by the principal investigator. Any SAEs will be reported to the sponsor within 24 hours of learning of the event and to the main Research Ethics Committee (REC) within 15 days in line with the required timeframe.[11]

Indemnity

EMmY is sponsored by Queen Mary University of London (QMUL) as defined by the Research Governance Framework for Health and Social Care (April 2005). EMmY is also

covered by the insurance brokers of QMUL on a "No Faults Compensation for Clinical Trials and/or Human Volunteer Studies". This policy covers or indemnifies the insured in respect of their legal liabilities arising out of the insured's activities.

ETHICS AND DISSEMINATION

EMmY has received ethical approval from the London Queen Square Research Ethics Committee (17/LO/1741) as well as site-specific approval for each participating site. EMmY is also registered online at ISRCTN.com (ISRCTN48872100). The CI will co-ordinate dissemination of data from this study. The results from the trial will be submitted for publication in a major journal. The PSC will be responsible for approval of the main manuscript prior to submission for publication. Authorship of presentations and reports related to the study will be in the name of the lead investigators. Publications will name local co-ordinators as well as those involved in central co-ordination and trial management. The writing will be the responsibility of a writing committee including all of the investigators.

DISCUSSION

Approximately 40% of all women who are diagnosed with gestational diabetes, progress to type 2 diabetes within five years post-delivery, in addition to their increased risk of gestational diabetes in future pregnancies.[12 13] Infants born to mothers with gestational diabetes are at an increased risk of impaired glucose regulation, obesity and diabetes, leading to a vicious cycle of accumulated risks in the next generation.[14 15] Therefore, preventing gestational diabetes provides intergenerational benefits, preventing chronic diseases in both mothers and their offspring.

With a projected increase in the NHS yearly spend (from £8.8 billion to £13 billion) on type 2 diabetes and its complications,[16] preventing gestational diabetes has significant societal and economic benefits. However, evidence on effective and acceptable approaches to preventing gestational diabetes is lacking.[17] Randomised trials on lifestyle changes has shown no significant difference in the incidence of gestational diabetes between groups. [6, 18] Women have reported on the difficulty of incorporating exercise into their daily routine as a result of child care, pregnancy symptoms and work commitments.[17] Trials on the use of metformin in preventing the incidence of gestational diabetes also reported on no statistically significant difference between groups. [18] There is therefore a need for a simple, effective, safe and acceptable intervention in preventing the onset of gestational diabetes in high-risk pregnant women.

Myo-inositol is a dietary nutritional supplement, which is present in staple foods such as meat and legumes, and is currently sold over the counter as a food supplement. Its use is not contra-indicated in pregnancy.[19 20] Existing trials have shown the potential benefits of peri-conceptual *myo*-inositol supplementation in preventing folate resistant neural tube defects. The dose and timing of *myo*-inositol supplementation specified within the study are based on the need to ensure completion of fetal organogenesis by 12 weeks of gestation, reducing any

theoretical risk to the fetus. [21] *Myo*-inositol supplementation until the end of pregnancy also has a resulting effect on reducing macrosomia.[22]

Preliminary evidence on the effects of *myo*-inositol in pregnancy, based on small trials, suggests a reduction in gestational diabetes by up to 60%.[6]

To examine whether *myo*-inositol supplementation prevents the incidence of gestational diabetes in high risk women, an estimated 1500 participants would be required, costing approximately £1.7 million. Prior to undertaking a large-scale trial on the effects of *myo*-inositol, there is a need to pilot trial procedures, assess our ability to recruit and randomise women in a timely fashion, and evaluate their adherence to study protocol and attrition rates. Evaluating adherence is vital to understanding women's perception of the intervention and the trial, as well as trial elements which may impact on their acceptability and hence retention in the trial.[23] This may include women's understanding of gestational diabetes, their perception of risk, their attitudes towards a screening test for early pre-gestational diabetes and possible side effects of *myo*-inositol. It is important to explore potential variability across sites in the management of women at risk of gestational diabetes, and subsequently women with a diagnosis of gestational diabetes. The knowledge of these factors can inform recruitment and intervention delivery strategies within the full scale trial, allowing for the adaptation of trial processes to its local context being more sensitive to the needs of participants.[24]

CONCLUSION

The EMmY pilot trial is to inform a large definitive randomised controlled trial on the effects of *myo*-inositol supplementation on preventing the incidence of gestational diabetes and further complications in pregnant women at risk of developing gestational diabetes.

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Authors' contributions

CEA- wrote the first draft of the manuscript, contributed to developing the qualitative evaluation plan of the study, will perform the qualitative data analysis and wrote the final version.

ZD and JDo- contributed to drafting the manuscript, contributed to the methodology and logistics of the project and approved the final version.

LS and AH- contributed to drafting the manuscript, developed the qualitative evaluation plan of the study, will supervise on the qualitative data analysis and has approved the final version of the manuscript.

EP- contributed to drafting the manuscript, developed the economic evaluation plan, will lead the economic analysis and has approved the final version of the manuscript.

JD- contributed to drafting the manuscript, contributed to the methodology and logistics of the project, provided clinical input and has approved the final version.

JR, LP, AK, JM, GH, KK and MSH- contributed to drafting the manuscript, provided clinical input and has approved the final version.

JZ- contributed to drafting the manuscript, developed the statistical analysis plan, will lead the analysis and has approved the final version of the manuscript.

ST- designed the project, developed the protocol, contributed to drafting the manuscript and approved the final version of the manuscript.

