Title page

A Randomised Placebo Controlled Trial of the effectiveness of Early MEtformin in Addition to Usual Care in the Reduction of Gestational Diabetes Mellitus Effects (EMERGE)

Protocol Version no.:	6.0	Date:02-May- 2019
Test Drug:	Metformin	
Clinical Phase:	III	
EudraCT number:	2016-001644-19	
Sponsor Number:	NUIG-2016-01	

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The study will be conducted in compliance with the protocol, International Conference on Harmonization – Good Clinical Practice (ICH-GCP) and any applicable regulatory requirements.

1. SPONSOR PROTOCOL AGREEMENT PAGE

I, the undersigned, am responsible for the overall conduct of the trial and agree to the content of the final clinical trial protocol, as presented.

Signed

_____ _____

Sponsor Representative Date

2. INVESTIGATOR PROTOCOL AGREEMENTS

2.1. Chief Investigator Agreement

I, the undersigned, agree to the content of the final clinical trial protocol, as presented.

Signed

_____ _____

Chief Investigator Date

2.2 Site Investigator Agreement

I, the undersigned, am responsible for the conduct of the trial at this site and agree to the following:
I understand and will conduct the trial according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
I will not deviate from the protocol without prior written approval from the HPRA and the Ethics Committee, except where necessary to prevent any immediate danger to the participant.
I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely. I will ensure that any staff at my site(s) who are involved in the trial conduct are adequately trained regarding the protocol and their responsibilities.

Signed

_____ _____

Principal Investigator Date

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3. DOCUMENT HISTORY

Document Version	Date of Issue	Summary of Change
1.0	5th August 2016	Original version
2.0	23rd September 2016	Update to inclusion criteria and exclusion criteria.
3.0	29th September 2016	• Update to Section 9.2.1. Exceptions from AE/SAE reporting • Updates to sections 7.3.1 and 7.4.4. have been made to reflect the previous changes to the exclusion/exclusion criteria made in the version 2 protocol • The MA holder has been updated in section 8.2. to Merck Santé • Section 8.2. has been updated to include bottle sizes of 170 tablets • Typographical Corrections
4.0	22nd August 2017	• Update to section 6.2. Rational for the Study, with reference to changes in inclusion criteria and typographical error in primary outcome timepoint. • Update to wording in section 7.1. Primary Objective • Timepoints of assessments have been removed in section 7.2. Secondary Objectives • Clarification provided on primary outcome measure section 7.3.1. • Update to section 8.1.3. Usual Care to include a trained delegate • Update to 8.2. Selection of Study Population, inclusion and exclusion criteria • Update to 8.3.1. to reflect changes in inclusion criteria. • Timepoints for study drug accountability, bio-banking, laboratory tests, updated in section 8.3.2. Prenatal Visits and Procedures. Study visit windows also removed. • Update to Figure 2 Schedule of Events to reflect changes in timepoints in section 8.3.2. • Section 8.3.4. 4 weeks post-partum visit updated to Visit 1 post-partum with updates to figure 2 • Section 8.3.5. 12 weeks post-partum visit with updates to figure 2 updated to Visit 2 post-partum

		• Section 8.4.1. updated to reflect changes in biobanking timepoints. • Updates to section 8.4.5. Laboratory Tests • Update to 8.4.6. Biobanking, to include a maternal biobanking sample at Visit 7 (week 12) • Type of glucometer used and quantity of data downloaded, and use of data updated in section 8.4.7. Glucometer Data. • Timepoints for study drug accountability updated in section 8.4.8. Study Drug Accountability • Update to 9.1.1. Usualcare to include a trained delegate. • Storage temperature updated in section 9.3. Storage of Study Treatment(s) to below 30°C • Medication supplied by the contracted packaging provider updated in section 9.4. Accountability of Study Treatments • Section 9.5. Assessment of Compliance updated to reflect change in timepoints for study drug accountability. • Update to section 9.7. Prior and Concomitant Therapy to include exceptions from con med recording. • Updates to Section 9.7.3. Cautionary medications • Update to section 10.2.1 Exceptions from SAE reporting. • Email address to report SAE's to the sponsor removed in section 10.3.1 Adverse Events/Serious Adverse Events as reporting will be via the eCRF. • Section 11.6 Level of Statistical Significance updated to include 95% confidence Intervals • Section 15.2 Indemity updated to include information from section 18. Section 18 removed. • Update to 15.7. Protocol Complaince • Removal of sections 17.1 and 17.2 as the information was contained within section 15 • Typographical Corrections throughout
5.0	27th November 2017	• Update to Table of contents page 10 • Typographical corrections in section 4.0 "Synopsis" and section 8.4.6 "Biobanking". • Updates to figure 1 to include addition of box for baby procedures at 4 week post partum visit and 12 week post partum visit to align with text in section 8.3.4. "Phone Visit (Visit 1 Post-Partum)" and section 8.3.5

		"12 Week Post-Partum Visit (Visit 2 Post-Partum)". • Updates to section 8.3.3. Delivery Visit include removal of height, weight and BMI measurements at the delivery visit • Update to figure 2 include: a) Addition of text "weeks post randomisation" b) Addition of status of baby and neonatal measurements at 12 week post partum visit to align with text in section 8.3.5 "12 Week Postpartum Visit" • Updates to section 8.4.5. Laboratory Tests include: a) Addition of visit window for 12 week post partum visit "+/- 4 weeks". b) addition of urea, creatine, alanine aminotransferase (ALT), and aspartate transaminase (AST) at the randomisation visit as per the requirements of protocol version 3.0. • Update to section 8.4.7 "Glucometer Data" to clarify data will be reviewed at each "on-site" visit. • Update to section 8.4.9. Neonatal Measurements to include 'weight' • Update to section 15.1. "Sponsorship" to change "Principal Investigator" to "Chief Investigator".
6.0	02-May- 2019	• Update to Table of contents page 5 and to the footer throughout the protocol • Updates to formatting and spacing have been made throughout the protocol • The abbreviation of GDPR has been added to the list of abbreviations in section 5 • Update to sections 4 "synopsis" and section 8.2.3. "exclusion criteria" ,and to all further references made throughout the protocol to study exclusion criteria: "Known foetal anomaly" which was the previous exclusion criteria has since been updated to "major congenital malformations or an abnormality deemed unsuitable for metformin by the site PI or attending consultant" to define congenital anomalies which are a study exclusion criteria • Update to sections 4 "synopsis", sections 8.1.2 and 8.3.4 and to all further references made throughout the protocol to the 4 week

		post partum visit: The visit window for the 4 week post partum visit has since been updated from +/- 5 days to +/- 7 days. • Update made to section 4 ”Synopsis” to remove reference to Cork University Hospital as a trial site. Portiuncula University Hospital and Mayo University Hospital have since been added to this section. • The words “subject” and “women” used throughout the protocol when referring to trial participants has since been replaced to simply “participant”. • Definition of “Neonatal hypoglycaemia” has been expanded in section 7.3.2 • Section 8.1 “Design Summary” has been updated to clarify that participants are followed up until 12 weeks post partum (+/- 4 weeks). The reference to the number of trial sites has since been updated to state that the trial will take place in upto 3 trial sites. • Section 8.1.2 “Placebo Group” has been updated to include the visit windows for the 4 week and the 12 week post partum study visits. • Updates to figure 1 include: o “Usual care received” to be obtained at randomisation and the week 4 visit has been added o “EQ5D-5L” and “medical resources” to be obtained at the randomisation visit has been added o Return of study drug every 4 weeks has been added o “Physical measurements” and “vital signs” have since been moved from the “2 weekly post randomisation” box to the box containing additional procedures to be undertaken during the prenatal treatment study phase, as per the protocol update o The maternal bio-banking sample at randomisation and week 12 post randomisation has been removed from figure 1, as this substudy has been removed from the main protocol o “Adverse events” has been added to the 4 week and 12 week post partum visits scheduled for the

		mother, as per the schedule of visits and procedures. “Adverse events” has also been added to the delivery, 4 week and 12 week post partum visits for the baby. o Addition of statement of “in person visits only” when referring to glucometer data download during the 2 weekly post randomisation study visits. o Addition of “last routine HbA1c” and “gastrointestinal events” to the box outlining the study procedures at the fortnightly post randomisation study visits o Removal of “laboratory samples” from the box containing the delivery procedures for the mother, which were removed in protocol version 4.0 o Removal of “cord blood bio-banking” from the box outlining the study procedures for the baby at the delivery visit, as this has been removed from the main study protocol o Removal of “height and weight” from the box outlining the study procedures for the baby at the 12 week post-partum study visit o “Vital signs” has been added to the box outlining the schedule of events at the 12 week post partum visit in the mother, as per the the protocol • Updates have been made to section 8.3.1 “Screening and Randomisation Visit and Procedures”. The previous sentence of “all con meds including herbal and vitamin supplements” has been removed when referring to the review of concomitant medications during this visit. The bio-banking component of the study has since been removed from the main study protocol into a sub-study protocol,which is acknowleded in the amended text. • Updates made to section 8.3.2 “prenatal visit and procedures”. Removed the requirement to obtain physical measurements and vital signs every 2 weeks, and instead specified these measurements are to be obtained at the 32

		week (+/- 1 week) and 38 week (+/- 1 week) gestation visits. Removed the requirement to obtain the maternal blood sample for bio-banking at gestational week 38 (+/- 1 week). A sentence was also added to the "glucometer data download" procedure, to acknowledge that this applies for in person visits only. Sentence was added to state "visits that do not require an in person physical measurement, laboratory assessment or drug dispensation can be completed over the telephone". • A sentence has been added to bullet point number 3 "adverse events" in section 8.3.3 "Delivery visit" to clarify that adverse events are to be collected for both the mother and baby • The collection of "adverse events" in both the mother and baby for the schedule of procedures at the week 4 and the week 12 post partum visits have been added to sections 8.3.4 and section 8.3.5, as per the protocol • Removed requirement to collect "height and weight of baby" from section 8.3.5 "12 week Post-Partum Visit". • Updates to Figure 2 include: o New column for "additional Visit(s)" which may occur pre-natally has been added o Additional superscripts have been added to certain procedures, which has updated previous letters as a result. These additional superscripts were added to clarify further when procedures are required. Additional footnotes have been added at the end of figure 2 as a result. o Reference to obtain neonatal measurements at the 12 week post partum visit has been removed o The figure has been updated to account for the return of study drug every 4 weeks during pre-natal study visits o The bio-banking sample which was previously listed as a study procedure at the week 12 post randomisation visit has been removed, as this substudy is being removed from the main protocol

		o "Adverse Events" has been added to the list of neonatal procedures at the delivery, 4 week post partum and 12 week post partum visits for clarity • The reference to obtaining additional consent for the maternal biobanking samples and the cord blood samples in section 8.4.1 "Informed consent" has been removed, as this will no longer form part of the main protocol study procedures • Section 8.4.2 "Medical history" has been updated to clarify the relevant required medical conditions to be documented at the screening visit • Section 8.4.5 "laboratory tests" has been updated. The word "fasting" has been removed from both the insulin and c-peptide laboratory assessments performed at the randomisation visit, as these particular assessments do not require the participant to be fasting. • Section 8.4.6 "Bio-banking" has been updated to remove the bio-banking component of the study from the main study protocol. Participants at all trial sites will be invited to partake in the bio-banking sub-study preapproved by the research ethics committee, as guided by local practice patterns and the availability of resources (including staff). All further references made to the collection of cord-blood biobanking samples at delivery and the maternal bio-banking samples at randomisation and week 12 post randomisation throughout the protocol have been revised accordingly. • Section 8.4.7 "glucometer data" has been updated to acknowledge that glucometer data will be downloaded at a subsequent in person study visit • Section 8.4.8 "study drug accountability" has been updated to revise the sentence "participants will be deemed compliant if they have taken 80% of study medication, i.e. 80% of the maximum tolerated dose" to 'Non-compliance is defined as less than 80% drug adherence of the participants maximum tolerated dose'. • Section 8.4.9 "Neonatal Measurements" has been updated to include the sentence "where available, abdominal circumference

		and mid-upper arm circumference will be taken” • Section 8.8 “Discontinuation/withdrawal of participant from study treatment” has been amended to clarify the difference between a participant discontinuing study medication, and a participant withdrawing study consent • Sections 9.3 and 9.4 have been updated to remove the previous references to storage of treatment in locked cabinets at the research pharmacy. The reference to the supply of study medication by the contracted packaging provider in section 9.4 has been updated to state that study medication will be supplied to the site as per the sponsor supply process. The reference to the “research nurse” in section 9.4 has been changed to “research delegate” • The list of exempted concomitant medications in section 9.7 “prior and concomitant therapy” has been updated to remove the exemptions d) betamethasone 12mg for foetal lung maturation and e) magnesium sulphate, which were listed in protocol version 5.0. New expected concomitant medications have since been added to the list. These include: (f) routine vaccines in the baby (BCG/TB, Diphtheria, Tetanus, Pertussis, Haemophilus Influenza B (Hib), Polio, Hep B, Pneumococcal (PCV), Meningococcal (Men B) (g) maternal vaccinations, (h) Vitamin K administration (baby only), (i) Anti D for mother, (j) Over-the-counter antenatal multivitamins • Additional clarification and definitions in relation to safety have been added to sections 10.1.1 and 10.1.3 • Additional safety event exemptions have been added to section 10.2 “Evaluation of AEs and SAEs”. • Figure 3 has been introduced to section 10.2 “Evaluation of AEs and SAEs” • Additional clarification has been added to section 10.3.2 to clarify site awareness and what is considered a valid SAE report • Section 10.4.1. has been updated to amend the information in relation to regulatory authorities • An additional sentence has been added to

		section 10.4.4 in relation to the safety reporting for the non-IMP • Section 11.2 “Determination of sample size” has been revised to include relevant information from Portiuncula and Mayo University Hospitals • Section 14 “Retention of essential documents” has been revised to clarify the storage of the trial master file and the investigator site files. • Section 15.7 “Protocol compliance” has been updated to remove references to the previous study procedure for reporting protocol deviations • Section 17.3 “Participant Confidentiality” has been updated to include reference to the General Data Protection Regulation 2018

