Statistical Analysis Plan

Protocol Title: 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)

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Table of Contents

1 REVISION HISTORY 6

2 ABBREVIATIONS AND DEFINITIONS 6

3 PREFACE 6

4 PURPOSE OF SAP 8

5 STUDY OBJECTIVES AND ENDPOINTS 8

5.1 STUDY OBJECTIVES 8

5.1.1 Primary Objective 8

5.1.2 Secondary objectives 8

5.2 STUDY ENDPOINTS 9

5.2.1 Primary endpoint 9

5.2.2 Secondary endpoints 9

5.3 DERIVED VARIABLES 10

6 STUDY METHODS 10

6.1 GENERAL STUDY DESIGN AND PLAN 10

6.2 GENERAL STUDY POPULATION 12

6.3 RANDOMISATION AND BLINDING 13

7 SAMPLE SIZE 13

8 TIMING OF ANALYSES 14

8.1 INTERIM ANALYSES 14

8.2 FINAL ANALYSES 14

9 ANALYSIS POPULATIONS 15

9.1 INTENTION-TO-TREAT ANALYSIS SET 15

9.2 PER-PROTOCOL 15

9.3 SAFETY ANALYSIS SET 15

10 GENERAL ISSUES FOR STATISTICAL ANALYSIS 15

10.1 SOFTWARE USED FOR THE ANALYSIS 15

10.2 METHODS FOR WITHDRAWALS, MISSING DATA, AND OUTLIERS 15

10.3 DATA TRANSFORMATIONS 16

10.4 MULTICENTRE STUDIES 16

10.5 MULTIPLE TESTING 16

10.6 PLANNED SUBGROUPS, INTERACTIONS, AND COVARIATES 16

11 STUDY SUBJECTS 16

11.1 SUBJECT DISPOSITION 16

11.2 PROTOCOL DEVIATIONS 17

11.3 INCLUSION AND EXCLUSION CRITERIA 17

12 DEMOGRAPHIC AND BASELINE VARIABLES 17

12.1 DEMOGRAPHICS 17

12.2 PRIOR AND CONCURRENT MEDICATIONS 17

12.3 BASELINE AND SCREENING CONDITIONS 18

12.4 TREATMENT COMPLIANCE 18

13 EFFICACY ANALYSES 18

13.1 PRIMARY EFFICACY ANALYSIS 18

13.2 SECONDARY EFFICACY ANALYSES 19

13.3 OTHER EFFICACY ANALYSIS 20

14 SAFETY ANALYSES 21

14.1 DRUG EXPOSURE 21

14.2 ADVERSE EVENTS 21

14.3 DEATHS, WITHDRAWAL, SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS 22

14.3.1 Withdrawal due to Adverse Events 22

14.3.2 Deaths *22*

14.3.3 Other AE Assessments *22*

14.4 PREGNANCIES 22

14.5 CLINICAL LABORATORY EVALUATIONS 22

14.6 HAEMODYNAMICS (VITAL SIGNS) 23

14.7 ECGS 23

15 OTHER PLANNED ANALYSIS 23

16 REPORTING CONVENTIONS 23

17 REFERENCES 24

18 LISTING OF TABLES, LISTINGS AND FIGURES 24

1 *Revision History*

Revision	Description
V1	First Release

2 *Abbreviations and Definitions*

AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BMI	Body mass index
CSR	Clinical Study Report
DTSQ	Diabetes Treatment Satisfaction Questionnaire
CRF	Case Report Form
GDM	Gestational Diabetes Mellitus
GWG	Gestational Weight Gain
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein cholesterol
HEPA	Health Economic and Policy Analysis
HIQA	Health information and Quality Authority
ICH	International Conference on Harmonisation
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
ITT	Intention to Treat
LDL	Low-density lipoprotein cholesterol
MNT	Medical Nutritional Therapy
OD	Once daily
OGTT	Oral glucose tolerance test
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
Tg	Triglycerides
QALY	Quality–adjusted life years
WHO	World Health Organisation

3 *Preface*

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the EMERGE (Early MEtformin in Addition to Usual Care in the Reduction of Gestational Diabetes Mellitus Effects) trial. This is a randomised, placebo-controlled

trial to determine the effectiveness of metformin (in addition to the usual care) in reducing the effects of Gestational Diabetes Mellitus (GDM) in pregnant women.