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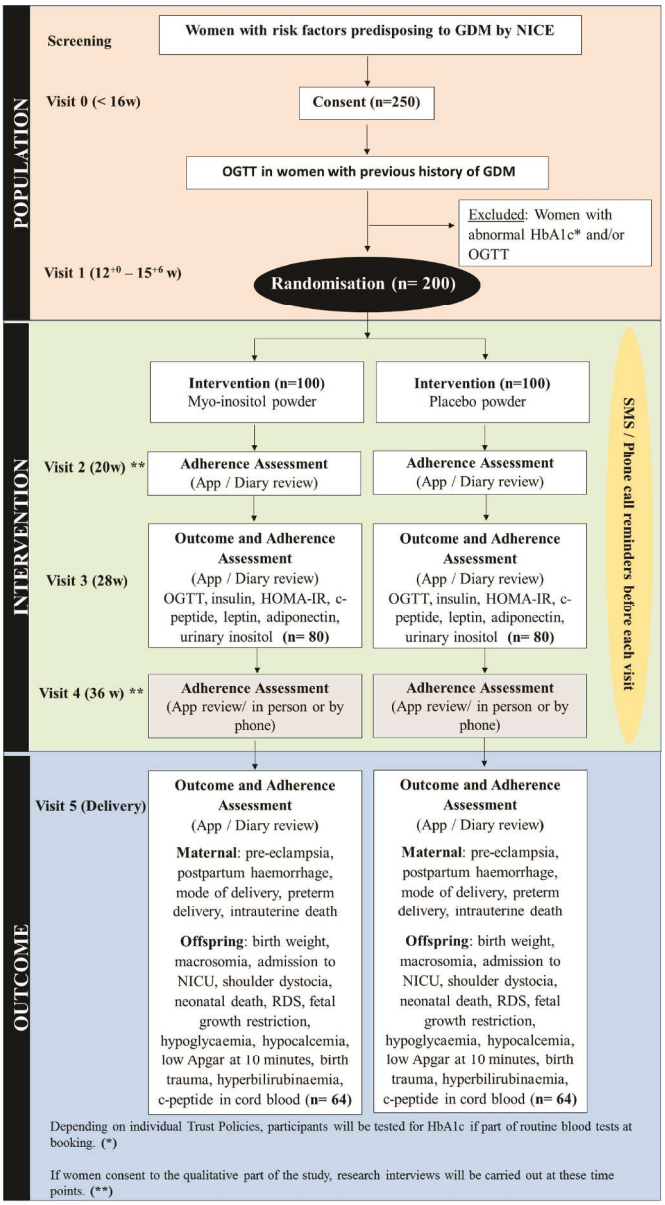
Competing interests

The authors declare that they have no competing interests.

Figure Legends

Figure 1: Trial scheme diagram on the conduct of the EMmY study.



242x441mm (300 x 300 DPI)

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preventing gestational diabetes with myo-inositol nutritional supplement

INFORMED CONSENT FORM

EMmY: Effectiveness and acceptability of myo-inositol supplement in the prevention of gestational diabetes: a pilot placebo controlled double blind randomised trial

REC Reference number: 17/LO/1741
IRAS ID: 232904

Please initial each box to confirm consent

1.	I confirm that I have read and understood the information sheet dated **23.11.2017**, version **3.0** for the above study. I have had the opportunity to consider the information, ask questions about the study and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3.	I understand that my healthcare professional will provide a copy of my consent form and personal information about me and my pregnancy, in confidence, to the central organisers at the Barts Research Centre for Women's Health at Queen Mary University London for use in the EMmY trial in accordance with the Data Protection Act (1998).	
4.	If in the course of the study I decide not to continue I understand that any collected data will be analysed, unless I specify otherwise.	
5.	I understand that if I lose the capacity to consent at any point during the study, additional tests will not be conducted for research purposes. In such a case, I agree for the researchers to use any previously collected research data and any further data collected as part of routine clinical practice.	
6.	I understand that the information and samples (blood and urine) collected will be used for medical research only, including academic publications, and may be shared anonymously with other researchers. I will be given a Unique Identification Number (UIN) in order to ensure that mine and my baby's data are anonymous.	
7.	I understand that the information held by the NHS may be used to keep in touch with me and to follow up the health status of me and my baby and that I may be contacted by the research team in the future to be invited to take part in future studies. I understand that I would not have to take part in any upcoming research if I did not wish to.	
8.	I understand that relevant sections of me or my baby's medical notes and data collected during the study may be looked at by individuals from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
9.	I agree to my GP being informed of my participation in the EMmY study.	
10.	I understand what is involved in the EMmY study and agree to participate.	

You will be provided with a signed copy of this consent form.

_____	_____	_____
Name of patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date

1 copy for Participant, 1 for hospital medical notes and original to be kept in EMmY Investigator Site File

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P 4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	P 4
Funding	4	Sources and types of financial, material, and other support	P 29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1-2, P 28
	5b	Name and contact information for the trial sponsor	P 29
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P 18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for	P 5
	6b	Explanation for choice of comparators	P 5
Objectives	7	Specific objectives or hypotheses	P 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority,	P 6, Figure 1

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P 17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P 9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P 7, P 17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 10-11, Figure 1, P 12 Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P 7-9, Figure1, P 12 Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7- 9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 8-9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P 8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P 8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P 8-9, P 11 P 12-14
	18b	**Plans to promote** participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P 9, P 13, P17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P 17-19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P 14 - 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P 19-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P 17-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P 18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 18-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7 - 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P 7-8 Consent Form (Supp.file)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P 18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P 20-21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 18, P21
	31b	Authorship eligibility guidelines and any intended use of professional writers	P 21

	31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	P 18

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp. file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	P 19

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Effectiveness and acceptability of myo-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial

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Manuscript ID	bmjopen-2018-022831.R1
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology, Qualitative

	research
Keywords:	pregnancy, gestational diabetes, myo-inositol, pilot, randomised controlled trials, protocol

Effectiveness and acceptability of *myo*-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial

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ABSTRACT

Introduction

Gestational diabetes increases maternal and offspring complications in pregnancy, and cardiovascular complications in the long term. The nutritional supplement *myo*-inositol may prevent gestational diabetes, however further evaluation is required, especially in multi-ethnic high-risk mothers. Our pilot trial on *myo*-inositol to prevent gestational diabetes will evaluate trial processes, assess acceptability to mothers, and obtain preliminary estimates of effect and cost data prior to a large full-scale trial.