4. SYNOPSIS

Title of study	A randomised placebo controlled trial of the effectiveness of Early MEtformin in addition to usual care in the Reduction of Gestational diabetes mellitus Effects (EMERGE)
Name of sponsor	Prof. Lokesh Joshi (Vice President of Research) National University of Ireland Galway, University Road Galway, Ireland
Clinical Study Phase	III
Objectives	The overall objective of the EMERGE trial is to determine whether metformin + usual care, compared to placebo + usual care (introduced at the time of initial diagnosis of GDM), reduces a) the need for insulin use, or hyperglycemia (primary outcome measure); b) excessive

	maternal weight gain; c) maternal and neonatal morbidities and, d) cost of treatment for participants with Gestational Diabetes Mellitus. Primary Objective: The primary objective is to determine if metformin reduces the requirement for insulin or the rate of fasting hyperglycaemia (≥ 5.1 mmol/l) at gestational weeks 32 or 38. Secondary Objectives: 1. To determine if metformin delays the initiation of insulin 2. To determine if metformin reduces the insulin dose required (and dose/kg/week of gestation) 3. To determine if metformin impacts on maternal body weight, BMI, waist circumference, blood glucose status, insulin resistance status and metabolic syndrome postpartum ; 4. To determine if metformin reduces the proportion of infants with morbidities; 5. To determine if metformin in addition to usual care reduces infant birth weight when compared to usual care alone 6. To determine if metformin reduces the proportion of maternal morbidities when compared to usual care alone 7. To determine if metformin in addition to usual care reduces excessive maternal gestational weight gain (GWG) 8. To determine if participants consider metformin a more acceptable treatment than insulin 9. To determine the cost, cost effectiveness, and budget impact of metformin in addition to usual care for GDM
Test Drugs Name of Active Ingredient Dose(s) Route of administration Duration of treatment	Metformin Metformin Dose will be titrated up, as tolerated, over a period of 10 days, from a starting dose of 500mg once daily to a maximum of 1.5g in the morning and 1g in the evening. Oral Until Delivery
Reference Drugs Name of Active Ingredient Dose(s) Route of administration Duration of treatment	Metformin placebo Not applicable Dose will be titrated up, as tolerated, over a period of 10 days, from a starting dose of 500mg once daily to a maximum of 1.5g in the morning and 1g in the evening. Oral Until Delivery
Usual care	Medical nutritional therapy and exercise advice provided by the Diabetes team or trained delegate

Indication	Gestational Diabetes Mellitus
Trial design	A phase III, parallel, randomised, double blind, placebo controlled trial
Inclusion criteria	a) Willing and able to provide written informed consent b) Participants aged 18-50 c) Pregnancy gestation up to 28 weeks (+ 6 days) confirmed by positive pregnancy test d) Singleton pregnancy as determined by scan e) Positive diagnosis of Gestational Diabetes Mellitus on a OGTT according to IADPSG criteria if any one of the following are achieved: i. Fasting glucose >/= 5.1mmol/l and <7mmol/l, or ii. 1 hour post glucose load of >/=10mmol/l, or iii. 2 hour post glucose load of >/=8.5 mmol/l and <11.1mmo/l f) Resident in the locality and intending to deliver within the trial site
Exclusion criteria	a) Participants who have an established diagnosis of diabetes (Type 1, Type 2, Monogenic or secondary) b) Participants with a fasting glucose ≥ 7mmol/l or a 2h value ≥ 11.1 mmol/l c) Multiple pregnancies (twins, triplets etc.) as determined by scan d) Known intolerance to metformin e) Known contraindication to the use of metformin which include: i. renal insufficiency (defined as serum creatinine of greater than 130 µmol/L or creatinine clearance <60 ml/min) ii. moderate to severe liver dysfunction (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) greater than 3 times the upper limit of normal) iii. shock or sepsis, and iv. previous hypersensitivity to metformin f) Major congenital malformations or an abnormality deemed unsuitable for metformin by the site PI or attending consultant g) Known small for gestational age[1] h) Known current gestational hypertension or pre-eclampsia or ruptured membranes i) Particiants who have a history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements j) Participants with significant gastrointestinal problems such as severe vomiting, Crohn's disease or colitis which will inadvertently affect absorption of the study drug k) Participants with congestive heart failure or history of congestive heart failure l) Participants with serious mental illness which would affect adherence to study medication or compliance with study protocol in the opinion of the investigator m) Patients with rare hereditary problems of galactose intolerance,

	the Lapp lactase deficiency or glucose-galactose malabsorption [1]Small for gestational age (SGA) refers to fetal growth less than the 10th percentile (RCOG, 2014), or if foetal growth is deemed unsatisfactory by the treating obstetrician.
Type of control	Placebo
Number of participants	550 participants will be randomised across 3 sites (Galway University Hospital, Portiuncula University Hospital and Mayo University Hospital)
Methodology	The study will comprise 3 periods; 1) screening, 2) treatment, and 3) follow up. During screening, informed consent will be obtained and evaluations of the participant's eligibility will be performed. At the beginning of the treatment period, participants will be randomised up to 28 weeks gestation (+ 6 days) in a 1:1 ratio, stratified by BMI and previous GDM to receive either metformin or matching placebo, in addition to usual care. The treatment period will be until delivery. Participants will be followed up at 4 weeks post-partum (+/- 7 days) by telephone, and 12 weeks postpartum (+/- 4 weeks) in the clinic for maternal and neonatal outcomes.
Statistical methods	The primary analysis will be a comparison of the incidence of the composite primary outcome of proportion of participants needing insulin or fasting blood glucose ≥ 5.1 mmol/l at gestational weeks 32 or 38 between treatment and control arms, using an exact test for a binomial response. A secondary analysis will involve a comparison of the time to insulin initiation between the treatment groups, using the log-rank test and the proportional hazards model.
Health Economic Analysis	The health economic analysis will consist of trial-based economic evaluation and will incorporate both cost effectiveness analysis and cost utility analysis to compare the alternative treatment strategies: 1) metformin in addition to usual care for GDM and 2) usual care for GDM.

5. ABBREVIATIONS

ACOG	American Congress of Obstetrics and Gynaecologists
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
APH	Antepartum haemorrhage
AR	Adverse reaction
AST	Aspartate Aminotransferase
b.i.d.	Twice daily
BCSH	British Committee for Standards in Haematology
BMI	Body mass index
CDMS	Clinical data management system
CI	Confidence interval
CRF	Case report form
CRFG	Clinical Research Facility Galway

333	CT	Clinical trial
334	CTA	Clinical trial authorisation
335	DNS	Diabetes Nurse Specialist
336	DMF	Data management file
337	DOB	Date of birth
338	DTSQ	Diabetes Treatment Satisfaction Questionnaire
339	DSMB	Data safety and monitoring board
340	DSUR	Development safety update report
341	EBCOG	European Board and College of Obstetrics and Gynaecology
342	e-CRF	Electronic case report form
343	EDC	Electronic data capture
344	EDTA	Ethylenediaminetetraacetic acid
345	EQ5D	Euroqol Five DimensionsMeasurement Tool
346	eGFR	Estimated glomerular filtration rate
347	EU	European Union
348	FBG	Fasting blood glucose
349	FIGO	Federation of International Gynaecological and Obstetric Societies
350	GCP	Good Clinical Practice
351	GDM	Gestational Diabetes Mellitus
352	GDPR	General Data Protection Regulation
353	GMP	Good manufacturing practice
354	GWG	Gestational Weight Gain
355	GP	General Practitioner
356	HbA1c	Glycated haemoglobin
357	Hb	Haemoglobin
358	HDL	High density lipoprotein cholesterol
359	HDPE	High density polyethylene
360	HEPA	the Health Economic and Policy Analysis
361	HIQA	the Health information and Quality Authority
362	HPRA	Health Products Regulatory Authority
363	IB	Investigators brochure
364	ICF	Informed consent form
365	ICH	International Conference on Harmonisation
366	IEC	Independent Ethics Committee
367	IFG	Impaired fasting glucose
368	IOM	Institute of Medicine
369	IUGR	Intrauterine growth restriction
370	IMP	Investigational medicinal products
371	IMPD	Investigational medicinal product dossier
372	ISO	International Organisation for Standardization
373	IADPSG	the International Association of the Diabetes and Pregnancy Study Groups
374	LDL	Low density lipoprotein cholesterol
375	LGA	Large for gestational age
376	MetS	Metabolic Syndrome
377	Mmol/l	millimole per litre
378	Ml/min	millilitre per minute
379	MNT	Medical Nutritional Therapy
380	NGT	Normal Glucose Tolerance
381	NIMP	Non-Investigational Medicinal Product
382	NNU	Neonatal unit
383	aOR	adjusted odds ratio
384	OB	Obese

o.d.	Once daily
OGTT	Oral glucose tolerance test
OR	Odds ratio
OW	Overweight
PCOS	Polycystic ovarian syndrome
PET	Preeclampsia
PI	Principal Investigator
PIH	Pregnancy induced hypertension
PIL	Patient/participant information leaflet
PPH	Post-partum haemorrhage
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
Tg	Triglycerides
t.i.d.	Three times a day
TMF	Trial master file
TSC	Trial steering committee
QALY	Quality–adjusted life years
q.i.d.	Four times a day
WHO	World Health Organisation

6. INTRODUCTION

6.1. BACKGROUND INFORMATION

6.1.1. What is Gestational Diabetes Mellitus?

Gestational Diabetes Mellitus (GDM) is defined by the World Health Organisation (WHO) as glucose intolerance resulting in hyperglycaemia during pregnancy (ADA 2004). There are a number of diagnostic criteria from National and International Organisations, which differ by the threshold of hyperglycaemia required to diagnose GDM, based on one of the following, i) fasting glucose, ii) random glucose and/or iii) oral glucose tolerance test OGTT. The IADPSG and WHO define GDM as fasting glucose ≥5.1mmmol/l or 1-hour glucose post-OGTT of ≥10.0mmmol/ or 2-hour glucose post-OGTT >/= 8.5mmol/l. Other North American guidelines define GDM as fasting glucose of ≥5.3mmmol/l. The rationale for selecting these cut-points are based on epidemiologic studies reporting the association between glycaemia and maternal and foetal outcomes in pregnancy, and evidence from clinical trials on the effect of reducing hyperglycaemia on clinical outcomes. The IADPSG criteria have now been accepted by WHO, American Diabetes Association (ADA), Endocrine society, Federation of International Gynaecological and Obstetric societies (FIGO), and European Board and College of Obstetrics and Gynaecology (EBCOG).

6.1.2. How common is Gestational Diabetes Mellitus?

ATLANTIC Diabetes in Pregnancy (Atlantic DIP) was established in 2006 and covers a population of 500,000 with 11,000 deliveries annually across 5 antenatal centres in Ireland. Women from both urban and rural locations are included as are those having both public and private health care. Atlantic DIP carries out observational cohort studies and randomised control trials in pregnant women with diabetes. One such study was a prospective cohort study to estimate GDM prevalence when applying universal screening and IADPSG criteria to a regional population. GDM prevalence was found to be 12.4% (O Sullivan 2011). Increasing age, previous GDM, obesity, and family history of diabetes are known risk factors. Internationally, GDM prevalence is quoted at 17% with a range of 9-25% across 15 centres (Sacks 2012).

6.1.3. Why is Gestational Diabetes Mellitus Clinically Important in the Short Term?

The association between maternal glycaemia and pregnancy outcome represents a continuum of increasing risk of adverse outcomes. In ATLANTIC-DIP, GDM was associated with increased adverse maternal and neonatal outcomes (O Sullivan 2011). In particular, maternal hypertensive disorders were increased 2 fold (OR1.5 CI 1-2), and delivery by Caesarean section increased by 30% (OR 1.3 CI 1-1.6). There was a significant increase in macrosomia (birth weight > 4kg) at 23.9% compared to 17% in women without diabetes (P<0.05) and also in the delivery of LGA babies (>90th centile) at 22.6% compared to 16.2% in normal glucose tolerant (NGT) women (P<0.01). The admission rate to neonatal unit care (NNU) was 26% compared to 9.1% in NGT women (P<0.0001) and the main reason for admission was hypoglycaemia at a rate of 2.4% compared to 0.6% in NGT women (P<0.0001). Obesity in pregnancy was shown to be a growing problem contributing to GDM but also causing significant independent morbidities for the mother and infant (Dennedy 2012). Caesarean deliveries increased in overweight (OW) and obese (OB) women significantly with OR of 1.57 (CI 1.24-1.98) and 2.65 (OR 2.03-3.46) respectively. Hypertensive disorders in pregnancy were also greater with an OR of 2.3 (CI 1.55-3.4) and 3.29 (CI 2.14-5.05) in OW and OB women respectively. Mean birth weight was 3.46Kg in offspring of normal BMI women rising to 3.56kg and 3.62 kg in OW and OB women respectively (P<0.01). Macrosomia occurred in 15.5%, 21.4% and 27.8% of normal OW and OB women respectively (P<0.01). The cost of diagnosing and managing GDM in Ireland is

substantial (Gillespie 2013). GDM pregnancies incur an additional cost of circa 30% driven mainly by NNU care admissions and delivery by Caesarean section. Obesity is also a significant contributor to costs.