GDM is defined by the World Health Organisation (WHO) as glucose intolerance resulting in hyperglycaemia during pregnancy (ADA 2004). GDM prevalence in Ireland is thought to be 12.4% (O Sullivan 2011). Internationally, GDM prevalence is quoted at 17% with a range of 9-25% (Sacks 2012). Increasing age, previous GDM, obesity, and family history of diabetes are known risk factors.

GDM results from reduced insulin sensitivity and/or reduced insulin production. Metformin increases insulin sensitivity and thus it has the potential as a treatment option for GDM. Metformin is weight neutral and is not associated with hypoglycaemia, two factors that increase its acceptability for pregnancy, and an advantage over insulin. Metformin has been shown to be safe in pregnancy (for mother and baby), when it is introduced after the failure of diet and exercise. However, in many countries (including Ireland), insulin therapy remains the standard of care for the treatment of GDM, in women who have failed to achieve normoglycemia 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 and not just those with elevated Body Mass Index (BMI).

The EMERGE trial will evaluate metformin introduced at the time of GDM diagnosis in women of all BMI categories, to determine whether treating all patients with GDM (rather than just those who fail Medical Nutritional Therapy (MNT) / exercise) results in better outcomes for mothers and babies. The primary outcome is the development of hyperglycemia, represented as the composite of a) initiation of insulin (as this reflects clinically meaningful hyperglycemia) and a venous fasting glucose measurement >5.1mmol/l at weeks 32 and 38 of gestation. Secondary outcome measures include excessive Gestational Weight Gain (GWG), and 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 considerably 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 (at or before 28 weeks gestation) to delivery or termination of the pregnancy (at or before 40 weeks). Metformin will be given in tablets of 500mg. The dose will be titrated over two-weeks and will commence at 500mg per day increasing to a maximum of 2500mg per day. This dosing regimen will minimize 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 women and an on-going trial in Type 2 diabetes in pregnancy (MiTy).

The structure and content of this SAP provides sufficient detail to meet all the requirements in accordance with the International Conference on Harmonisation guidance of Statistical Principles in Clinical Trials (ICH E9). All work planned and

reported for this SAP will follow internationally accepted guidelines. The following documents were reviewed in the preparation of this SAP:

- Clinical Research Protocol for EMERGE (Version 6) – issued 02/05/2019
- Case Report Forms (CRFs).
- ICH E9 and E3

The reader of this SAP is encouraged also to read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

4 *Purpose of SAP*

The purpose of this SAP is to detail the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for the EMERGE protocol. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned analyses not specified in this SAP, will be identified as such in the respective CSR.

5 *Study Objectives and Endpoints*

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 women with Gestational Diabetes Mellitus.

5.1 Study objectives

5.1.1 Primary Objective

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

5.1.2 Secondary objectives

Additional secondary objectives of this study are to determine:

1. if metformin delays the initiation of insulin
2. if metformin reduces the insulin dose required (and dose/kg/week of gestation)

3. if metformin impacts maternal body weight, BMI, waist circumference, blood glucose status, insulin resistance status and metabolic syndrome postpartum;
4. if metformin reduces the proportion of infants with morbidities;
5. if metformin in addition to usual care reduces infant birth weight when compared to usual care alone;
6. if metformin reduces the proportion of maternal morbidities when compared to usual care alone;
7. if metformin in addition to usual care reduces excessive maternal GWG;
8. if women consider metformin a more acceptable treatment than insulin;
9. the cost, cost effectiveness, and budget impact of metformin in addition to usual care for GDM;

5.2 Study endpoints

5.2.1 Primary endpoint

A composite primary outcome of insulin initiation or fasting hyperglicemia (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. The introduction of insulin reflects clinically meaningful hyperglycaemia, and is measured at any time during clinical trial. In addition, a standardised fasting glucose will be completed at gestational weeks 32 and 38, to capture additional participants who have fasting hyperglycaemia but have not had insulin introduced during the clinical trial.