Methods and analysis

EMmY is a multi-centre, placebo-controlled, double-blind pilot randomised trial, with qualitative evaluation. We will recruit pregnant women at 12-15^{+6} weeks gestation, with gestational diabetes risk factors, from five maternity units in England between 2018-2019. We will randomise 200 women to take either 2g of *myo*-inositol powder (intervention) or placebo, twice daily until delivery. We will assess rates of recruitment, randomisation, adherence to intervention, and follow-up. Gestational diabetes will be diagnosed at 24-28 weeks as per NICE (National Institute for Health and Care Excellence) criteria (fasting plasma glucose ≥ 5.6mmol/l, 2 hr plasma glucose ≥7.8 mmol/l). We will assess the effects of *myo*-inositol on glycaemic indices at 28 weeks, and on other maternal, fetal and neonatal outcomes at postnatal discharge. Qualitative evaluation will explore the acceptability of the trial and the intervention amongst women and healthcare professionals. Cost data and health related quality of life measures will be captured. We will summarise feasibility outcomes using standard methods for proportions and other descriptive statistics, and where appropriate, report point estimates of effect sizes (e.g. mean differences and relative risks) and associated 95% CIs.

Ethics and Dissemination

Ethical approval was obtained through the London Queen Square Research Ethics Committee (17/LO/1741). Study findings will be submitted for publication in peer-reviewed journals. Newsletters will be made available to participants, healthcare professionals and members of Katie's Team (a patient and public advisory group) to disseminate.

Trial registration number: International Standard Randomised Controlled Trial Number: ISRCTN48872100

Key words: Pregnancy, *myo*-inositol, gestational diabetes, pilot, randomised controlled trials, protocol

Protocol version and date: Version 4.0, 15th January 2018.

Strengths and limitations of this study

Strengths

- Pilot study on trial processes, clinical outcomes, and cost data to inform definitive trial.
- Qualitative evaluation on the acceptability of the trial and intervention.
- Pragmatically designed and reviewed by a patient and public involvement advisory group to allow for integration into current routine NHS clinical practice.

Limitations

- Trial applicable only to women with proficiency in English language.
- Intervention available over the counter and may be accessible to trial participants.

INTRODUCTION

Increasing rates of obesity worldwide, combined with sedentary lifestyle, has contributed to the rise in the number of women with gestational diabetes, a condition with high blood glucose levels diagnosed in pregnancy. The rates of gestational diabetes approach 24% in inner city maternity units in the UK.[1] This is likely to be due to the multi-ethnic populations in inner city areas with high levels of 'at-risk' populations, who are at greater risk of gestational diabetes. For instance, women of South Asian origin are 10 times more likely to develop gestational diabetes compared with Caucasian women.[2]

Gestational diabetes is associated with an increased risk of pregnancy complications including pre-eclampsia, macrosomia, caesarean section, postpartum haemorrhage, stillbirths and neonatal deaths.[3 4] Therefore, pregnant women who are considered to be at high risk are offered a screening test for gestational diabetes.[5] Pharmacological interventions such as metformin have not been shown to prevent gestational diabetes, and lifestyle interventions are challenging to implement, given their complexity. [6] *Myo*-inositol, a nutritional supplement has been reported to have beneficial effects in preventing gestational diabetes in some randomised trials.[6]

Existing randomised trials on *myo*-inositol are of poor quality, with small sample sizes, and involve homogeneous populations, mainly of Caucasian mothers from Italy. [7] The generalisability of these findings to the NHS setting is not known. Given the large sample size, and resources required to undertake a large-scale trial on the effects of *myo*-inositol on preventing gestational diabetes and its complications, there is a need to pilot trial procedures[8], ensure acceptability to participants and healthcare professionals, and obtain relevant preliminary data.

METHODS AND ANALYSIS

Study design

EMmY is a multi-centre, randomised, placebo controlled, double-blind, pilot trial with a nested qualitative evaluation.

Study aim and objectives

The aim of the EMmY trial is to pilot study procedures and assess acceptability prior to undertaking a full-scale trial on *myo*-inositol supplementation during pregnancy to prevent gestational diabetes in high risk women. Our primary objectives are to evaluate trial processes and procedures, obtain real time data on the study design, assess adherence and report any side effects. Our secondary objectives are to assess the acceptability of the study and the intervention to pregnant women and healthcare professionals, identify reasons for non-participation and non-retention, and identify barriers in recruitment and standardisation of care pathways for clinicians. Finally, we aim to obtain preliminary estimates on the effects of the intervention on glycaemic status, costs, and quality of life measures.

Study setting

The EMmY trial will be conducted in five inner city maternity units including Barts Health NHS Trust (The Royal London Hospital, Whipps Cross University Hospital and Newham University Hospital), St George's University Hospitals NHS Foundation Trust, and Manchester University Hospital NHS Foundation Trust (Manchester Royal Infirmary) over a period of 12 months (Feb 2018-Jan 2019).

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the EMmY trial are those with a singleton, viable pregnancy from 12^{+0} - 15^{+6} weeks gestation, able to provide written informed consent in English, and with at least one of the following risk factors: family history of diabetes in any one of their first degree relatives, gestational diabetes in a previous pregnancy, obesity (BMI ≥ 30 Kg/m2), minority ethnic family origin with a high prevalence of diabetes (such as South Asian and Black Caribbean/African), polycystic ovary syndrome, or previous macrosomic baby (birth weight > 4.5 kg). Women on corticosteroids, metformin or insulin treatment are not eligible for recruitment. Women with known pre-existing type 2 diabetes or diagnosed with pre-gestational diabetes in early pregnancy will not be randomised. This will be based on first trimester glycated haemoglobin (A1c) (HbA1c) levels and/or fasting and 2-hour postprandial Oral Glucose Tolerance Test (OGTT) depending on individual Trust policy.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Where possible, eligible participants will receive the EMmY Patient Information Sheet (PIS) at least twenty-four hours (24hrs) prior to their hospital booking visit or first trimester routine ultrasound scan depending on site policy. This is to make sure they have had ample time to consider the trial. The PIS will be accompanied by an invitation letter from the principal investigator (PI) informing patients that they may be approached by a member of the clinical research team, typically a research midwife to discuss participation in the trial at their hospital-booking visit or first trimester ultrasound scan. The PIS will be discussed with eligible women by a member of the research team, typically a research midwife. Potential participants will have the opportunity to ask any questions and to clarify the study processes. If women are keen to join the study after these discussions, informed written consent will be

obtained. Additional consent forms will be completed prospectively with regards to participating in qualitative interviews and the collection and storage of umbilical cord blood samples for future research. Women who do not wish to take part in the research interviews or consent to cord blood collection and storage, can still participate in the trial. The informed written consent form is submitted as supporting information. (See online supplementary file 1).