6.1.4. Why is Gestational Diabetes Mellitus Clinically Important in the Long Term?

Atlantic DIP found persistent glucose abnormalities in 19% of GDM women in the first 6 month's post-partum compared with 2.7% in women with NGT in pregnancy (O Reilly 2011). Gestational insulin use increased the chance of having persistent post-partum glucose abnormalities (OR 2.62; CI 1.17-5.87), while breast-feeding compared to bottle feeding had a protective effect (8.2% vs. 18.4%; P<0.001) (O Reilly 2011). Women were again rescreened up to 5 years post the index pregnancy (mean 2.6 years) and on-going glucose abnormalities were present in 26% of women with prior GDM compared to 4% of women with NGT in the index pregnancy (Noctor 2016). Persistent glucose abnormalities correlated with fasting blood glucose > 5.1 mmol/l on pregnancy OGTT (OR 2.9; CI 1.5 to 5.3). The likelihood of persistent glucose abnormalities increased in OW and OB women with OR 2.5; CI 1.1 to 5.7 and OR 3.7; CI 1.6 to 8.5 respectively. Breast feeding was once again protective OR 0.5; CI 0.3 to 0.9 (Noctor 2012). As well as glucose related problems, women also have an increased risk of metabolic syndrome (Noctor 2015). Internationally GDM mothers are seven times more likely to develop type 2 diabetes (RR 7·43, 95% CI 4·79—11·51)(Bellamy 2009). As well as the perinatal impacts of GDM, children of GDM mothers are at increased risk of glucose abnormalities in childhood (Zhu 2016) metabolic syndrome (MetS) and obesity (Vaarasmaki 2009; Clausen 2009) in adolescence and pre-diabetes and diabetes in early adult life (Launenborg 2011). In addition, there is a growing body of evidence linking metabolic diseases in pregnancy to Autism Spectrum Disorders (ASD) in offspring (Krakowiak 2012).

6.1.5. Does Treating GDM Improve Clinical Outcomes?

While active management of GDM is associated with significantly improved perinatal outcomes (Crowther 2005; Landon 2009) there are limitations to our current approach. Once a mother is diagnosed with GDM, the initial approach to management is medical nutritional therapy (MNT) and exercise (30 minutes per day) for 2 weeks, which is successful in controlling glucose levels in approximately 60% of women with GDM and in reducing perinatal morbidities and infant size to that of women with NGT (Kgosidialwa 2015). When glucose targets are not met (approximately 35-40% of GDM women), insulin therapy is ordinarily prescribed usually after 2-4 weeks, and considered usual care in Ireland. Insulin therapy is also effective in normalising perinatal outcomes to that of women with NGT (Bogdanet 2016) but is associated with increased rates of Caesarean delivery and need for NNU care. In the USA glyburide is advocated as first line therapy by the American College of Obstetrics and Gynaecology (ACOG) while the recently updated NICE guidelines advocate metformin as first line therapy in the UK. A recent meta-analysis of treatments for GDM found metformin to be slightly better than insulin with glyburide inferior to both treatments (Balsells 2015). In the USA analysis of glyburide compared to insulin for treatment of GDM found glyburide to be associated with an increase in adverse perinatal outcomes (Castillo 2015).

6.1.6. Limitations of Insulin Therapy

Insulin therapy administered by injection is associated with an increased risk of maternal hypoglycaemia, excess maternal weight gain and increased risk of operative delivery (Egan 2013). In addition, the excess weight gain, associated with insulin use, increases insulin requirements further. Furthermore, 40% of women have an extended period (2-4 weeks) of possible hyperglycaemia between initiation of MNT and exercise and introduction of insulin therapy. This may predispose to sub optimal glycaemic control, which is associated with an increased risk of hypoglycaemia in the

infant following delivery. Gestational weight gain (GWG) is defined by the American Institute of Medicine (IOM) according to the woman's booking BMI. Excessive GWG is gaining momentum as an additional independent risk factor contributing to a higher odds ratio of development of macrosomia and LGA. We recently carried out analysis of the Atlantic DIP dataset to determine how many women exceeded the IOM guidelines for appropriate weight gain in pregnancy and whether excessive GWG was associated with a further increase in adverse outcomes in pregnancies already at risk. We found that excessive GWG occurred in > 60% of women with GDM. Excessive GWG defined by IOM guidelines further increased the odds ratio of LGA (aOR 2.008; CI 1.241 to 3.248) and macrosomia (aOR 2.166; CI 1.321 to 3.550) significantly on a multivariate analysis when all other contributing variables were adjusted for (Egan 2013). Treatment with insulin further increased the adjusted odds for LGA (aOR 2.802; CI 1.231 to 6.379). Excessive GWG in women with GDM also increased OR of pregnancy induced hypertension (aOR 1.719; CI 1.037 to 2.852). This suggests that a focus on minimising excessive GWG is important and opens the debate regarding the usefulness and effectiveness of insulin as the preferred treatment modality in women where MNT fails.

6.1.7. Metformin use for GDM

In many European countries oral hypoglycaemic agents (e.g. metformin or glyburide) are used for glucose control, when diet and exercise interventions have failed. National Irish guidelines do not advocate the use of oral hypoglycaemic agents for glucose control in GDM. However, there is now a good body of research that has evaluated the use of metformin in GDM. The most conclusive evidence on the safety of metformin comes from the MiG study (Rowan 2008) in which 752 participants were randomly assigned to metformin or insulin. Metformin did not increase the risk of perinatal morbidities, compared to insulin. However, in that trial, metformin was only used in obese patients (BMI >30) who had failed lifestyle interventions. An open label prospective RCT (Ljas 2011) reported less macrosomia especially in lean (BMI < 25) or moderately overweight (BMI > 25<30) participants with metformin treatment. Studies on the long-term effects of metformin are also encouraging. Glueck (2004) followed offspring whose mothers received metformin and found normal weight, height, social and motor skills at 18 months with no differences when compared to unexposed infants. Rowan (2011) showed reassuring results when 2 year olds were examined following the MiG trial, and found no difference in total body fat in children of mothers treated with metformin compared to those treated with insulin, but a suggestion of more favourable metabolic distribution of fat. Rowan et al also reported metformin to be a more acceptable and satisfying treatment than insulin (Rowan 2008), more participants said they would choose metformin in a subsequent pregnancy (76.6%) compared with 27.2% in the insulin group (p<0.001). In a cross-sectional study of 197 participants with GDM, Latif (2013) found that participants treated with metformin alone were more satisfied with treatment and had higher Quality of Life scores than participants treated with insulin. It seems likely therefore that metformin may have an important role to play in patient reported outcomes affecting the lives of women diagnosed with GDM. Finally a recent meta-analysis of treatments for GDM found metformin to be slightly better than insulin with glyburide inferior to both treatments (Balsells 2015).

While metformin crosses the placenta (Vanky 2005), there are a large number of studies reporting the safety of metformin in pregnancy, for mother and child. Metformin has been used extensively in women with Polycystic Ovarian Syndrome (PCOS) who have become pregnant (Tang 2010), and no increase in adverse effects has been reported. Metformin has been used in South Africa since the 1970s and perinatal mortality is similar in women treated with metformin and insulin (Coetzee 1984). Goh (2011) examined pregnancy outcomes for 1269 women, 465 of whom received metformin. Those receiving metformin had fewer adverse outcomes compared to those treated with insulin. Three meta-analyses (Gutzin 2003; Gilbert 2006; Juan Gui 2013) including over 1500 participants reported no increase in congenital abnormalities or neonatal deaths with metformin. Juan Gui (2013) concluded that metformin was comparable with insulin for glycaemic control and neonatal outcomes, favouring metformin in respect of GWG, size at delivery, incidence of pregnancy induced hypertension (PIH)

and preeclampsia (PET) and that metformin might be especially suitable for mild GDM patients. A recently published study looking at the benefits of metformin in obese pregnant participants without GDM (EMPOWER) was not associated with adverse events related to metformin use (Chiswick 2015). Finally a large RCT is being conducted to examine the benefits of metformin in participants with Type 2 diabetes in pregnancy (MiTy trial).

The evidence to date on the safety of metformin in GDM is robust in selective and selectively screened populations. However, the evidence of the benefits of metformin in a broader spectrum of 'all' GDM pregnancies in women of all Body Mass Index (BMI) categories and irrespective of the success of lifestyle interventions for the treatment of GDM undergoing universal screening with IADPSG criteria is absent. Additionally, interventions to improve glycaemia and at the same time minimise excess gestational weight gain in GDM are also needed.

Overall therefore we have found a rising prevalence of GDM and obesity in women in Ireland, both associated with an increase in adverse outcomes for mother and infant in the index pregnancy and a worrying prevalence of persistent glucose abnormalities over time. More recently the impact of excessive GWG and insulin treatment on the already established increased adverse outcomes adds further complexity to this condition and its management. We now wish to explore if the introduction of metformin in addition to usual care at the time of initial GDM diagnosis (i.e. along with diet and exercise interventions) in all women screened and diagnosed by IADPSG criteria, is effective in reducing the incidence of hyperglycemia, measured by the need for insulin treatment during pregnancy or reducing rate of fasting glucose ≥5.1 mmol/l at gestational week 32 or 38. We will also determine its effect on excessive GWG, and translating these effects into better outcomes for mothers and their babies. We also wish to establish if early intervention with metformin is more cost effective and acceptable to, and increases satisfaction for women with GDM. Finally, this study will form the basis of future applications to establish the benefits of metformin on prevalence of Type 2 diabetes and obesity in the mother and offspring longitudinally.

6.2. RATIONALE FOR THE STUDY

GDM results from a combination of reduced insulin sensitivity and/or reduced insulin production. Metformin increases insulin sensitivity and thus it has potential as a treatment option in GDM. Metformin is weight neutral and not associated with hypoglycaemia, two factors that would increase its acceptability for pregnancy, and represents an advantage over insulin. Metformin has been shown to be safe in pregnancy (for mother and baby), when it is introduced after failure of diet and exercise. However, in many countries (including Ireland), insulin therapy remains the standard of care for treatment of GDM, in women who have failed to achieve normo-glycemia after diet and exercise. Distinct from previous clinical trials, we plan to evaluate the use of metformin (compared to placebo) at the time of initial GDM diagnosis (i.e. at the same time as diet and exercise interventions), and evaluate its use in all women with GDM, not just those with elevated BMIs.

The EMERGE trial will evaluate metformin introduced at the time of GDM diagnosis in participants of all BMI categories, to determine whether treating all participants with GDM (rather than just those who fail MNT/exercise) results in better outcomes for mothers and babies. The primary outcome is the development of hyperglycemia, represented as the composite of initiation of insulin (as this reflects clinically meaningful hyperglycemia) or a venous fasting glucose measurement ≥5.1mmol/l at weeks 32 or 38 of gestation. Secondary outcome measures include excessive GWG, neonatal and maternal outcomes. Finally, we will conduct an extensive cost benefit and cost utility analysis of metformin use in GDM pregnancy. Results of the EMERGE trial may have a considerable impact on clinical practice by providing evidence to support early active management with metformin at the time of diagnosis in a broader GDM population.

Study Drug administration: Metformin and matched placebo are administered orally. Both will be administered from the time of GDM diagnosis (up to 28 weeks + 6 days gestation) to delivery or termination of the pregnancy. Metformin will be given in tablets of 500mg. The dose will be titrated over a two-week period and will commence at 1 tablet per day (500mg) increasing to maximum of 5 tablets per day (2500mg). This dosing regimen will minimise any possible nausea associated with metformin and is in line with the dosing schedule of metformin in a previous GDM trial (MiG), the EMPOWER study of obese pregnant participants and an on-going trial in Type 2 diabetes in pregnancy (MiTy).

7. STUDY OBJECTIVES

The overall objective of the EMERGE trial is to determine whether metformin + usual care, compared to placebo + usual care (introduced at the time of initial diagnosis of GDM), reduces a) the need for insulin use or hyperglycemia (primary outcome measure); b) excessive maternal weight gain; c) maternal and neonatal morbidities and, d) cost of treatment for participants with Gestational Diabetes Mellitus.

7.1. Primary objective

The primary objective is to determine if metformin reduces the requirement for insulin or reduces the rate of fasting hyperglycaemia (≥ 5.1 mmol/l) at gestational weeks 32 or 38.