5.2.2 Secondary endpoints

The secondary outcomes:

1. Time to insulin initiation and insulin dose required
2. Maternal morbidity at delivery (hypertensive disorders, antepartum and postpartum haemorrhage)
3. Mode of delivery
4. Gestational age at delivery
5. Postpartum glucose status, insulin resistance, and metabolic syndrome

6. Postpartum BMI, gestational weight gain, and waist circumference
7. Infant birth weight
8. Infant size (large/small/appropriate for gestational age)
9. Neonatal height and head circumference at delivery
10. Neonatal morbidities (Need for neonatal care unit, respiratory distress, jaundice, congenital anomalies, Apgar score)
11. Neonatal hypoglycaemia (defined as plasma glucose <2.6mmol/L on one or more occasions starting 30-60 minutes after birth)
12. Cost effectiveness and budget impact of metformin treatment in addition to usual care
13. Treatment acceptability (Diabetes Treatment Satisfaction Questionnaire DTSQ and Rowan questionnaires)
14. Glycemic control, measured by participant glucocometer.

Quality of Life determined by EQ5D-5L questionnaire

5.3 Derived Variables

Sex-specific birth weight-for-gestational age centiles will be calculated according to Norris et al (2018) in order to determine the proportions of large/small/appropriate for gestational age babies.

6 *Study Methods*

6.1 General Study design and Plan

The EMERGE study is a phase III, parallel, randomised double-blind, placebo-controlled, trial of metformin (in addition to usual care) versus usual care in 550 women with Gestational Diabetes Mellitus (GDM) across 2 sites in Ireland, followed until 12 weeks post-partum (+/- 4 weeks).

It will comprise 3 steps; 1) screening, 2) treatment, and 3) follow up. Eligible women will be randomised to one of two groups; treatment group or placebo group.

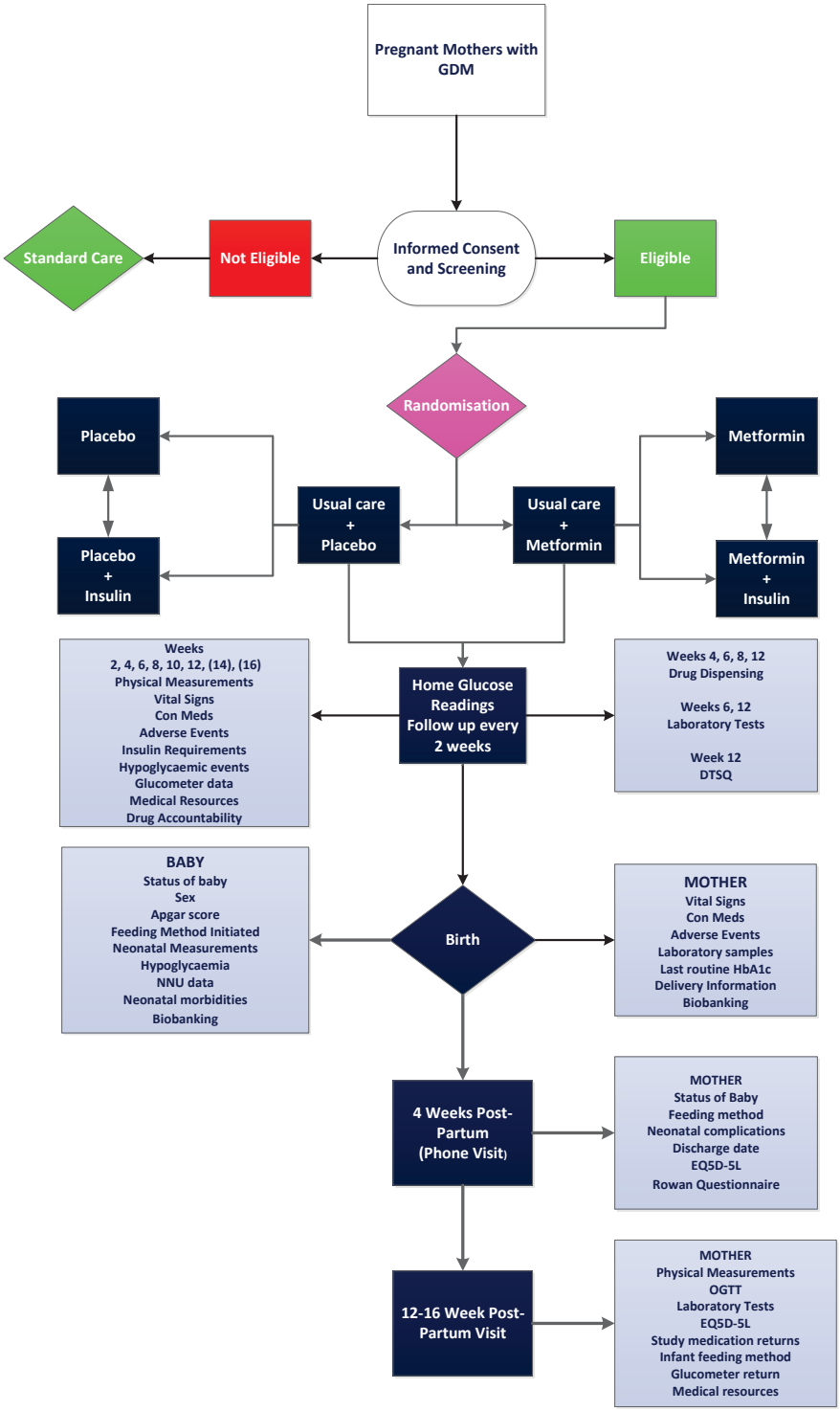
Women randomised to the metformin group will receive metformin 500mg Once Daily (OD), with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg metformin daily (5 tablets) or maximum tolerated dose, in addition to usual care (exercise and MNT), and taken until delivery.