Following consent, participants with a history of gestational diabetes, will undergo an HbA1C and/or an OGTT test depending on individual trust policy before 16 weeks gestational age. These tests are conducted to rule out any potentially pre-existing but undiagnosed type 2 diabetes or early pre-gestational diabetes. Based on the NICE criteria, abnormal HbA1c results are defined as HbA1c levels > 48mmol/l and abnormal OGTT results defined as a fasting blood glucose level ≥ 5.6mmol/l and/or a 2-hour blood glucose level ≥7.8 mmol/l post 75g glucose load.[5]

Women with borderline HbA1c levels (41 – 47 mmol/l) at the booking visit will undergo first trimester OGTT. If the OGTT test shows an abnormal reading, these women will not be randomised. This process also allows us to assess the proportion of women with previous gestational diabetes, who enter subsequent pregnancies with potentially undiagnosed type 2 diabetes or pre-gestational diabetes. Participants eligible for randomisation will be randomly allocated to either the intervention group or the control group. The senior statistician will generate the allocation sequence. The randomisation and group allocation will be carried out through a secure online randomisation system. The randomisation scheme will be based on permuted blocks of random block size (sizes 4, 6 and 8), stratified by participating site. Research midwives will enrol and assign interventions to participants. Except for the senior statistician, study participants, care providers, data analysts and outcome assessors will be

blinded to the group allocation. The research team will be un-blinded only if necessary for the safety of the trial participant.

Following randomisation, baseline information on demographic and clinical characteristics will be collected from participants' maternity notes. The European Quality of life 5-Dimensions 5-Level scale (EQ-5D-5L), a validated questionnaire, will be administered at baseline and at the end of the trial to capture QALYs (Quality-Adjusted Life-Years) in all participants. Participants in the intervention group will be provided with the *myo*-inositol powder supplement to be taken in a dose of 2g twice daily from 12^{+0} - 15^{+6} weeks gestational age until delivery. Participants in the control group will be provided with a placebo identical in colour, flavour and texture to the *myo*-inositol powder to be taken in the same dose and for the same duration of time. Information regarding supplement intake and dosage will be provided to prevent misinterpretation of instructions or ambiguity.

Adherence to the intervention

The participants will be provided with the intervention or placebo packs in two stages, with half of their supply being provided at **Visit 1** (recruitment and randomisation, at 12-15^{+6} gestational weeks), and the remaining half of their supply at **Visit 3** (approximately 28 gestational weeks). A paper based diary and/or a mobile application (depending on participant's preference) will be provided to participants to self-report on adherence, with reminder features which we anticipate will encourage adherence. Participants will also be asked to bring any remaining sachets to their 28 week visit, where they will receive the next batch of intervention or placebo. A count of unused sachets (supplements) will be recorded as an additional measure of adherence to the intervention. Urinary inositol levels will also be tested at **Visit 3** (approximately 28 gestational weeks) as an additional measure of adherence in both groups. Text messages or phone calls will be made by the research team, to remind

participants of their upcoming appointments during the study. A participant will be deemed non-adherent if she has used 75% or less of her trial sachets. **Figure 1** below provides details of trial processes and procedures.

Sample size calculation

We expect that 1500 women will be booked for antenatal care each month at the participating hospitals, and at least 300 of those will be eligible. Assuming 1000 eligible women were approached, we expect about 25% (250/1000) to be consented. We expect that 20% (50) of women who consent to the study will have a previous history of gestational diabetes. These women will undergo an early HbA1C and/ or an OGTT test before 16 weeks gestational age to rule out any potentially pre-existing but undiagnosed type 2 diabetes or early pre-gestational diabetes. Any of these women with abnormal HbA1C (> 48mmol/l) and/ or OGTT (fasting blood glucose ≥ 5.6mmol/l and/or a 2-hour 75g blood glucose level ≥7.8 mmol/l) results and hence a diagnosis of early gestational diabetes will be excluded from the study. This will result in 200 women being randomised to either the *myo*-inositol or placebo arm. With an estimated attrition rate of 20%, we expect that 160 (160/200) women will remain in the study. Amongst these 160 women, we expect 80% of them (128/160) to be adherent to the study processes. These numbers will allow for estimation of the 95% confidence intervals for trial feasibility outcomes with amplitudes of around 10%.

Primary and secondary outcome measures and outcome assessment

The primary outcomes are the proportion of eligible, consented, and randomised participants. The secondary outcomes include the acceptability of the study and the intervention as well as the proportion of outcome measures obtained in the trial. Laboratory outcomes will be assessed at 28 weeks gestation including plasma glucose levels and the diagnosis of

gestational diabetes. This will be achieved through fasting and 2-hour postprandial 75 g oral glucose tolerance test (OGTT). Gestational diabetes will be diagnosed according to the 2015 National Institute for Health and Care Excellence (NICE) criteria (fasting glucose ≥ 5.6mmol/l, 2 hr ≥7.8 mmol/l). Other laboratory outcomes include insulin levels, leptin and adiponectin levels, c-peptide levels at fasting and 2hrs post-glucose load, HOMA-IR and urinary inositol levels.