7.2. Secondary objectives

Additional secondary objectives of this study are:

1. To determine if metformin delays the initiation of insulin
2. To determine if metformin reduces the insulin dose required (and dose/kg/week of gestation)
3. To determine if metformin impacts on maternal body weight, BMI, waist circumference, blood glucose status, insulin resistance status and metabolic syndrome postpartum
4. To determine if metformin reduces the proportion of infants with morbidities
5. To determine if metformin in addition to usual care reduces infant birth weight when compared to usual care alone
6. To determine if metformin reduces the proportion of maternal morbidities when compared to usual care alone
7. To determine if metformin in addition to usual care reduces excessive maternal gestational weight gain (GWG)
8. To determine if participants consider metformin a more acceptable treatment than insulin
9. To determine the cost, cost effectiveness, and budget impact of metformin in addition to usual care for GDM

7.3. Primary and secondary outcome measures

7.3.1. Primary Outcome Measure

A composite primary outcome of insulin initiation or fasting venous glucose ≥ 5.1 mmol/l on study specific fasting laboratory glucose at gestational weeks 32 or 38 will be used. This approach allows us to measure ‘treatment failure’ in two discreet ways. Introduction of insulin reflects clinically meaningful hyperglycaemia, and is measured at any time during the clinical trial. In addition, a standardised fasting glucose will be completed at gestational weeks 32 or 38 to capture additional participants who have fasting hyperglycaemia but have not had insulin introduced during the clinical trial.

7.3.2. Secondary Outcome Measures

1. Time to insulin initiation and insulin dose required
2. Maternal morbidity at delivery (hypertensive disorders, antepartum and postpartum haemorrhage)
3. Mode and time of delivery
4. Postpartum glucose status, insulin resistance, and metabolic syndrome
5. Postpartum BMI, gestational weight gain, and waist circumference
6. Infant birth weight
7. Neonatal height and head circumference at delivery
8. Neonatal morbidities (Need for neonatal care unit, respiratory distress, jaundice, congenital anomalies, Apgar score)
9. Neonatal hypoglycaemia (defined as plasma glucose <2.6mmol/L on one or more occasions starting 30-60 minutes after birth)
10. Cost effectiveness and budget impact of metformin treatment in addition to usual care
11. Treatment acceptability (DTSQ and Rowan questionnaires)
12. Quality of Life determined by EQ5D-5L questionnaire

8. TRIAL DESIGN

8.1. Design Summary

A phase III, parallel, randomised double-blind, placebo-controlled, trial of metformin (in addition to usual care) versus usual care in 550 participants with Gestational Diabetes Mellitus (GDM) across upto 3 sites in the Republic of Ireland, followed until 12 weeks post-partum (+/- 4 weeks).

Eligible participants will be randomised to one of two groups; treatment group or placebo group.

8.1.1. Treatment Group

Participants randomised to the metformin group will receive metformin 500mg OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg metformin daily (5 tablets) or maximum tolerated dose, in addition to usual care (exercise and MNT), and taken until delivery.

8.1.2. Placebo Group

Participants randomised to the placebo group will receive 1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily, in addition to usual care (exercise and MNT), and taken until delivery.

Participants will be followed up at 4 weeks (+/- 7days) and at 12 weeks (+/- 4 weeks) post-partum for additional maternal and neonatal outcomes.

8.1.3. Usual Care

Both the treatment and metformin group will receive usual care which consists of medical nutritional therapy (MNT) and information on exercise provided by the Diabetes team or trained delegate. The Diabetes team or trained delegate will instruct participants on the use of a glucometer and the participants will perform 7-point glucose testing before and 1 hour after meals and before bed. Participants will be supported by telephone contact from the Diabetes team or trained delegate

716 weekly throughout gestation and attend at 2-4 weekly intervals at an antenatal/diabetes clinic. Usual
717 care is outlined in more detail in section 9.1.1.
718

719 Figure 1: Schematic Diagram of Trial Design
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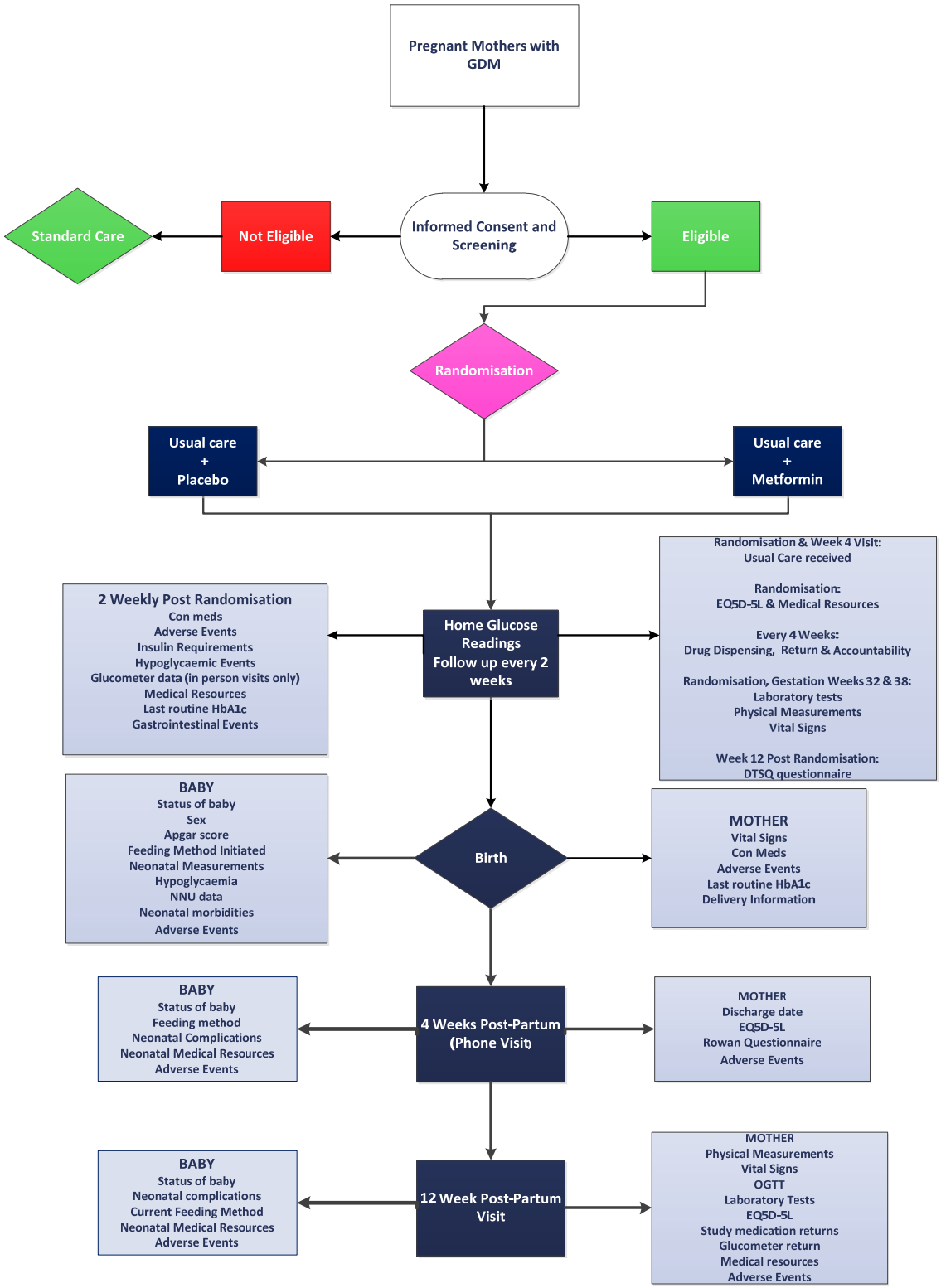

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8.2. Selection of Study Population

8.2.1. Population

The population for the trial is pregnant participants between the ages of 18-50 years, with a diagnosis of GDM up to 28 weeks gestation (+ 6 days).

Participants diagnosed using a 75g oral glucose tolerance test (OGTT) and International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria for diagnosis will be eligible to be enrolled in the study. Eligible participants must be resident and intending to deliver within the selected trial sites. The geographical area and study population includes participants from urban and rural locations and participants in both public and private health care.

In order to be eligible for the trial participants must meet all of the inclusion criteria and none of the exclusion criteria listed below.

8.2.2. Inclusion Criteria

a) Willing and able to provide written informed consent
b) Participants aged 18-50 years
c) Pregnancy gestation up to 28 weeks (+ 6 days) confirmed by positive pregnancy test
d) Singleton pregnancy as determined by scan
e) Positive diagnosis of Gestational Diabetes Mellitus on a OGTT according to IADPSG criteria if any one of the following are achieved:
    a. Fasting glucose >/= 5.1mmol/l and <7mmol/l, or
    b. 1 hour post glucose load of >/=10mmol/l, or
    c. 2 hour post glucose load of >/=8.5 mmol/l and <11.1mmol/l
f) Resident in the locality and intending to deliver within the trial site

8.2.3. Exclusion Criteria

Participants who meet <u>any</u> one or more of the following exclusion criteria will not be eligible to take part in the trial:

a) Participants who have an established diagnosis of diabetes (Type 1, Type 2, Monogenic or secondary)
b) Participants with a fasting glucose ≥ 7mmol/l or a 2h value ≥ 11.1 mmol/l
c) Multiple pregnancies (twins, triplets etc.) as determined by scan
d) Known intolerance to metformin
e) Known contraindication to the use of metformin which include:
    i. renal insufficiency (defined as serum creatinine of greater than 130 µmol/L or creatinine clearance <60 ml/min)
    ii. moderate to severe liver dysfunction (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 times the upper limit of normal)
    iii. shock or sepsis, and
    iv. previous hypersensitivity to metformin
f) Major congenital malformations or an abnormality deemed unsuitable for metformin by the site PI or attending consultant.
g) Known small for gestational age[1]
h) Known current gestational hypertension, pre-eclampsia, or ruptured membranes

i) Participants who have a history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements
j) Participants with significant gastrointestinal problems such as severe vomiting, Crohn's disease or colitis which will inadvertently affect absorption of the study drug
k) Participants with congestive heart failure or history of congestive heart failure
l) Participants with serious mental illness which would affect adherence to study medication or compliance with study protocol in the opinion of the investigator
m) Participants with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

[1]Small for gestational age (SGA) refers to fetal growth less than the 10th percentile (RCOG, 2014), or as determined by the treating obstetrician

8.3. Study Visits and procedures

8.3.1. Screening and Randomisation Visit and Procedures

Screening for GDM will be conducted in the trial sites for all participants. Participants will receive a 75g OGTT scheduled as part of routine care which they can opt out of if they wish. GDM will be diagnosed according to the IADPSG criteria if any one of the following are achieved; fasting glucose >/= 5.1mmol/l and <7mmol/l, 1 hour post glucose load of >/= 10 mmol/l, and 2 hour post glucose load of >/= 8.5 mmol/l and <11.1mmol/l. Those with a positive OGTT will receive usual care of MNT and exercise advice from the Diabetes team or trained delegate, and will also be approached for consent for screening into the trial. Consenting participants will then be screened for eligibility.

Screening will consist of the following procedures:
1. Review of inclusion/exclusion criteria
2. Review of medical history including previous pregnancy history
3. Review of concomitant medications
4. Current pregnancy information including date of last menstrual period, estimated date of delivery, gestational week, para and gravida.

All screening procedures will be documented in the medical notes by the research nurse.

The results of the screening visit will be reviewed and eligibility will be signed off by the investigator or delegate. Once eligibility has been confirmed, participants will be randomised to a study arm and assigned a Participant ID using the web based randomisation service. The timeline for randomisation is up to 28 weeks (+6 days) gestation, which can occur on the same day as screening or up to 7 days post-screening.

Participants at all trial sites will also be invited to partake in a bio-banking sub-study which involves obtaining maternal blood samples at randomisation and gestational age 38 weeks (+/- 1 week) and also a cord blood sample at delivery. This is executed under a separate Ethics Committee approved protocol and is executed as guided by local practice patterns and the availability of resources (including staff).

Once the participant has been randomised, additional data collected will include:

1. Physical measurements and vital signs (heart rate, BP, height, weight)
2. Demographics (date of birth (DOB), race)

3. Social history (smoking and alcohol)
4. Socioeconomic status
5. Baseline gastrointestinal symptoms
6. EQ5D-5L Questionnaire
7. Laboratory tests (see section 8.4.5)
8. Medical resources used since diagnosis of pregnancy
9. Usual care received

The participant will then be dispensed study medication and administration instructions. The pack numbers of dispensed medication will be documented on the dispensation log.

8.3.2. Prenatal Visit and Procedures

Prenatal visits will occur approximately every 2 weeks post randomisation in line with routine antenatal clinic visits. Visits that do not require an in person physical measurement, laboratory assessment or drug dispensation can be completed over the telephone. The following data will be collected and procedures will be performed:

1. Gestational age in weeks
2. Review of concomitant medications
3. Review of insulin requirements
4. Review of adverse events
5. Gastrointestinal symptom review
6. Review of hypoglycaemic events
7. Review of medical resources used
8. Glucometer data download (at in person visits only, see section 8.4.7.)