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 (+/- 7days) and 12 weeks (+/- 4 weeks) post-partum for additional maternal and neonatal outcomes.

The control and metformin groups will receive usual care, which consists of medical nutritional therapy (MNT) and information on exercise provided by the Diabetes team. The Diabetes team or trained delegate will instruct women on using a glucometer, and the women will perform 7-point glucose testing before and 1 hour after meals and before bed. Women will be supported by telephone contact from the Diabetes team or trained delegate weekly throughout gestation and attend at 2-4 weekly intervals at an antenatal/diabetes clinic. Usual care is outlined in more detail in section 9.1.1 of the protocol.



6.2 General Study Population

The population for the trial is pregnant women between the ages of 18-50 years, with a diagnosis of GDM between 24-28 weeks gestation (+ 6 days).

Women 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 women must be resident and intend to deliver within the selected trial sites. They must also fulfil all of the Inclusion criteria and none of the Exclusion criteria of the EMERGE Protocol. The geographical area and study population include women from urban and rural locations and women in public and private health care.

6.3 Randomisation and Blinding

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; allowing equal numbers of women with a BMI ≤/>30 and a history of GDM to be distributed between groups.

A web-based randomisation system will 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

This trial will be conducted in a double-blind fashion with a placebo control identical to metformin tablets to avoid bias in assessing 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.

7 *Sample Size*

Our sample size for testing this hypothesis is based on the following; a) 35% of women 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 the proportion of women requiring insulin in the experimental (metformin) group (40% to 28% absolute reduction; in the MiG trial only 40% of women 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 13,000 deliveries annually in both 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%. In a second study examining uptake rates in primary v secondary care, the screening uptake rate was 88% for screening in secondary care. With universal screening, we expect to pick up 1,560 pregnancies with GDM annually. There is a greater concern with loss to follow-up for the secondary outcome of baseline to post-partum weight change, 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 several strategies to enhance follow-up for this outcome (e.g. home monitoring of weight).

8 *Timing of analyses*

8.1 Interim analyses

There were no planned interim analyses for this study. However, an analysis was carried before full accrual was completed to reassess some of the assumptions used in the sample size calculations. As a result of this analysis it was observed that the overall proportion of women taking insulin in the study was larger than the one estimated in the original sample size calculations. Based on this information, it was established that a reduced sample of 535 participants would achieve the same 80% power to answer the primary research question. Therefore, the total sample size will be 535.