Maternal, fetal and neonatal outcomes will also be assessed at delivery and/or discharge. Maternal outcomes include pre-eclampsia, gestational age at delivery, postpartum haemorrhage, mode of delivery, preterm delivery before 34 and 37 weeks, perineal trauma, admission to high dependency unit (HDU) or intensive care unit (ITU), maternal death and maternal infection. Fetal and neonatal outcomes include, birth weight, macrosomia (birth weight>4.5Kg), admission to neonatal intensive care unit (NICU), shoulder dystocia, neonatal death, respiratory distress syndrome, septicaemia, stillbirth, small for gestational age ($< 10^{th}$, $< 5^{th}$, $< 3^{rd}$) as per population-based centile, hypoglycaemia, hypocalcaemia, Apgar at 10 minutes, birth trauma such as shoulder dystocia fracture, and hyperbilirubinaemia. Cord blood will be collected and tested for c-peptide levels in the neonate. In addition, cost data and health related quality of life measures will be captured. Cost data include the cost of *myo*-inositol and placebo administration, cost of routine tests, additional laboratory tests and other investigations in both groups, cost of clinic visits, hospital admissions, type of delivery, cost to treat adverse events, antenatal costs, postnatal costs, and neonatal costs. Being a pilot trial, a sample size of 200 is adequate to assess feasibility outcomes but inadequate to show a difference in clinical outcomes between groups. However, we will be collecting these outcomes in this pilot trial to inform the future definitive full scale trial on the feasibility of collecting and assessing these outcomes in our population groups.

A schedule of assessments is shown below in **Table 1**.

Visit number		**0**	**1**	**2**	**3**	**4**	**5**
Gestational Weeks		**<16w**	**12-15^{+6}w**	**~20w**	**~ 28w**	**~ 36w**	**Delivery**
Tasks	Consent	**x**					
	Participant demographic data	**x**					
	OGTT/HbA1c pre-randomisation (if previous GDM history)	**x**					
	Randomisation		**x**				
	Delivery of intervention		**x**	**x**	**x**	**x**	
	OGTT to diagnose GDM				**x**		
	Assess Adherence (App / Diary)			**x**	**x**	**x**	**x**
	Maternal, fetal and neonatal outcomes						**x**
	Qualitative data collection (interviews)			**x**		**x**	
* Assessments will be completed as near to the scheduled date as possible, depending on participant's appointment date.							

Table 1 shows the schedule of assessments for the EMmY study

Qualitative evaluation

The qualitative evaluation will explore the acceptability of the trial and the intervention amongst participating women and healthcare professionals. This will be achieved through direct observation of recruitment, and semi-structured interviews as outlined below.

Recruitment observation

A sample of recruitment appointments (approximately 3-4 participants at each site) will be observed, in order to gain detailed knowledge of women's specific needs or concerns, as well as factors in the recruitment setting/environment that may impact on the recruitment process and outcomes.

Brief interview/open ended questionnaire with those who decline recruitment

Women who decline to participate in the pilot trial will be invited to complete an open-ended questionnaire (either verbally or in writing) on (i) their reasons for declining to participate and (ii) their feedback on the recruitment process. Responses will inform recruitment procedures both for the pilot trial and the potential future full-scale trial. This model has been recently used in a pilot trial of group antenatal care at Barts Health NHS Trust (Pregnancy Circles study) and was found to work well as a means of identifying barriers to trial participation. [9]

Interviews with randomised participants

Following consent, semi-structured interviews will be conducted with a purposive sample of approximately 15-20 women at different points in the trial. Interviews will be conducted approximately two months after randomisation (20-24 weeks of pregnancy) and towards the end of pregnancy (36-38 weeks) to capture women's experiences throughout pregnancy. The first interview will explore participants' experience of their pregnancy so far, their understanding, beliefs and perception of gestational diabetes, perceived acceptability of the study procedures and intervention, and other factors that can influence adherence. The second phase of interviews will purposively include 10 participants from the first interview phase who found intervention compliance and adherence particularly difficult or easy in the early

stages of the study. This will be to address any further difficulties and supports for managing adherence to the intervention, and any further experiences with study participation, data collection methods, and follow up procedures. We will also endeavour to interview a sample of women who drop out of the trial.

All interviews will be audio-recorded with consent, and participants will also be offered a £10 voucher for each interview.

Interviews and/or focus groups with healthcare professionals

Semi-structured interviews or focus groups, will be conducted with a cross-section of key healthcare professionals (approximately10-15 consisting of obstetricians, diabetologists, and midwives) who are involved in delivering the intervention, and/ or who have expertise in the area of gestational diabetes. Here, we will explore various approaches to managing/preventing GDM in multi-ethnic populations in the NHS setting. We will obtain their views on barriers to recruitment, compliance, retention, and any suggestions on how these could be overcome. Informed consent will be gained and a prepared interview guide will include questions arranged in topics.

Patient and public involvement

Prior to the grant application, the development of the EMmY research question was informed by patients' priorities and preferences. In our survey of pregnant women (n=71) within the Barts Health NHS Foundation Trust, 83% (59/71) agreed that there was a need to prevent gestational diabetes. More women indicated that they would be inclined to take *myo*-inositol (79%, 56/71) than follow a complex lifestyle intervention (60%, 43/71); and 8 out of 10 informed that they may or would definitely join a trial on *myo*-inositol. Additionally, two-

thirds of healthcare professionals surveyed (66%, 58/88) were keen to participate in a trial on *myo*-inositol.

We have collaborated with "Katie's Team", a women's health and childbirth specific patient and public involvement advisory group [10] to inform several elements of the EMmY pilot trial. Katie's Team members contributed to the development of the study design, reviewed the trial documents such as the patient information sheets and informed consent forms and developed the interview schedule. Patients and public representatives are not involved in recruitment or the conduct of the study

We will submit study findings for publication in published in peer-reviewed journals. Study results will be circulated to participants, healthcare professionals and members of Katie's Team through newsletters, who in turn will further disseminate through traditional means and social media platforms.