The following data will be collected in addition to the above:

1. Study drug dispensing (every 4 weeks)
2. Physical measurements and vital signs (heart rate, BP and weight to be taken at gestational weeks 32 (+/- 1 week) and 38 (+/- 1 week))
3. Usual care received (week 4)
4. Laboratory tests (at gestational week 32 (+/- 1 week) AND at gestational week 38 (+/- 1 week), see section 8.4.5.)
5. DTSQ (gestational week 38 (+/- 1 week) or as soon as possible thereafter)
6. Study Drug Accountability (every 4 weeks)

8.3.3. Delivery Visit

The delivery visit will occur up to 72 hours post-delivery, while the participant is in the post natal ward. Should the participant be discharged early, or it is not possible to see the participant within the visit window (e.g. delivery occurs out of hours), every effort will be made to gather the information from the medical notes or through telephone contact. The following data will be collected and procedures will be performed:

1) Vital signs (heart rate, BP)
2) Review of concomitant medications
3) Review of adverse events (mother and baby)
4) Last routine HbA1c recorded
5) Delivery information (time, date and mode of delivery, and complications)

6) Feeding method initiated
7) Neonatal procedures (status of baby, sex, neonatal measurments, Apgar score, hypoglycaemia, respiratory distress, jaundice and congenital anomalies)
8) Neonatal care unit data
9) Neonatal medical resources

8.3.4. Phone Visit (Visit 1 Post-Partum)

A phone visit will take place 4 weeks (+/- 7 days) post-partum. The following data will be collected:

1) Status of the baby
2) Current Feeding method
3) Neonatal complications
4) Discharge date
5) Questionnaires (EQ5D-5L, Rowan Questionnaire)
6) Adverse Events (mother and baby)

An appointment will be scheduled for the 12 week post-partum visit by the research nurse.

8.3.5. 12 Week Post-Partum Visit (Visit 2 Post-Partum)

The post-partum visit will take place 12 weeks post-partum (+/- 4 weeks) and will be conducted in person. The following data will be collected and procedures will be performed:

1) Physical measurements (heart rate, BP, height, weight and waist circumference)
2) 75g OGTT
3) Laboratory tests (see section 8.4.5)
4) Questionnaires (EQ5D-5L)
5) Study medication returns
6) Status of baby
7) Neonatal complications
8) Current feeding method
9) Return Glucometer and data download
10) Medical care received since delivery
11) Adverse Events (mother and baby)

An outline of scheduled study assessments and procedures are outlined below in figure 2.

Schedule of Visits											
	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	Visit7	Additional Visit (s)	Delivery Visit	Visit1 pp	Visit2 pp
Weeks Post-Randomisation	Week 0[a]	Week 2[c]	Week 4[c]	Week 6[c]	Week 8[c]	Week 10[c]	Week 12[c]	Additional Visit (s)[bc]	Delivery[d]	4 weeks Post-partum[e]	12 weeks Post-partum[f]
Maternal Procedures											
Informed Consent	X										
Inclusion/Exclusion	X										
Medical History	X										
Demographics/social history	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Current Pregnancy	X										
Randomisation	X										
Socioeconomic status	X										
Gastrointestinal symptoms	X	X	X	X	X	X	X	X			
Medical resources	X	X	X	X	X	X	X	X			X
Vital signs	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X		X
Height and Weight	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]			X
Waist Circumference											X
OGTT	X										X
Laboratory tests	X		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]			X
Usual Care	X		X								
Study Drug Dispensing	X		X		X		X	X[j]			
Glucometer Data		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]			X
Hypoglycaemic events		X	X	X	X	X	X	X			
Insulin Initiation data		X	X	X	X	X	X	X			
Study Drug Accountability			X		X		X	X[l]			X
Return Study Drug			X		X		X	X[l]			X
Delivery information									X		
Mode of Delivery									X		
Time of Delivery									X		
Delivery complications									X		
DTSQ							X[h]				
EQ5D-5L	X									X	X
Rowan Questionnaire										X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Neonatal Procedures											
Status of Baby									X		X
Sex									X		
Feeding Method									X	X	X
Neonatal measurements									X		
Apgar Score									X		
Hypoglycaemia (<2.6mmol/l)									X		X
NNU care									X	X	X
Jaundice									X		X

Neonatal medical resources									X	X	X
Neonatal morbidities									X		X
Discharge date										X	
Adverse Events									X	X	X

Figure 2: Schedule of Visits and Procedures for the EMERGE Trial

[a] Participants may be randomised up to 28 weeks gestation (+6 days)
[b] Additional 2 weekly visits may occur before delivery
[c]Visits that do not require an in person physical measurement, laboratory assessment or drug dispensation can be completed over the telephone
[d]The delivery visit should take place within 72 hours of birth
[e] The 4 week post-partum visit window is +/- 7days
[f] The 12 week post-partum visit window is +/- 4 weeks
[g] Lab tests should be completed at 32 gestational weeks (+/- 1 week) AND at 38 gestational weeks (+/- 1 week)
[h]The DTSQ will be administered at the 12 week visit, or as soon as possible thereafter
[i] Vital signs and height and weight measurements should be completed at 32 gestational weeks (+/- 1 week) AND at 38 gestational weeks (+/- 1 week), in line with routine antenatal clinic visits.
[j]Study drug dispensing should be completed every 4 weeks
[k]In cases where study visits are completed over the telephone, glucometer data should be downloaded at a subsequent in-person study visit
[l]Study Drug Return and Accountability should be completed every 4 weeks during the pre-natal study period

8.4. Description of Study Procedures

8.4.1. Informed Consent

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with ICH-GCP. Eligible participants may only be included in the trial after providing written informed consent. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the patient's medical records (source documents which will be reviewed at the time of on-site monitoring visits).

The central ethics committee (EC) approved Patient Information Leaflet and Informed Consent Form (PIL and ICF) will be provided to potential participants, which the Principal Investigator and/or delegate will explain and discuss the nature of the study. Participants will have ample time to ask and have answered any questions by the investigator prior to making a decision regarding participation.

Upon providing consent, the ICF will be signed and dated by the participant, and the investigator who administered the ICF. The complete original ICF will be filed by the site in the site file, a copy of the ICF will be given to the participant and a copy will be filed in the participant's notes.

8.4.2. Medical History

A review of each participants medical history will be completed at the screening visit to document the following relevant medical conditions:

- Psychiatric disorders
- Asthma
- Gastrooesophageal reflux disease
- Cardiovascular disease
- Irritable bowel syndrome
- Inflammatory bowel disease
- Coeliac disease
- Polycystic ovary syndrome
- Hypercholesterolemia
- Epilepsy
- Cancer
- Thyroid disorder
- Essential Hypertension
- Any longstanding medical condition for which the participant is currently taking treatment

A review of all concomitant medications will be documented by interview or review of medical records at the screening visit. Changes in medical history and concomitant medications will be reviewed at each subsequent visit.

8.4.3. Physical Assessments

Standardised measurement of BP will be used. Weight will be measured in kg, height in meters and body mass index (BMI) as kg/m2. BMI will be calculated categorised according to World Health Organization (WHO) standards: underweight, <18.5 kg/m 2; normal, 18.5–24.5 kg/m2; overweight (OW), 25–29.9 kg/m2; obese (OB), >30 kg/m2. Waist circumference will be taken using a tape measure half way between the hip bone and the lowest rib, about 5 cm (2 in) above the belly button.

8.4.4. OGTT

A 75g OGTT will be carried out at screening and 12 weeks (+/- 4 weeks) post-partum.
The OGTT at screening will determine the presence of GDM according to IADPSG/WHO 2013 criteria based on any one of the following values: Fasting >/= 5.1 and <7, 1 h >/=10, and 2h >/= 8.5 and <11.1 mmol/l. Results of the post -partum OGTT will categorize participants as one of the following: 1) Negative: fasting blood glucose (FBG) < 5.6 mmol/l, 2h blood glucose <7.8 mmol/l; 2) Impaired fasting glucose (IFG) FBG >5.6 <7mmol/l; 2h blood glucose <7.8mmol/l. 3) Impaired glucose tolerance FBG 5.6-7mmol/l; 2h blood glucose 7.8-11.1mmol/. 4) Diabetic FBG >7mmol/l or 2h blood glucose >11.1mmol/l. We will use a fasting venous sample as venous glucose is more accurate than capillary measurements.

8.4.5. Laboratory Tests

Lab tests should be completed at the randomisation visit, 32 gestational weeks (+/- 1 week) AND at 38 gestational weeks (+/- 1 week), and 12 weeks post-partum (+/- 4 weeks). If the participant is administered steroids at 32 weeks gestation or 38 weeks gestation, defer lab tests for 48 hours.

The following laboratory assessments will be analysed locally:

Randomisation: HbA1c, fasting glucose, Insulin, c-peptide, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (Tg), urea, creatinine, alanine aminotransferase (ALT), and aspartate transaminase (AST).

32 weeks gestation: HbA1c, fasting glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (Tg), urea, creatinine, alanine aminotransferase (ALT), and aspartate transaminase (AST).

38 weeks gestation: HbA1c, fasting glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (Tg), urea, creatinine, alanine aminotransferase (ALT), and aspartate transaminase (AST).

12 weeks post-partum: fasting glucose, 2h glucose, fasting insulin, fasting c-peptide, HbA1c, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (Tg).

8.4.6. Bio-banking

Participants at all trial sites will also be invited to partake in a GDM bio-banking sub-study which involves obtaining maternal blood samples at randomisation and gestational age 38 weeks (+/- 1

week) and also a cord blood sample at delivery. This is executed under a separate Ethics Committee approved protocol and is executed as guided by local practice patterns and the availability of resources (including staff).

8.4.7 Glucometer data

Home capillary blood glucose measurements will occur as per routine practice in both groups using a Contour Next One Glucometer (Ascensia). Capillary glucose values will be downloaded from the glucometer at a subsequent in person study visit. The downloaded glucometer data will be stored and analysed as part of a future observational study, and will not be monitored as part of trial care. All clinically relevant glucometer readings will be reviewed at each on-site visit, as per usual care.

8.4.8. Study Drug Accountability

A pill count will be performed by the study nurse/site staff at prenatal visits every 4 weeks and at the 12 week post-partum visit to facilitate study medication accountability and check compliance.

Non-compliance is defined as less than 80% drug adherence of the participants maximum tolerated dose.

8.4.9. Neonatal Measurements

The neonatal anthropometric measurements will be taken within 72 hours of delivery by trained personnel and will include:

- Crown-heel length
- Head circumference
- Weight

Where feasible, abdominal circumference and mid-upper arm circumference measurements will also be taken.

8.5. Randomisation

Participants will be randomly assigned to receive either metformin or placebo in a 1:1 ratio. Random permuted blocks will be used to ensure similar numbers of participants in each intervention arm throughout the trial and equal numbers in each arm by the end of the study. A minimisation strategy will be used; this will allow equal numbers of participants with a BMI ≤/>30 and with a past history of GDM to be distributed between groups.

A web-based randomisation system will be used to allow participating sites to login and obtain allocated treatment numbers and participant IDs after confirming eligibility through inclusion and exclusion criteria. The treatment number will correspond to a treatment kit at the site. This centralised system will ensure allocation concealment; preventing trial staff from knowing which treatment group will be allocated. Blocks of varying length will also be used to reduce the predictability of the allocation sequence.

8.6. Blinding

This trial will be conducted in a double-blind fashion with placebo control identical to metformin tablets to avoid bias in the assessment of outcomes. Site Investigators, site personnel, participants, and outcome assessors will be blinded to treatment allocation.

In the case of an emergency, when knowledge of the participants's study treatment assignment is essential for the clinical management of the participant, an investigator may un-blind a participant. Any intentional or unintentional breaking of the blind will be recorded and reported to the sponsor as soon as possible.

8.6.1. Emergency Unblinding

Emergency unblinding should only be undertaken when it is essential for the participants safety and will only be provided for the treatment that requires unblinding. Most often, study drug interruption and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. In case of unblinding, only those individuals who are required to know treatment allocation may be given this information. Should the treating clinician consider it necessary to un-blind for clinical care of the participant, the treating clinician will be un-blinded. All other staff must remain blinded to treatment, including the participant. All participants should resume study treatments after recovery if it is medically appropriate to do so and should be followed until the end of the study.

Emergency unblinding will be available on the web-based randomisation service.

8.7. Definition of end-of-trial

The end of trial will be the date of the last visit of the last participant post-partum. The Sponsors and/or Data safety and monitoring board/trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the approving EC and HPRA within 90 days of the end of the clinical trial, or within 15 days if the study is terminated prematurely by the Sponsor or the Sponsors

Representative. The EU Declaration of the End of Trial form must be used for this. The investigators will inform participants and ensure that the appropriate follow-up is arranged for all involved.

8.7.1. Premature termination of the study

The trial may be terminated prematurely if:

- new information about safety or efficacy appears
- there is unsatisfactory progress of the study
- if deemed necessary by the DSMB

If the trial ends prematurely then the HPRA and the approving EC will need to be informed as required.

8.8. Discontinuation/withdrawal of participants from study treatment

Participants have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a participant from study treatment or withdraw a participant from the study at any time if it is in the best interest of the participant, in circumstances such as:

1. any medical condition that the investigator or sponsor determines may jeopardise the participant's safety if she continues receiving the study treatment
2. ineligibility (either arising during the study or retrospectively having been overlooked at screening)
3. an adverse event which requires discontinuation of the study medication
4. renal or hepatic concerns, shock or sepsis
5. lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits).

All participants who discontinue study medication will be invited to continue with protocol specified follow-up procedures. The only exception to this requirement is when a participant withdraws consent for all study procedures and contact.