8.2 Final analyses

An analysis of the primary outcome of insulin initiation or hyperglycaemia and the secondary perinatal (maternal and infant) outcomes will be performed after the last participant has given birth but before the database lock, to initiate dissemination of key results. This analysis, which requires the randomization codes, will be carried out by an independent statistician, to maintain the blind among the relevant members of the statistics and data management team and other potential outcomes assessors. All other analyses identified in this SAP will be performed after the last participant has completed the study. Before carrying out the final analyses, the data management team are responsible for the database cleaning process to ensure the integrity of the analyses. No database will be locked until the SAP has been approved. Key statistics and study results will be made available following database lock and before completion of the final CSR.

Any post-hoc exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

9 *Analysis populations*

9.1 Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all randomised participants regardless of what study medication they received. The primary and secondary analyses will be performed on an ITT basis.

9.2 Per-protocol

This set will exclude the subset of participants in the Intention-to-treat analysis set who are non-compliant with the protocol, including errors in treatment assignment, violation of inclusion/exclusion criteria, major protocol deviations and poor adherence with study medication (defined as less than 80% overall adherence). A per-protocol analysis will supplement the ITT analysis as a secondary analysis.

9.3 Safety Analysis Set

The safety analysis set will include all randomised participants who received at least one dose of study medication. This set will be considered for the analysis of all the safety outcomes.

10 *General issues for Statistical Analysis*

10.1 Software used for the analysis

All primary and secondary statistical analyses will be validated by an independent statistician, or using independent software (R, SAS, SPSS, Minitab or Stata). All of the code generated will be kept by both the study statistician and the independent statistician.

10.2 Methods for Withdrawals, Missing Data, and Outliers

An analysis of missing data for secondary analyses 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 be employed (if deemed appropriate) to determine the sensitivity of missing data on the inference gleaned from the final model.

10.3 Data Transformations

Due to the nature of the primary and secondary endpoints analysis, it is not expected that any of the data will have to be transformed.

10.4 Multicentre Studies

This is a two-center clinical study, with standardization of participant enrolment, data entry and adverse event reporting. Investigational sites will follow the requirements of a common protocol, data collection procedures and forms.

Given the nature of the intervention, women from the two centers are considered exchangeable. Demographic and baseline data will be presented by each centre in the CSR to explore differences in patient characteristics between the centers.

10.5 Multiple Testing

Since the primary analysis for performance is based only on one endpoint (i.e. the reduction of the effects of Gestational Diabetes Mellitus in pregnant women), no multiple comparisons will be necessary.

10.6 Planned Subgroups, Interactions, and Covariates

Variation of treatment effects for primary outcome induced by baseline/demographic variables will be explored using interaction analysis. Relevant variables will be race (Caucasian vs non-caucasian), age (<30 years vs >=30 years), previous GDM (Yes/No) and whether this is the participant's first pregnancy.

11 *Study Subjects*

11.1 Subject Disposition

Different variables from the CRF will be considered to determine the number of patients who reached the various stages of the study. The following counts will be reported by study group:

- Number of participants randomised
- Number of randomised participants who received study medication at least once
- Number of participants who completed the study medication.
- Number of participants who had the delivery.
- Number of participants who completed the post-delivery follow-up visit.
- Number of participants who withdrew the study before completion.

11.2 Protocol Deviations

The investigators will conduct the study in compliance with the protocol. Protocol compliance will be monitored by a monitor who will undertake site visits to ensure that the trial protocol is adhered and that necessary paperwork (CRF's, patient consent) is being completed appropriately. Any deviations from the protocol will be reported to a sponsor representative per the process and timelines communicated and reported in the final CSR report. A listing of major protocol violations (significant occurrences which may adversely affect the rights, safety or wellbeing of the participants and/or the scientific value of the trial) will be provided.

11.3 Inclusion and Exclusion Criteria

A listing will be generated showing the number and percentage of participants that fulfilled the inclusion and exclusion criteria listed in sections 8.2.2 and 8.2.3 of the Protocol.

12 *Demographic and Baseline variables*

12.1 Demographics

Age and race (Caucasian vs non-Caucasian) will be considered demographic variables. Mean, standard deviation, median, max and min will be reported for age, and counts and percentages will be reported for race.

12.2 Prior and Concurrent medications

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 of the Protocol. 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

A listing of the prior and concurrent medications will be provided as an appendix in the CSR.