Data analysis

Statistical analysis

Data will be analysed using descriptive statistics in order to inform trial feasibility and process. Given that this is a pilot study, the sample size is not adequately powered to assess the effect of the intervention on outcomes. However, where appropriate, we will present point estimates of effect sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals. The primary analysis will also involve the estimation of the proportions of the primary outcomes (i.e. eligible women recruited into the trial, recruited women who complete the trial and adhere to the intervention treatment until delivery). We will also test if the proportions of the primary outcomes differ between the treatment group and the control group. We will explore the effect of mother's ethnicity, history of previous gestational diabetes, and maternity unit attended, on recruitment, adherence and attrition. All analysis

will be performed using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Economic analysis

A cost-utility analysis will be undertaken using a short term time horizon (the 'within trial' period) to obtain preliminary estimates of the cost-effectiveness of *myo*-inositol supplementation versus placebo in the prevention of gestational diabetes, which will inform the full-scale trial. The cost utility measures in the short-run will be the incremental cost per unit of change per Quality-Adjusted Life-Year (QALY) gained. Unit costs will be collected and assessed from the perspective of the NHS and personal social services via standard sources. QALYs will be calculated based on the health related quality of life (HRQL) collected during the trial from the EQ-5D-5L questionnaires. The QALYs experienced from baseline to end of trial will be calculated as the area underneath this profile. Cost-utility will be calculated as the mean cost difference between the intervention and control group divided by the mean difference in outcomes to give the incremental cost-effectiveness ratio (ICER). Cost-effectiveness acceptability curves will be constructed and we will subject the results to extensive deterministic sensitivity analysis.

Qualitative data analysis

Interview data will be subjected to thematic analysis. Transcripts will be coded for themes and concepts relating to women's and health professionals' experiences and perceptions of this intervention and the study. In this way we will develop an analytical framework to identify key themes and how these inter-relate. Where possible, we will use constant comparison techniques and examine deviant cases to refine our analysis.

Clinical management

Besides *myo*-inositol and placebo, EMmY does not involve any other intervention. All aspects of antenatal care will be at the discretion of local clinicians. Further management of women diagnosed with gestational diabetes will be as per local guidelines for management of gestational diabetes.

Participant withdrawal

After consent, a participant can decide to self-withdraw from the trial. Clear distinctions will be made if the participant is only withdrawing from the trial but allowing further follow-up or withdrawing from both the trial and follow-up. A participant can also be withdrawn from the trial treatment if based on the opinion of the clinical carers and the investigators, it is medically necessary to do so. However, with any post randomisation exclusions, the research team will endeavour to obtain and record the reasons for withdrawal and any adverse events in the case report form. Where appropriate, efforts will be made to follow up women who withdraw for all safety and efficacy outcomes.

If a participant explicitly withdraws consent to any further data collection, her decision will be respected, noted in the final study form and no further data will be collected from that participant. The participant will continue with NHS standard practice for follow-up care.

Data management

All participants in the EMmY trial will be given a unique trial number and will be identified to their local sites by their NHS hospital number. The Chief Investigator has a responsibility to ensure that participant anonymity is protected, maintained and associated participant information kept confidential and managed in accordance with the Data Protection Act (1998-UK), the sponsor's data management Standard Operating Procedures (SOPs), The

Research Governance Framework for Health and Social Care, The Research Ethics Committee Approval and the NHS Caldicott Guardian. All data will be monitored centrally and locally at the trials coordinating centre- Barts Research Centre for Women's Health (BARC) for consistency, viability and quality using bespoke data management systems. All participants' data obtained for the trial, including personal information, will be anonymised, held securely and treated as strictly confidential. The data will be entered onto a secure computer database, either by a member of the research team or directly via a secure internet connection. All staff at each participating site and at the trials unit, share a responsibility of care to prevent unauthorised disclosure of personal information. No identifiable individual data will be published. In accordance to the MRC guidelines on data retention, participants' data collected will be kept for 20 years following the end of trial to allow for verification and further data sharing via an individual patient data meta-analysis for instance.

Monitoring and auditing

The study sites will perform remote trial monitoring according to the agreed trial monitoring plan and self-monitoring template, at the trials coordinating centre, Barts Research Centre for Women's Health (BARC). Trial monitoring will include source data verification, checks on all informed consent forms (ICF) and eligibility for randomisation log, and a sample set of case report forms (CRFs). Any major discrepancies with respect to trial regulatory matters and study protocol found at a site visit will trigger an audit of trial data by the coordinating team at the site involved, independently of the sponsor and investigators. The Chief Investigator (CI) will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements, including, but not limited to, the Trust and Research Office policies and

procedures, the Research Governance Framework, guidelines for good clinical practice (GCP) and any subsequent amendments. Any form of non-compliance will be captured through communications and updates, monitoring visits, CRFs and other sources. In order to identify and verify any developing trends, the sponsor will maintain a log of any non-compliances, assess them and action a timeframe in which they need to be dealt with. In the event of any safety information which may require significant changes to the risk/benefit analysis of the study, the protocol, the ICF and the PIS will be amended and submitted to REC for revision and approval. All participants of the EMmY study will be duly informed and provided with a revised copy of the PIS and the ICF to confirm their wish to continue where possible.

Sample handling, labelling and logging

Participants' samples collected will be processed by either NHS laboratory services, or by Affinity Biomarker Labs (Imperial College London, W12 0BZ). Samples will be labelled with the date of collection and participant's unique trial number. Upon arrival at the laboratories, samples will be handled as per routine clinical practice and local policies. Samples will be stored, processed and analysed by laboratory staff as defined by study standard operating procedures (SOPs), with any inconsistencies referred back to the research team or the clinical team. All samples received and processed in the NHS Labs will be logged onto the NHS database, and samples received and processed by the Affinity Biomarker Labs will be logged onto the trial specific secure database.

Trial organisation

EMmY has a Project Steering Committee (PSC) that provides independent supervision of the trial, providing advice to the Chief and Co-Investigators and the Sponsor on all aspects of the

trial and affording protection for patients by ensuring the trial is conducted according to the principles of Good Clinical Practice in Clinical Trials**.** The trial will also be overseen by a Trial Management Group (TMG), who will meet regularly up until the end of the trial to evaluate trial progress and resolve any potential challenges. The TMG consists of the lead investigators, research midwives, and the project team at BARC.