If a participant discontinues study medication, or withdraws full study consent before completing the study, the reason for this must be entered on the appropriate case report form (CRF) page.

If a participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised.

9. TREATMENT OF TRIAL PARTICIPANTS

9.1. Description of study treatments

Once a diagnosis of GDM is made, participants will be randomised to either the placebo or metformin arm and medication will commence and continue in addition to usual care.

9.1.1. Usual Care

All participants participating in the Emerge trial will receive usual care as follows: Following a diagnosis of GDM participants will be seen by the diabetes team or trained delegated personnel within 1 week of diagnosis who will explain the diagnosis of GDM and its implications for her and her infant. The DNS or trained delegated personnel will instruct participants on the use of a glucometer and the participants will perform 7-point glucose testing before and 1 hour after meals and before bed. Glucose targets of </=5 mmol/l fasting and before meals and </= 7mmol/l 1 hour after meals will be given. Literature will be given and a contact name and telephone number given for any queries or urgent matters. Participants will be seen either by the diabetes physician/DNS/or trained delegate to impart dietary advice (medical nutritional therapy (MNT)) and information on exercise. Participants will be supported by telephone contact from the DNS or trained delegate weekly throughout gestation and attend at 2-4 weekly intervals at an antenatal/diabetes clinic.

Two weeks following the commencement of MNT and exercise, each participant is reviewed at the diabetes/antenatal clinic to review blood sugars and decide on the need for insulin intervention. At this time, an ultrasound scan to assess fetal growth is available, which contributes to the decision making progress. If/when insulin is required; the participant is seen by the Investigator, DNS, or trained delegate for instruction on insulin type and frequency, dealing with low and high glucose and use of a glucagon pen, and sick day rules. Diet, exercise, and principles of monitoring are re-enforced at each visit and participants are encouraged to phone the service as necessary.

At each subsequent clinic visit, the following measurements are taken; weight, blood pressure, urinalysis, and glycated haemoglobin (HbA1C). Ultrasound scanning occurs every 4 weeks for fetal growth. Mode of delivery is individualised according to mother and fetal health, fetal growth and previous delivery type. A detailed plan is written in the case notes and protocols are available for management of delivery of women with GDM; both treated with MNT only or requiring insulin. Following delivery, all insulin is discontinued and participants resume usual diet and lifestyle. Breastfeeding is encouraged and infant glucose is tested by heel prick within the first 4 hours and as required thereafter. Prior to discharge participants are scheduled for a repeat 75g oral glucose tolerance test (OGTT) at 12 weeks post-partum through the diabetes service.

9.1.2. Treatment Group

Participants randomised to the treatment arm will receive active metformin in addition to usual care. Metformin tablets will be titrated according to a dosing schedule to achieve the pre-specified glucose targets (fasting ≤ 5mmol/l, 1hour post prandial ≤ 7mmol/l). Tablets will be in 500mg doses and will commence at 1 tablet per day (500mg) increasing to a maximum of 5 tablets per day (2500mg) as follows:

- Stage 1) Day 1, 2: 1 tablet with breakfast each day
- Stage 2) Day 3, 4: 1 tablet with breakfast and 1 tablet with dinner each day
- Stage 3) Day 5, 6: 2 tablets with breakfast and 1 tablet with dinner each day

- Stage 4) Day 7, 8: 2 tablets with breakfast and 2 tablets with dinner each day
- Stage 5) Day 9, 10: 3 tablets with breakfast and 2 tablets with dinner each day

If a participant experiences uncomfortable side effects (e.g. diarrhoea or nausea) at any stage, the site will instruct the participant to go back to the previous dose and then try again to increase the dose after 4-7 days. If the participant cannot tolerate the study medication at the higher dose, but can tolerate the study medication at a lower dose, the participant may continue at that lower dose for the treatment period.

9.1.3. Placebo Group

Participants randomised to the placebo arm will receive placebo in addition to usual care. Placebo will be titrated according to the dosing schedule to achieve the pre-specified glucose targets (fasting ≤5mmol/l, 1hour post prandial ≤ 7mmol/l). Placebo tablets will commence at 1 tablet per day and will be increased to a maximum of 5 tablets per day over 10 days as with the treatment group.

9.1.4. Requirement for Insulin

Insulin will be commenced in each group as per normal practice if 2 or more home glucose readings are outside the pre-specified glucose targets (fasting ≤ 5mmol/l, 1hour post prandial ≤ 7mmol/l) (without reason) despite maximum oral therapy and MNT at any clinic visit. For this reason, insulin is considered a non-IMP in this trial (see safety reporting for NIMP section 10.3.3.). If insulin is initiated, tablets will also be continued at the maximum tolerated dose. Off study metformin is unlikely to be used as this is not routine clinical practice currently. The intervention will continue up to birth of the infant or end of pregnancy due to pregnancy loss.

9.2. Formulation, packaging, and handling

The IMPs are Glucophage (Metformin) 500mg film-coated tablets and placebo to match tablets supplied to the trial by the marketing authorisation holder Merck Santé (France).

The tablets will be repacked for the trial into bottles containing 170 active or placebo tablets and each bottle will be labelled according to Annex 13 requirements.
The Sponsor has contracted MODEPHARMA for arranging the clinical trials packaging, labelling, QP release and distribution of trial IMPs in compliance with Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). Please refer to the Summary of product Characteristics and Investigational Medicinal Product Dossier (IMPD) for further details about the IMP manufacture and labelling.

9.3. Storage of study treatments(s)

Metformin and placebo tablets are packaged in high density polyethylene (HDPE) bottles with a desiccant cartridge inside. They must be stored at room temperature (below 30°C) in a secure location with restricted access. A temperature log recording storage temperature should be maintained. Any deviations from the normal range should be reported to the sponsor.

9.4. Accountability of the study treatment(s)

The study medication will be supplied to site as per the sponsor supply process. Shipment records must be maintained by the investigator at the site. The investigator will use a standard prescription form and the investigator/research delegate will collect the medication from its designated storage space.
Metformin and matching placebo will be dispensed by authorised personnel according to local regulations. A dispensing log will be kept for each participant to document all pack numbers dispensed to the participant.

9.5. Assessment of compliance

The investigator should promote compliance by counselling the participant to take the study drug as prescribed. Participants will be provided with a medication instruction sheet to aid with the titration phase of the study. The participant should be instructed to contact the investigator if unable for any reason to take the study drug as prescribed. Treatment compliance will be assessed by confirmatory tablet counts to be conducted at each study dispensing visit every 4 weeks post randomisation.

Participants will be asked to return all unused study drug and packaging at study dispensing visits, the end of the study or at the time of study drug discontinuation. The Research Nurse or delegate will perform a pill count and calculate adherence. Drug accountability will also be noted by the clinical monitor during site visits and at the completion of the trial. Compliance of the participant with study treatments will be assessed by maintaining return records. Non-compliance is defined as less than 80% drug adherence of the participants maximum tolerated dose. In the event of non-compliance, women will be re-counselled about drug adherence.

9.5.1. Missed Dose

If the participant forgets to take a dose of Metformin / placebo she should wait for the next dose at the usual time. She should not double the dose to make up the forgotten dose.

9.6. Overdose of study treatment

Overdose of metformin hydrochloride has occurred if the ingestion amount is greater than 50 grams (100 x 500mg tablets). Hypoglycaemia has been reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from participants in whom metformin over dosage is suspected.

Available information concerning treatment of a massive over dosage of metformin is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhoea**,** drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

9.7. Prior and concomitant therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 9.7.2. Participants will be instructed to inform the investigator prior to starting any new medications. Any medication, including non-prescription medication(s) and herbal product(s), other than the study medication taken during the study will be recorded in the CRF from the date the participant signs informed consent to the last visit, except those listed below which are expected pregnancy related concomitant medications;

a) Pain relief [entonox, pethidine, fentanyl (for epidural), bupivicaine (for epidural)]
b) Local Anesthesia for perineal repair
c) Prophylactic uterotonic administration or drugs for active management of the third stage of labour i.e., oxytocin (syntocinon) 10 units IM or ergometrine maleate/oxytocin (Syntometrine) 500mcg/5 units IM
d) Ranitidine
e) Sodium Citrate
f) Routine vaccines in the baby (BCG/TB, Diphtheria, Tetanus, Pertussis, Haemophilus Influenza B (Hib), Polio, Hep B, Pneumococcal (PCV), Meningococcal (Men B)
g) Maternal vaccinations
h) Vitamin K administration (baby only)
i) Anti D for mother
j) Over-the-counter antenatal multivitamins

9.7.1. Permitted Medications/Non-Investigational Medicinal Products

The following medications are permitted for routine use throughout the duration of the trial:

1. Paracetamol
2. Aspirin
3. Low molecular weight heparin
4. Antihypertensives
5. Routine pregnancy supplements
6. Folic Acid
7. Vitamin D
8. Antacids
9. Prescribed medications for established chronic diseases
10. Insulin

Insulin taken for less than 72 hours will be recorded but will not be considered a primary outcome measure.

9.7.2. Prohibited Medications

The following medications are not permitted for routine use throughout the duration of the trial:

- Non-study oral hypoglycaemic medications
- Intravascular contrast studies with iodinated materials

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin/placebo must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

If for any clinical reason the patient requires treatment with any of the above, the patient must discontinue study treatment either temporarily or permanently and this must be documented in the CRF.

9.7.3. Cautionary Medications

Some medicinal products, such as NSAIDs (including selective cyclo-oxygenase (COX) II inhibitors), ACE inhibitors, angiotensin II receptor antagonists and diuretics (particularly) loop diuretics) may adversely affect renal function and may increase the risk of lactic acidosis. When starting or using such products in combination with metformin/placebo, monitoring of renal function may be required.

Medicinal products with intrinsic hyperglycaemic activity (e.g. systemic or local glucocorticoids and sympathomimetics) may require more frequent blood glucose monitoring.

As metformin is a substrate of the OCT1 and OCT2 organic cation transporters, co-administration with agents that are metabolised via these transporters may modify the efficacy of metformin. Coadministration of metformin/placebo with inhibitors of OCT1 (such as verapamil) may reduce the efficacy of metformin, and coadministration with inducers of OCT1 (such as rifampicin) may increase the gastrointestinal absorption and efficacy of metformin. Coadministration of metformin/placebo with inhibitors of OCT2 (such as cimetidine, dolutegravic, ranolazine, trimethoprim, vandentanib and isavuconazole) may decrease the renal eliminiation of metformin thereby leading to an increase in the plasma concentration of metformin. Coadministration if metformin/placebo with inhibitors of both OCT1 and OCT2 (such as crizotinib and olaparib) may alter the efficacy and renal elimination of metformin.

Caution is therefore advised, when these drugs are co-administered with metformin/placebo, as metformin plasma concentration may increase. Investigators should review if dose adjustment of metformin/placebo is required.

10. SAFETY REPORTING

10.1. Definitions

10.1.1. Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Each individual unintended sign, symptom or disease is considered a separate adverse event unless an overarching diagnosis can be made for a collection of signs or symptoms that are clinically linked and temporally related. The overarching diagnosis should be as specific as possible, using all available clinical data.

All events in the mother and baby must undergo an assessment to determine if any of the seriousness criteria (section 10.1.3) are met and each event must be reported to the Sponsor.

10.1.2. Adverse reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.
The phrase 'responses to a medicinal product' means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

10.1.3. Serious adverse event (SAE)

Any untoward medical occurrence or affect that at any dose meets one or more of the following criteria:

- results in death,
- is life-threatening*,
- requires hospitalisation (defined as >24 hour hospital stay, or formal admission to an inpatient hospital area) or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect
- is medically important**

* this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as 'medically important') should also be considered as 'serious' in accordance with the definition.

10.1.4. Severe adverse events

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'.

10.1.5. Suspected unexpected serious adverse reactions

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised medicinal product).

10.2. Evaluations of AEs and SAEs

The investigator or delegate will report all AEs and SAEs to the sponsor as outlined in section 10.3, except for those identified as outcomes identified below. Figure 3 outlines the cases whereby safety exemptions may require AE/SAE reporting.