12.3 Baseline and Screening Conditions

Social history (smoking and alcohol), previous pregnancies, current pregnancy, vital signs, glucose tolerance test results, history of gastrointestinal events, lab test results, standard care (dietary and physical exercise advice) received, socioeconomic status and EQ5D-5L questionnaire responses will be summarised. Numerical values will be summarised using the mean, standard deviation, median, minimum and maximum, while categorical values will be summarized using counts and percentages.

A listing of all Diseases/Conditions will be provided for the analysis of the medical history. If possible, the most common conditions will be summarized using counts and percentages.

12.4 Treatment Compliance

The date, pack number and number of tablets dispensed is recorded at screening and drug accountability is documented at Weeks 2, 4, 6, 8, 10 and 12. Drug dispensation and return (along with expected consumption and adherence) are recorded at weeks 4, 8, 12, with the final date and quantity of drugs returned recorded at 12 weeks post-partum.

Non-compliance is defined as less than 80% drug adherence of the participant's maximum tolerated dose. These data will be shown in a listing and summary table (per visit and overall).

13 *Efficacy Analyses*

13.1 Primary Efficacy Analysis

The primary efficacy outcome is a composite of:

- Insulin initiation (Yes/No) or
- Fasting hyperglicemia ≥ 5.1 mmol/l at week 32 or 38.

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 women needing insulin between treatment and control arms. A logistic regression model will be used to adjust for the stratifying variables, BMI and past history of GDM, along with other patient characteristics as appropriate.

A small number of participants (24) were randomised in more than one occasion for this study, each corresponding to a new pregnancy (49 in total). Note that the primary analysis described above will treat these duplicated pregnancies as independent. Although it is not expected that this issue will be influential in the overall conclusions derived from the analysis of the primary outcome, a sensitivity analysis will be performed considering only the first pregnancy per woman, among the 24 women who entered the study more than once.

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. Longitudinal data analyses based on linear mixed models will be used to evaluate the effect of intervention on secondary outcome of mean change in weight (from baseline to postpartum follow-up).

13.2 Secondary Efficacy Analyses

Secondary efficacy outcomes include:

- Maternal morbidity at delivery (hypertensive disorders, antepartum and postpartum haemorrhage)
- Mode and time of delivery
- Maternal post-partum BMI, waist circumference, maternal gestational weight gain (GWG) blood glucose status, insulin resistance status and metabolic syndrome postpartum
- Proportion of maternal morbidities
- Infant birth weight
- Infant size (large/small/appropriate for gestational age)
- Neonatal height and head circumference at delivery
- Neonatal morbidities (Need for neonatal care unit, respiratory distress, jaundice, congenital anomalies, Apgar score)
- Neonatal hypoglycaemia (defined as plasma glucose <2.6mmol/L on one or more occasions starting 30-60 minutes after birth)

- Proportion of infants with morbidities
- Treatment acceptability (Diabetes Treatment Satisfaction Questionnaire DTSQ and Rowan questionnaires)
- Quality of Life determined by EQ5D-5L questionnaire

Exploratory analyses based on generalised linear models will be used to estimate the treatment effect for each of the secondary outcomes while adjusting for the stratification variables and relevant baseline characteristics.

13.3 Other Efficacy Analysis

Health economic outcomes include:

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

The Health Economic and Policy Analysis (HEPA) research team at the University of Galway have previous experience in the design and conduct of economic evaluation alongside randomised controlled trials within an Irish healthcare context. The health economic analysis will consist of trial-based economic evaluation. It 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 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 for 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 be paid to collecting relevant data on health outcomes alongside the trial. For the cost effectiveness analysis, the treatment strategies will be compared based on the effectiveness data for the primary clinical outcome. For the cost utility analysis, effectiveness will be evaluated based on 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

comparing 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 calculating 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.

14 *Safety Analyses*

14.1 Drug Exposure

The analysis of drug exposure will include summaries of the total dose received by treatment arm and visit (mean, Standard Deviation (SD), median, min and max). An exploratory analysis of how drug exposure may be related to changes in safety assessments will also be performed.