EMmY is a pilot study with a low risk intervention and therefore no major safety concerns. In addition, EMmY aims to primarily assess the feasibility of conducting a potential full-scale trial rather than the effectiveness of the intervention and therefore does not require a data monitoring committee (DMC).

Safety assessment

Adverse events (AEs), are defined as any untoward medical occurrences in a participant which are not necessarily related to the intervention administered. AEs will be recorded by the principal investigator in the CRF and the participant's medical notes. Participants experiencing AEs will be followed up by the research team. Serious adverse events (SAEs) are defined as any untoward occurrences that results in death, that is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, that results in persistent or significant disability or incapacity, or is otherwise considered medically significant by the principal investigator. Any SAEs will be reported to the sponsor within 24 hours of learning of the event and to the main Research Ethics Committee (REC) within 15 days in line with the required timeframe.[11]

Indemnity

EMmY is sponsored by Queen Mary University of London (QMUL) as defined by the Research Governance Framework for Health and Social Care (April 2005). EMmY is also

covered by the insurance brokers of QMUL on a "No Faults Compensation for Clinical Trials and/or Human Volunteer Studies". This policy covers or indemnifies the insured in respect of their legal liabilities arising out of the insured's activities.

ETHICS AND DISSEMINATION

EMmY has received ethical approval from the London Queen Square Research Ethics Committee (17/LO/1741) as well as site-specific approval for each participating site. EMmY is also registered online at ISRCTN.com (ISRCTN48872100). The CI will co-ordinate dissemination of data from this study. The results from the trial will be submitted for publication in a major journal. The PSC will be responsible for approval of the main manuscript prior to submission for publication. Authorship of presentations and reports related to the study will be in the name of the lead investigators. Publications will name local co-ordinators as well as those involved in central co-ordination and trial management. The writing will be the responsibility of a writing committee including all of the investigators.

DISCUSSION

Approximately 40% of all women who are diagnosed with gestational diabetes, progress to type 2 diabetes within five years post-delivery, in addition to their increased risk of gestational diabetes in future pregnancies.[12 13] Infants born to mothers with gestational diabetes are at an increased risk of impaired glucose regulation, obesity and diabetes, leading to a vicious cycle of accumulated risks in the next generation.[14 15] Therefore, preventing gestational diabetes provides intergenerational benefits, preventing chronic diseases in both mothers and their offspring.

With a projected increase in the NHS yearly spend (from £8.8 billion to £13 billion) on type 2 diabetes and its complications,[16] preventing gestational diabetes has significant societal and economic benefits. However, evidence on effective and acceptable approaches to preventing gestational diabetes is lacking.[17] Randomised trials on lifestyle changes has shown no significant difference in the incidence of gestational diabetes between groups. [6, 18] Women have reported on the difficulty of incorporating exercise into their daily routine as a result of child care, pregnancy symptoms and work commitments.[17] Trials on the use of metformin in preventing the incidence of gestational diabetes also reported on no statistically significant difference between groups. [18] There is therefore a need for a simple, effective, safe and acceptable intervention in preventing the onset of gestational diabetes in high-risk pregnant women.

Myo-inositol is a dietary nutritional supplement, which is present in staple foods such as meat and legumes, and is currently sold over the counter as a food supplement. Its use is not contra-indicated in pregnancy.[19 20] Existing trials have shown the potential benefits of peri-conceptual *myo*-inositol supplementation in preventing folate resistant neural tube defects. The dose and timing of *myo*-inositol supplementation specified within the study are based on the need to ensure completion of fetal organogenesis by 12 weeks of gestation, reducing any

theoretical risk to the fetus. [21] *Myo*-inositol supplementation until the end of pregnancy also has a resulting effect on reducing macrosomia.[22]

Preliminary evidence on the effects of *myo*-inositol in pregnancy, based on small trials, suggests a reduction in gestational diabetes by up to 60%.[6]

To examine whether *myo*-inositol supplementation prevents the incidence of gestational diabetes in high risk women, a large sample size will be required costing approximately £1.7 million. Prior to undertaking a large-scale trial on the effects of *myo*-inositol, there is a need to pilot trial procedures, assess our ability to recruit and randomise women in a timely fashion, and evaluate their adherence to study protocol and attrition rates. Evaluating adherence is vital to understanding women's perception of the intervention and the trial, as well as trial elements which may impact on their acceptability and hence retention in the trial.[23] This may include women's understanding of gestational diabetes, their perception of risk, their attitudes towards a screening test for early pre-gestational diabetes and possible side effects of *myo*-inositol. It is important to explore potential variability across sites in the management of women at risk of gestational diabetes, and subsequently women with a diagnosis of gestational diabetes. The knowledge of these factors can inform recruitment and intervention delivery strategies within the full scale trial, allowing for the adaptation of trial processes to its local context being more sensitive to the needs of participants.[24]

CONCLUSION

The EMmY pilot trial is to inform a large definitive randomised controlled trial on the effects of *myo*-inositol supplementation on preventing the incidence of gestational diabetes and further complications in pregnant women at risk of developing gestational diabetes.

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Authors' contributions

CEA- wrote the first draft of the manuscript, contributed to developing the qualitative evaluation plan of the study, will perform the qualitative data analysis and wrote the final version.

ZD and JDo- contributed to drafting the manuscript, contributed to the methodology and logistics of the project and approved the final version.

LS and AH- contributed to drafting the manuscript, developed the qualitative evaluation plan of the study, will supervise on the qualitative data analysis and has approved the final version of the manuscript.

EP- contributed to drafting the manuscript, developed the economic evaluation plan, will lead the economic analysis and has approved the final version of the manuscript.

JD- contributed to drafting the manuscript, contributed to the methodology and logistics of the project, provided clinical input and has approved the final version.

JR, LP, AK, JM, GH, KK and MSH- contributed to drafting the manuscript, provided clinical input and has approved the final version.