The following maternal events related to prenatal period, labour, delivery and the postnatal period are commonly experienced and are therefore exempt from safety reporting unless fatal, life threatening, medically important or results in persistent disability or incapacity:

i. Peripheral Oedema

ii. Leg cramping
iii. Back, hip or pelvic pain/discomfort or symphysis pubis dysfunction
iv. Ketonuria, proteinuria, haematuria, glycosuria or leucocytes in the urine that do not require intervention
v. Vaginal discharge, unless requiring treatment
vi. Haemorrhoids or pregnancy related rectal bleeding
vii. Varicose veins
viii. Palpitations
ix. Carpal tunnel syndrome
x. Maternal tachycardia, transient hypotension, epidural related hypotension, nausea or vomiting occurring during the time of hospitalisation for labour or delivery
xi. Group B Strep colonisation
xii. Non-medically significant events associated with breast feeding

The following maternal events are considered study outcomes and collected on case report forms, and are therefore exempt from safety reporting unless fatal, life threatening, medically important or results in persistent disability or incapacity:

i. Symptoms common and expected during pregnancy, unless requiring hospitalisation:
    a. Nausea
    b. Heartburn
    c. Vomiting
    d. Flatulence
    e. Constipation

ii. Gastro-intestinal side effects from metformin therapy, unless requiring hospitalisation or cessation of study drug:
    a. Nausea
    b. Vomiting
    c. Diarrhoea
    d. Flatulence

iii. Anaemia, unless requiring hospitalisation (anaemia in pregnancy is defined as first trimester haemoglobin (Hb) less than 11.0 g/dl, second/third trimester Hb less than 10.5 g/dl, and postpartum Hb less than 10.0 g/dl, in line with British Committee for Standards in Haematology (BCSH) guidance)
iv. Hypoglycaemia, unless requiring hospitalisation
v. Polyhydramnios, unless requiring hospitalisation
vi. Abnormal OGTT at the 12 week post partum follow up visit (+/- 4 weeks)
vii. Hypertensive disorder of pregnancy (including elevated blood pressure, pregnancy induced hypertension (PIH) or Preeclampsia (PET)) not requiring hospitalisation, throughout the study period
viii. Admission to hospital for pre-natal or post-natal care, including:
    a. Cardiotocograph monitoring (day case)
    b. BP monitoring
    c. Monitoring or management of elevated blood pressure, pregnancy induced hypertension or preeclampsia
    d. Bed rest
    e. External cephalic version
    f. Observation of placenta praevia or other placental location abnormality
    g. Unstable fetal lie *in utero*

h. Antepartum Haemorrhage
i. Postpartum haemorrhage
j. Cholestasis
k. Unexplained vaginal bleeding
l. Iron infusion
m. Betamethasone administration
n. Premature rupture of membranes
o. Anti-D administration

ix. Wound infection (obstetric origin)
x. Mastitits
xi. Admission to hospital for delivery
a. Early stages of labour
b. Elective or emergency caesarean section (ELCS)
c. Induction of labour
d. Spontaneous labour

If a baby is admitted to the Neonatal Intensive Care Unit (NICU) for monitoring or care-giving purposes only, with monitoring all within normal parameters, without evidence of any abnormality, sign, diagnosis or therapeutic intervention, this is not considered an adverse event. All other admissions to the NICU are considered medically important; the primary reason for NICU admission should be reported as serious adverse events.

The following neonatal events are exempt from safety reporting unless fatal, life threatening, medically important or results in persistent disability or incapacity:

i. Non-medically significant events related to delivery
ii. Non-medically significant events occurring during the postpartum study follow-up phase

The following neonatal events are considered study outcomes and collected on case report forms, and are therefore exempt from safety reporting unless fatal, life threatening, medically important or results in persistent disability or incapacity:

iii. Neonatal jaundice (with or without phototherapy)
iv. Neonatal hypoglycaemia (defined as plasma glucose <2.6mmol/L on one or more occasions starting 30-60 minutes after birth)

	Non-Serious Event	Seriousness Criteria^						
		New Hospitalisation	Prolongation of Hospitalisation	Medically important	Life-threatening	Fatal	Results in persistent or significant disability or incapacity	Congenital anomaly or birth defect
Symptoms common or expected during pregnancy: nausea, heartburn, vomiting, flatulence or constipation	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gastro-intestinal side effects from metformin therapy*, nausea, vomiting, diarrhoea and flatulence	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anaemia	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cardiotocograph monitoring (day case)	No	No	No	Yes	Yes	Yes	Yes	Yes
BP monitoring	No	No	No	Yes	Yes	Yes	Yes	Yes
Monitoring or management of elevated blood pressure, pregnancy induced hypertension or preeclampsia	No	No	No	Yes	Yes	Yes	Yes	Yes
Bed rest	No	No	No	Yes	Yes	Yes	Yes	Yes
External cephalic version	No	No	No	Yes	Yes	Yes	Yes	Yes
Betamethasone administration	No	No	No	Yes	Yes	Yes	Yes	Yes
Anti-D administration	No	No	No	Yes	Yes	Yes	Yes	Yes
Iron Infusion	No	No	No	Yes	Yes	Yes	Yes	Yes
Hypoglycaemia	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Polyhydramnios	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abnormal OGTT at the 12 week post partum follow up visit (+/- 4 weeks)	No	No	No	Yes	Yes	Yes	Yes	Yes
Observation of placenta praevia or other placental location abnormality	No	No	No	Yes	Yes	Yes	Yes	Yes
	Non-	Seriousness Criteria^						

	Serious Event	New Hospitalisation	Prolongation of Hospitalisation	Medically important	Life-threatening	Fatal	Results in persistent or significant disability or incapacity	Congenital anomaly or birth defect
Hypertensive disorder of pregnancy (including elevated blood pressure, pregnancy induced hypertension (PIH) or preeclampsia (PET)) not requiring hospitalisation, throughout the study period	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Unstable fetal lie *in utero*	No	No	No	Yes	Yes	Yes	Yes	Yes
Antepartum haemorrhage	No	No	No	Yes	Yes	Yes	Yes	Yes
Postpartum haemorrhage	No	No	No	Yes	Yes	Yes	Yes	Yes
Unexplained vaginal bleeding	No	No	No	Yes	Yes	Yes	Yes	Yes
Premature rupture of membranes	No	No	No	Yes	Yes	Yes	Yes	Yes
Cholestasis	No	No	No	Yes	Yes	Yes	Yes	Yes
Wound Infection (Obstetric Origin)	No	No	No	Yes	Yes	Yes	Yes	Yes
Mastitis	No	No	No	Yes	Yes	Yes	Yes	Yes
Neonatal jaundice (with or without phototherapy)	No	No	No	Yes	Yes	Yes	Yes	Yes
Neonatal hypoglycaemia	No	No	No	Yes	Yes	Yes	Yes	Yes

Figure 3: Instances requiring reporting for AE and SAE safety exemptions

Yes = Event is reportable as an adverse event; No = Event is not reportable as an adverse event
^Where 'Yes' is indicated, the event must be reported to the Sponsor in an expedited manner
*If study drug is stopped, the event is reportable as an adverse event

Admission to hospital for symptoms suggestive of the early stages of labour, or admission to hospital for spontaneous labour, induction of labour or elective or emergency caesarean section are expected outcomes of pregnancy and are not reportable as safety events. All of these hospitalisations must be reviewed for other events that could be reportable adverse events.

10.2.1. Assessment of seriousness

The investigator should make an assessment of seriousness as defined in section 10.1.3.

10.2.2. Assessment of casuality

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product or with the non-investigational medicinal product qualify as adverse reactions.

The investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- Unrelated: Where an event is not considered to be related to the study medication.
- Unlikely: where a temporal relationship to the study medication makes a relationship improbable (but not impossible) and disease or other drugs provide plausible explanations.
- Possible: Although a relationship to the study medication cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study medication.
- Definite: Plausible temporal relationship and cannot be explained by disease or other drugs.

The causality assessment given by the investigator should not be downgraded by the sponsor. All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. definite, possible, probable) to the study medication will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. definite, possible, probable) to the non-IMP will also be considered to be ARs/SAR. All AEs/SAEs judged as being related (e.g. definite, possible, probable) to an interaction between the IMP and non-IMP will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.
The causality assessment will also be reviewed by the sponsor.

10.2.3. Assessment of severity

The investigator will make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe or medically significant: An event that prevents normal everyday activities.
- Life threatening: An event that has life-threatening consequences

Note: the term ‘severe’, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria

10.2.4. Assessment of expectedness

An expectedness assessment will be carried out by the sponsor for each serious adverse reaction to the IMP or an interaction between the IMP and non-IMP. The expectedness of a serious adverse reaction will be determined by the sponsor according to the reference safety information as contained in section 4.8. of the SmPC for Metformin.

10.3. Reporting Responsibilities of the investigator

10.3.1. Adverse Events/Serious Adverse Events

Any AE whose onset occurred after the time of informed consent and the last completed visit, observed by the investigator or reported by the participant, whether or not attributed to the study medication, will be recorded on the AE form in the CRF. The Site Investigator or delegate will follow AE's and SAE's reported during the treatment period until resolved, considered stable, or completion of participant participation in the EMERGE trial (i.e. 12 week Postpartum Visit). Follow up information will be sought and submitted as it becomes available. All SAEs will be followed up until resolution or they are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

The following information will be recorded in the adverse event form: Adverse event term, description, date of onset, outcome, date of resolution, seriousness, severity, assessment of relatedness to the study medication, assessment of relatedness to non-IMP, and assessment of relatedness to interaction between IMP and non-IMP, and action taken with study drug. The Site Investigator is responsible for the assessment of severity (intensity), causality/relatedness to IMP, non-IMP or an interaction between IMP and non-IMP, for all AEs and SAEs. An SAE should also be substantiated by a source document(s). Follow-up information should be provided as necessary.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from medication. A participant may also voluntarily withdraw from medication due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

10.3.2. Timelines for reporting

Adverse event information will be reported by site personnel in a timely fashion from the time the site becomes aware of the event.

Serious adverse event information will be reported by site personnel within 24 hours to the sponsor from the time the site becomes aware of the event, except for those that the protocol identifies as not requiring immediate reporting. The site team are considered aware of an adverse event from the time of first notification of the first member of the EMERGE site team, as per the Site Delegation Log. All SAE's will be submitted by the site by completing the required fields on the AE CRF within 24 hours of site awareness of the event. A valid SAE report must include all of the following:

- Adverse event term (based on what is known at the time of reporting)
- Seriousness criteria
- Severity

- Causality assessments (for metformin/placebo, insulin [if applicable] and the potential interaction betweem metformin/placebo and insulin [if applicable])
- Investigator sign-off

The immediate report will be followed by detailed, written reports. The immediate and follow-up reports will identify participants by unique code numbers.

10.3.3. Safety Reporting for Non-IMP

Insulin is considered a non-IMP and therefore must follow safety reporting guidelines for non-IMP.
All AEs and SAEs considered by the investigator to be related to the non-IMP will be reported to the sponsor within the required timeframes (section 10.3.2).
All AEs and SAEs which are considered by the investigator to be related to an interaction between IMP and non-IMP will be reported to the sponsor within the required timeframes (section 10.3.2).

10.4. Reporting responsibilities of the sponsor

10.4.1. Regulatory Authorities

The sponsor will keep detailed records of all adverse events which are reported to him by the investigator or investigators. The sponsor will report all SUSARs to the competent authority (HPRA) or EudraVigilance (as required) and the approving ethics committees concerned, and all principal investigators. Fatal or life-threatening SUSARs must be reported within 7 days.

If the initial report is incomplete, e.g. all the information/assessment has not been provided, the sponsor will submit a completed follow up report within an additional eight days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days to the sponsor.
If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information will be reported as a follow-up report within 15 days.

10.4.2. Safety Reports

The sponsor will distribute masked expedited SUSAR reports, to each participating Site Investigator, as appropriate.
SUSARs of which the treatment allocation of the participant is un-blinded should be reported by the sponsor to the national competent authority as well as the Ethics Committee.

10.4.3. Annual Reports

In addition to the expedited reporting above, the sponsor shall submit once a year throughout the clinical trial or on request, a safety report to the competent authority (HPRA) and ethics committees.
The annual safety report will be presented in the development safety update reports (DSUR) format as per ICH guideline E2F - Note for guidance on DSUR.

10.4.4. Safety reports for non-IMP

The sponsor will report SARs for non-IMP to the Regulatory Authorities or the marketing authorisation holder. The sponsor will report SUSARs for interactions between the IMP and non-IMP to the competent authority (HPRA) or EudraVigilance (as required) and Ethics Committee.

The sponsor will distribute masked expedited SUSAR reports for interactions between IMP and non-IMP to each participating Site Investigator, as appropriate.

10.5. Data safety monitoring board (DSMB)

A DSMB is established and members will serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB will be to:

1. Become familiar with the research protocol and the procedures for data safety/monitoring.
2. Review interim analyses of outcome data/adverse event reports.
3. Make written recommendations to the TSC concerning the continuation, modification, or termination of the trial.
4. Consider any requests for release of interim trial data and make recommendations to the TSC on the advisability of this.
5. Review major proposed modifications to the study prior to their implementation (e.g., termination, increasing target sample size).
6. Maintain confidentiality during all phases of DSMB review and deliberations.
7. Review SAEs and SUSARs as appropriate

The responsibilities of the DSMB are outlined further in the DSMB charter. The membership of the DSMB reflects the professions necessary to interpret the data and results from the study and to evaluate participant safety fully.

10.6. Trial Steering and Advisory Group

The purpose of the TSAG is to provide strategic oversight for the overall direction and strategy for a clinical trial. The primary responsibilities of the TSAG are:

1. To contribute to the design of the study
2. Increase information exchange at an early stage of trial development
3. Increase the efficiency of clinical trial collaboration
4. To monitor and review a) Recruitment progress, b) Quality control, c) Ethical amendments, d) Financial aspects, and e) Publications
5. To determine action points to facilitate the satisfactory progress of the EMERGE study.

This committee includes investigators, other experts not otherwise involved in the trial, and representative of the sponsor. The responsibilities of the TSAG are outlined further in the TSAG charter.

11. STATISTICS

11.1. General Considerations

General description of the statistical methods is outlined below. A more detailed statistical analysis plan (SAP) will be provided in a separate document. The SAP document will provide a more technical

and detailed elaboration of the principal features of the planned analyses. The SAP will be finalised prior to study enrolment, at the latest before any substantial information in the trial has accumulated.