14.2 Adverse Events

Some 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 (see Appendix for the list of exempted AEs). However, exempted AEs were recorded prior to protocol version 6.0 (dated 02 May 2019) and before the implementation of exemptions in safety reporting. The exempted AEs will be excluded in the analyses below.

The analysis of adverse events will include:

- A summary (by treatment arm) of the number of Adverse Events (AEs) reported (counts), and the number of participants experiencing any adverse event (counts and percentages) will be presented. Treatment arms will be compared using the chi-squared test.

- Summaries of each adverse event (coded as Preferred Term and System Organ Class) by treatment arm will be provided. Summaries will include number of events, number of participants (counts and percentages), severity and highest grade. Comparisons between treatment arms using chi-squared or Fisher's exact test (where enough information is available) will be presented. Note that the highest grade will be considered if a participant has different grades for the same adverse event.

- Summaries of patients with AEs definitely, probably or possibly related to metformin, Insulin or interaction between metformin and Insulin, by preferred term and treatment arm will be given.

Separate table summaries will be presented for AEs occurring on the mother and for AEs occurring in the baby.

14.3 Deaths, withdrawal, Serious Adverse Events and other Significant Adverse Events

Serious adverse events (SAEs) will be analysed in the same fashion as AEs. Withdrawals will be summarised as the number and percentage of patients who were withdrawn from the study by treatment arm.

14.3.1 Withdrawal due to Adverse Events

Withdrawals due to adverse events will be summarised as the number and percentage of patients who were withdrawn by treatment arm.

14.3.2 Deaths

In the unlikely case that deaths occur they will be summarised as the number and percentage of participants (mother or baby) who died within the study period by treatment arm.

14.3.3 Other AE Assessments

No other assessments or analyses are planned.

14.4 Pregnancies

Not applicable.

14.5 Clinical Laboratory Evaluations

Lab tests will 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).

The following laboratory assessments will be analysed locally:

At 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).

At 32 weeks gestation: HbA1c, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, Tg, urea, creatinine, ALT, and AST.

At 38 weeks gestation: HbA1c, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, Tg, urea, creatinine, ALT, and AST.

At 12 weeks post-partum: fasting glucose, 2h glucose, fasting insulin, fasting c-peptide, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, Tg.

Descriptive summaries (mean, SD, median, minimum, and maximum) of changes from baseline will be presented for clinical laboratory values by treatment group and visit for the Safety Population.

The number of participants (counts and percentages) with clinically significant laboratory abnormalities at each visit will be highlighted for each lab test, for the Safety Population by treatment group.

14.6 Haemodynamics (Vital Signs)

The analysis of Vital signs will include the measurements specified in the corresponding CRF form. These measurements are the heart rate, blood pressure, weight, height and BMI. For each of these measurements, the analysis will include:

- Summaries of the results by visit (mean, SD, median, min and max) and by treatment arm.
- Summaries of the absolute changes from baseline by visit (mean, SD, median, min and max) and by treatment arm.

14.7 ECGs

Not applicable.

15 *Other Planned Analysis*

No other analyses planned.

16 *Reporting conventions*

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as the median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

17 *References*

- WHO. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization guideline. Diabetes Res Clin Pract 2014;103:341-63.
- ADA. American Diabetes Association Position statement: Gestational Diabetes Mellitus. Diabetes Care. 2004;27(Suppl 1):S88-S90.
- O Sullivan EP, Avalos G, O Reilly M, Dennedy C, Dunne F. ATLANTIC DIP: The prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. Diabetologia 2011; 54(7):1670- 1675.
- Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJ, Persson B, Trimble ER; HAPO Study Cooperative Research Group Frequency of gestational diabetes mellitus at collaborating centres based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care. 2012 Mar;35(3):526-8. doi: 10.2337/dc11-1641.
- Norris T, Seaton SE, Manktelow BN, Baker PN, Kurinczuk JJ, Field D, Draper ES, Smith LK. Updated birth weight centiles for England and Wales. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2018 Nov 1;103(6):F577-82.

18 *Listing of Tables, Listings and Figures*

Tables, listings and figures will be used to summarise the results of the analyses described in this SAP. Tables, listings and figures in the CSR will clearly display the title, endpoint(s) population, summary statistics calculated, type of analysis used, time points and any relevant footnotes.