JZ- contributed to drafting the manuscript, developed the statistical analysis plan, will lead the analysis and has approved the final version of the manuscript.

ST- designed the project, developed the protocol, contributed to drafting the manuscript and approved the final version of the manuscript.

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Data Sharing Statement

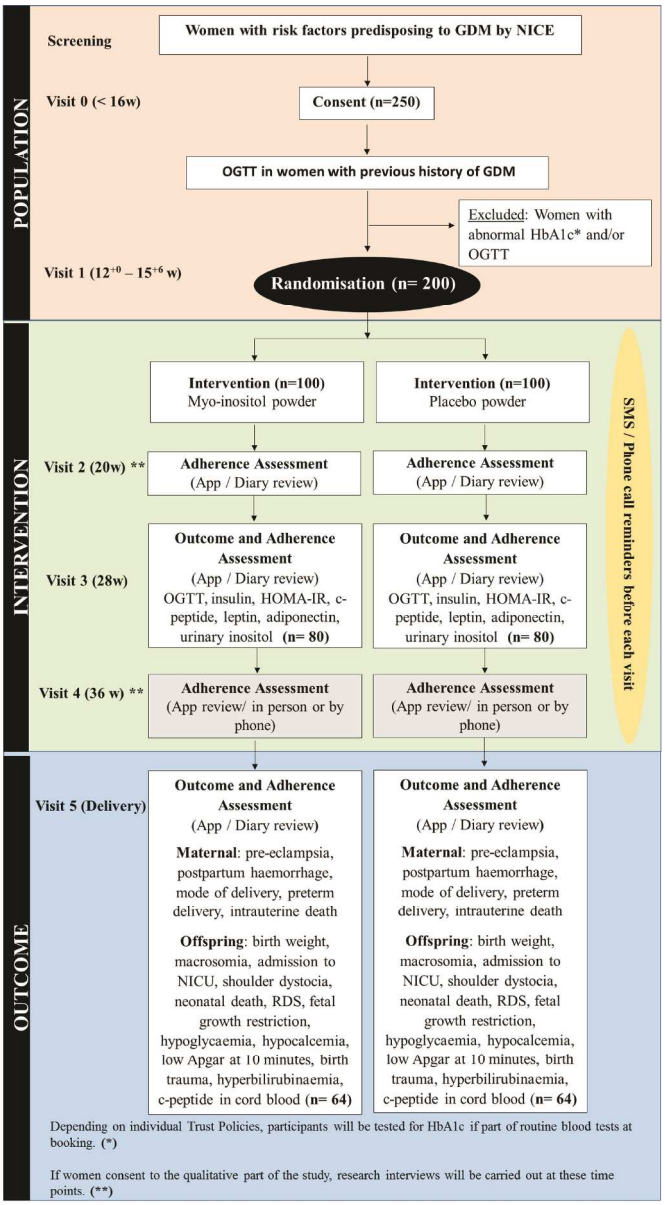
No data to share

Competing interests

The authors declare that they have no competing interests.

Figure Legends

Figure 1: Trial scheme diagram on the conduct of the EMmY study.



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preventing gestational diabetes with myo-inositol nutritional supplement

INFORMED CONSENT FORM

EMmY: Effectiveness and acceptability of myo-inositol supplement in the prevention of gestational diabetes: a pilot placebo controlled double blind randomised trial

REC Reference number: 17/LO/1741
IRAS ID: 232904

Please initial each box to confirm consent

1.	I confirm that I have read and understood the information sheet dated **23.11.2017**, version **3.0** for the above study. I have had the opportunity to consider the information, ask questions about the study and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3.	I understand that my healthcare professional will provide a copy of my consent form and personal information about me and my pregnancy, in confidence, to the central organisers at the Barts Research Centre for Women's Health at Queen Mary University London for use in the EMmY trial in accordance with the Data Protection Act (1998).	
4.	If in the course of the study I decide not to continue I understand that any collected data will be analysed, unless I specify otherwise.	
5.	I understand that if I lose the capacity to consent at any point during the study, additional tests will not be conducted for research purposes. In such a case, I agree for the researchers to use any previously collected research data and any further data collected as part of routine clinical practice.	
6.	I understand that the information and samples (blood and urine) collected will be used for medical research only, including academic publications, and may be shared anonymously with other researchers. I will be given a Unique Identification Number (UIN) in order to ensure that mine and my baby's data are anonymous.	
7.	I understand that the information held by the NHS may be used to keep in touch with me and to follow up the health status of me and my baby and that I may be contacted by the research team in the future to be invited to take part in future studies. I understand that I would not have to take part in any upcoming research if I did not wish to.	
8.	I understand that relevant sections of me or my baby's medical notes and data collected during the study may be looked at by individuals from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
9.	I agree to my GP being informed of my participation in the EMmY study.	
10.	I understand what is involved in the EMmY study and agree to participate.	

You will be provided with a signed copy of this consent form.

_____	_____	_____
Name of patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date

1 copy for Participant, 1 for hospital medical notes and original to be kept in EMmY Investigator Site File

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P 4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	P 4
Funding	4	Sources and types of financial, material, and other support	P 29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1-2, P 28
	5b	Name and contact information for the trial sponsor	P 29
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P 18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for	P 5
	6b	Explanation for choice of comparators	P 5
Objectives	7	Specific objectives or hypotheses	P 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority,	P 6, Figure 1

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P 17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P 9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P 7, P 17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 10-11, Figure 1, P 12 Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P 7-9, Figure1, P 12 Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7- 9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 8-9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P 8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P 8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P 8-9, P 11 P 12-14
	18b	**Plans to promote** participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P 9, P 13, P17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P 17-19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P 14 - 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P 19-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P 17-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P 18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 18-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7 - 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P 7-8 Consent Form (Supp.file)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P 18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P 20-21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 18, P21
	31b	Authorship eligibility guidelines and any intended use of professional writers	P 21

	31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	P 18

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp. file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	P 19

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.