Analyses will be performed using R software.

11.2. Determination of sample size

Our sample size is based on the following; a) 35% of participants will require insulin in the control arm, based on information from the MiG trial and data from University Hospital Galway and University Hospital Cork; b) ability to detect a minimum of 33% relative risk reduction in proportion of participants requiring insulin in the experimental (metformin) group (40% to 28% absolute reduction; in the MiG trial only 40% of participants on metformin required insulin); c) significance level of 0.05 and 80% power; d) drop-out rate of 5% or less; and e) non-adherence rate of 8% in metformin group. Based on these assumptions, we require a total of 550 participants. This sample size will also have 80% power to demonstrate a difference between the proportions of 12% or more (i.e. a reduction from 60-48%) in the secondary outcome of excessive GWG.

There are 7,000 deliveries annually in participating sites. From ATLANTIC DIP 1 we have identified a prevalence of 12.4% for GDM using IADPSG criteria. In our previous universal screening project, we had a consent rate of 75% but a testing rate of circa 50%. On a second study examining uptake rates in primary v secondary care, the screening uptake rate was 88% for screening in secondary care. With prevalence of 12% we would expect to diagnose upto 840 pregnancies with GDM annually. For the secondary outcome of baseline to post-partum weight change, there is a greater concern with loss to follow-up, as post-pregnancy follow-up rates have been reported in some studies to be less than 70%. For this outcome, even with a loss-to follow- up of 50% the resulting 138 per arm will have 80% power, at the 0.05 significance level, to detect a minimum difference in mean weight change of 1.36kgs (assuming a standard deviation of the change in weight of 4kgs). However, every effort will be made to achieve follow-up rates of >95% for post-partum follow-up, and we will implement a number of strategies to enhance follow-up for this outcome (e.g. home monitoring of weight).

11.3. Analysis Sets

11.3.1. Intention-to-Treat Analysis Set

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all randomized participants.

11.3.2. Safety Analysis Set

The safety analysis set will include all randomized participants who received at least one dose of study medication.

11.4. Demographic and baseline disease characteristics

Demographic and baseline characteristics of the study population will be summarized using graphical displays and descriptive statistics for each treatment group.

11.5. Effectiveness Analysis

Suitable numerical and graphical techniques will be used to compare the primary and secondary responses and the balance in explanatory variables at baseline. The primary analysis will be a two-sample comparison of reduction in the proportion of participants needing insulin between treatment and control arms using an exact test for a binomial response.

We will also conduct a logistic regression analysis, to adjust for differences of baseline co-variates between treatment groups. Several strategies for including explanatory variables will be employed where penalisation for multicollinearity will be achieved using ridge penalties. Following this the most parsimonious subset of predictor variables will be identified using computationally intensive data driven techniques such as the classification trees and the Lasso penalty.

A secondary exploratory analysis will involve a comparison of the time to insulin initiation between the treatment groups, initially using the log-rank test and then the proportional hazards model in order to adjust for patient characteristics as appropriate. Repeated measures ANOVA will be used to evaluate the effect of intervention on secondary outcome of mean change in weight (from baseline to post-partum follow-up).

11.5.1. Primary Effectivness Outcomes

The primary efficacy outcome is a composite of:

- Insulin initiation (Yes/No)
- Fasting glucose value <5.1 mmol/l and ≥5.1 mmol/l

11.5.2. Secondary Effectiveness Outcomes

Secondary efficacy outcomes include:

- Maternal BMI, waist circumference, maternal gestational weight gain (GWG) blood glucose status, insulin resistance status and metabolic syndrome postpartum
- Proportion of infants with morbidities;
- Infant birth weight
- Proportion of maternal morbidities

11.5.3. Health Economic Outcomes

Health economic outcomes include:

- EQ5D-5L
- Quality Adjusted Life Years (QALYs)
- Costs of healthcare associated with the intervention and control arms

11.6. The level of statistical significance

The level of statistical significance will be set at α=0.05 for all analyses i.e. a p-value <0.05 with 95% CI's not containing zero will be considered statistically significant.

11.7. Procedure for accounting for missing, unused and spurious data

An analysis of all missing data will be carried out to identify the likely missing data mechanism (e.g. missing completely at random, missing at random, and missing not at random). A suitable multiple

imputation strategy will then be employed to determine the sensitivity of missing data on the inference gleaned from the final model.

11.8. Health economic analysis

The Health Economic and Policy Analysis (HEPA) research team at NUI Galway have previous experience, within an Irish healthcare context, in the design and conduct of economic evaluation alongside randomised controlled trials. The health economic analysis will consist of trial-based economic evaluation and will incorporate both cost effectiveness analysis and cost utility analysis to compare the alternative treatment strategies: (1) metformin in addition to usual care for GDM (that is, MNT and/or insulin); and (2) usual care for GDM. The economic evaluation will be undertaken in a manner consistent with the guidelines issued by Health Information and Quality Authority (HIQA) (2014) for the evaluation of technologies in Ireland. The basic tasks of the evaluation are to identify, measure, value and compare the costs and outcomes of the alternatives being considered. Evidence collected on resource use and clinical outcome measures alongside the trial will provide the basis for the analysis over the trial follow up period. A healthcare provider perspective will be adopted with respect to costing. This will reflect the healthcare resources consumed in operating both treatment strategies including those relating to health professional time input, diagnostic testing, dietary, exercise and prescription medication interventions (metformin and insulin), consumables and materials, equipment and overheads. Healthcare resource use for both treatment arms will be recorded alongside the trial. Unit costs will be applied to value resource use data and calculate the various costs of care.

As detailed above, significant attention will also be paid to collecting relevant data on health outcomes alongside the trial. For the cost effectiveness analysis, the treatment strategies will be compared on the basis of the effectiveness data for the primary clinical outcome. For the cost utility analysis, effectiveness will be evaluated on the basis of Quality Adjusted Life-Years (QALYs), which is the preferred outcome measure for economic evaluation as it allows for comparison of relative cost effectiveness both within and beyond the clinical area of interest (Drummond et al, 2015). In this case, patient responses to the EQ5D 5L questionnaire (Euroqol Group, 1990) at baseline and follow up will be used to compute QALYs for the two treatment arms. The health economic analysis will employ the standard approach for the comparison of alternative treatment strategies in terms of costs and health outcomes. An incremental analysis will be undertaken to provide information on the marginal costs and effects of the metformin plus standard GDM care intervention relative to the standard GDM care alternative through the calculation of incremental cost effectiveness ratios. The analysis will report the incremental cost effectiveness from a publicly funded health system perspective in line with HIQA guidance (HIQA, 2014). Univariate, multivariate and probabilistic sensitivity analyses will be employed to address uncertainty in the study. Budget impact analysis will be undertaken for metformin in addition to usual care for GDM strategy.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The agreement with the investigator will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients/legal representatives for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data collection, source documents and case report forms (CRF):

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. All data entered on CRFs must be entered legibly. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated.

Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the participant will be referred to by the study participant identification number/code.

Patient identification on the CRF and questionnaires will be through participant initials and their unique trial identifier allocated at the time of enrolment. No names or other identifying details will be recorded on the CRF or in any other format.

13.2. Data reporting

The Data Manager will develop a Data Management Plan (DMP) which will detail all activities relating to the management of the clinical data. All project specific data management documentation will be filed in a Data Management File (DMF). The Data management team will also develop a Clinical Data Management System (CDMS) to store the clinical data. This will be developed following the relevant Data Management SOPs and adhering to ISO guidelines.

Once registered to a trial the patient will be provided with a unique, study-specific participant identifier and this and their initials will be the only way the patient will be identified in the database. Data collected on CRFs will be entered directly from the CRF onto the Clinical Data Management System by data processers at the CRFG. Data entry is by single data entry. A 100% manual verification of all data entered on the database will be performed prior to interim analysis to ensure consistency between the original CRF and the database.

Data queries will be generated for the investigational site as required to clarify data discrepancies or request missing information. The designated site staff will be required to respond to these queries and send them back to the Data Management Team after they have been reviewed and signed by the Principal Investigator/delegated staff member. Any amended information will then be entered in the database. A copy of the signed query form should be retained with the CRF at the investigator site.

14. RETENTION OF ESSENTIAL DOCUMENTS

The investigator will maintain all trial records according to GCP and the applicable regulatory requirements. The trial master file (TMF) will be established at the beginning of the trial by the sponsor. The investigator site files will be maintained at the investigators site. These will contain the essential documents in line with ICH-GCP. On completion of the trial the essential documents will be maintained by the investigator for a period of at least 15 years or as otherwise specified in the regulations.

Following confirmation, the sponsor will notify the investigator when they are no longer required to maintain the files. If the investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the sponsor.

15. REGULATIONS, ETHICS, COMPLIANCE AND GOVERNANCE

This clinical study was designed and shall be implemented and reported in accordance with the principles of ICH GCP, the requirements and standards set out by the EU Directives 2001/20/EC and 2005/28/EC, the applicable regulatory requirements and their updates in Ireland and with the ethical principles laid down in the Declaration of Helsinki.

15.1. Sponsorship

National University of Ireland, Galway (NUIG) is the Sponsor for the trial. The Chief Investigator will take overall responsibility for the conduct of the trial.

15.2. Indemnity

The sponsor maintains clinical trial insurance coverage for this study in accordance with Irish laws and regulations. The State Claims Agency, Clinical Indemnity Scheme, will provide clinical indemnity for any harm caused to patients by the design of the research protocol. Additionally, indemnity to allow for no-fault compensation will be provided for by NUI Galway for Irish sites. The Agreements put in place between the Sponsors and individual participating sites will cover the indemnity provision for negligent harm.

15.3. Finance

The study is funded by the Health Research Board. There is no industry funding provided for this study.

15.4. Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a recognised Research Ethic Committees (REC) for all participating sites before start of the study.
The trial will be conducted in accordance with the EU Directive 2001/20/EC and 2005/28/EC and will adhere to all regulatory requirements or updates as required. A CTA will be obtained from the HPRA before the start of the trial.

15.5. Audits and Inspections

This trial may be subject to external auditing or inspections to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

15.6. Ethical Considerations

The vulnerability of this study group is fully appreciated and every effort will be undertaken to protect their safety and well-being. In line with the applicable regulatory requirements consenting processes will be standardised and a robust SOP for consenting participants will be adhered to.

15.7. Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the appropriate regulatory authority and as per investigator responsibilities outlined in ICH-GCP E6 R2. Changes to the protocol will require competent authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The TSC in collaboration with the Sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations.

Protocol compliance will be monitored by a monitor who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (CRF's, patient consent) are being completed appropriately. Any deviations from the protocol will be reported to a sponsor representative as per the process and timelines communicated.

15.8. Patient Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.9. Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org).

16. AUDITS AND INSPECTIONS

This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

17. ETHICS

17.1. Approvals

Required documents including the protocol, ICF, participant information leaflet, investigational medicinal product dossier, investigators brochure and any other required documents will be submitted to a recognised research ethics committee and the competent authority for written approval.

The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

17.2. Benefits and risks assessment

Participants with a contraindication to the use of metformin will be excluded from the trial (see section 8.2.3.) If such maternal contraindications develop, the study medication will be discontinued. Reduced vitamin B12 levels due to metformin use are not expected in this trial as this has been documented only in patients with long-term metformin use (4-6 years) (Tomkin et al. 1971). In order to reduce the known gastrointestinal side effects of metformin use, the dose will be titrated slowly upwards in 500mg increments up to 2500mg over 10 days.

Potential benefits for trial participants include delayed insulin initiation, reduced dose of insulin required, or insulin not required, hence minimising the risks associated with insulin use on maternal and neonatal outcomes.

17.3. Participant confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's identification number on the CRF and any database. All documents will be stored securely. The study will comply with the General Data Protection Regulation (GDPR) and any applicable data protection updates. Information on GDPR and rights of the participant will be provided to the participant on the ICF.

18. CLINICAL STUDY REPORT AND PUBLICATION POLICY

The results of this study will be disseminated to a wide audience locally nationally and internationally. Initially the results will be shared with the key stakeholders in the Disciplines of Medicine, Obstetrics, and economics and with a wider diabetes audience locally through the recently established Galway Diabetes Research Centre (GDRC). Results will be presented to the regional Diabetes Services Implementation group (DSiG). Nationally outcomes will be discussed with key workers and decision makers in the Health Services Executive (HSE) especially the lead for Quality and Improvement, the lead for Diabetes and the lead for obstetrics. We will communicate outcomes with the national professional body in diabetes, the diabetes subsection of the Irish Endocrine Society, the Institute of Obstetrics and Gynaecology, and the Faculty of Paediatrics.

The results will be presented at national Diabetes, Obstetric, and Health Economics meetings. There will be dissemination in peer reviewed journals in Diabetes Obstetrics and Health Economics. We will aim for journals of high impact factor e.g. Lancet, NEJM, Diabetes Care, Diabetologia and JCEM. Internationally the results will be shared at the American, British and European meetings in Diabetes Obstetrics and Health Economics in particular the ADA EASD and DPSG through poster and podium presentations. We will also work with the Diabetes Federation of Ireland for dissemination using the media of radio television and print to reach participants with prior and current GDM. Dissemination in the Irish Times Medical Supplement will be important to reach a wide audience including patient's professionals and policy makers.

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