A Feasibility study looking at the use of Glibenclamide and metformin versus standard care in gestational diabetes
# Study Protocol

**Glibenclamide and Metformin vs. Insulin and Metformin in the treatment of Gestational Diabetes Feasibility Study**

## GRACES TRAIL

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<td>Funder</td>
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- GRACES Trial
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PROTOCOL APPROVAL

Glibenclamide and Metformin in Pregnancy Feasibility Study
EudraCT number 2013-004706-25

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**LIST OF ABBREVIATIONS**

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<td>ACCORD</td>
<td>Academic and Clinical Central Office for Research &amp; Development - Joint office for University of Edinburgh and NHS Lothian</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CTIMP</td>
<td>Clinical Trial Investigational Medicinal Product</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DSN</td>
<td>Diabetes Specialist Nurse</td>
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<td>GDM</td>
<td>Gestational Diabetes Mellitus</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>ISF</td>
<td>Investigator Site File</td>
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<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
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<tr>
<td>NIMP</td>
<td>Non Investigational Medicinal Product</td>
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<tr>
<td>NNU</td>
<td>Neonatal Unit</td>
</tr>
<tr>
<td>NPEU CTU</td>
<td>National Perinatal Epidemiology Unit Clinical Trials Unit</td>
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<tr>
<td>PPH</td>
<td>Postpartum haemorrhage</td>
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<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
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<tr>
<td>RIE</td>
<td>Royal Infirmary of Edinburgh</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>TTN</td>
<td>Transient Tachypnea of the newborn</td>
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<tr>
<td>WGH</td>
<td>Western General Hospital Edinburgh</td>
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STUDY FLOW CHART

Assessed for eligibility (n= )

Inclusion criteria
- Pregnant women diagnosed with gestational diabetes mellitus (GDM) between 16th and 36th weeks of gestation who are no longer responding to metformin monotherapy

Exclusion criteria
- Aged <16 or >50 years
- Requiring insulin <16 weeks of gestation
- Not taking ≥500 mg metformin daily
- Suspected Type 1 diabetes mellitus presenting in pregnancy
- Allergy to glibenclamide or insulin or any of their excipients
- Any contraindications to sulfonylurea therapy
- Inability to give written informed consent

Excluded (n= )
- Not meeting inclusion criteria (n= )
- Declined to participate (n= )
- Other reason (n= )

Randomised (n= )

- Web-based randomisation (1:1 ratio) hosted by NPEU Clinical Trials Unit

Intervention
- Glibenclamide therapy up to 20 mg daily in addition to maximum tolerated dose of metformin

Standard care
- Insulin therapy in dose decided by clinician in addition to maximum tolerated dose of metformin

OR

Data collection
- Baseline demographics and maternal and neonatal well-being at clinic visits and in the immediate postnatal period

Primary outcome
- Number and throughput of women who agree to be randomised

Other key feasibility outcomes
- Uptake rate – proportion of eligible women who agree to be randomised
- Retention – proportion of women randomised who remain in the study to provide outcomes
- Adherence – proportion of clinicians who adhere to the treatment regimen(s) and the protocol per se
- Safety – number of hypoglycaemic episodes needing treatment, any other adverse events and SUSARs

Secondary outcomes
- Glycaemic control on a range of endpoints. (Note: all biochemical measures of maternal glycaemic control will be recorded from regular downloads from participant’s own glucose meter)
- Participant satisfaction with allocated treatment
- Clinical outcomes including maternal and fetal neonatal outcomes
SUMMARY

An open label randomised external feasibility study comparing the use of glibenclamide and metformin with standard care in women with gestational diabetes mellitus (GDM) who are no longer responding to metformin monotherapy.

Both metformin and glibenclamide are useful in maintaining normoglycaemia in women with GDM, and current data from large RCTs and systematic reviews suggests each is as safe as insulin. Neither agent is sufficient to maintain normoglycaemia in all women with GDM – supplemental insulin is required in a proportion of women with GDM treated with either agent. In non-pregnant individuals, the metformin and glibenclamide given together are more effective than either agent given alone, with no evidence of an increase in serious adverse events including severe hypoglycaemia. The aim of this open label feasibility study is to determine recruitment rates to a randomised trial of glibenclamide compared with insulin (both in addition to maximum tolerated metformin) for the treatment of GDM.

Women with GDM in NHS Lothian and Greater Glasgow who are no longer responding to monotherapy with metformin will be recruited and randomised to either receive glibenclamide (test arm) or standard care with insulin, both in addition to their maximum tolerated dose of metformin. Participants will be recruited from women who attend diabetic/metabolic antenatal clinics in NHS Lothian and NHS Greater Glasgow and Clyde.

This is a feasibility study in preparation for a large UK multicentre randomised trial to test the hypothesis that the addition of glibenclamide to metformin (combination therapy) could reduce the number of pregnant women with gestational diabetes mellitus requiring insulin, without compromising glycaemic control or other clinical outcomes. We hypothesise that combination therapy with metformin and glibenclamide is likely to be preferable to metformin and insulin in terms of acceptability and cost effectiveness.
1 INTRODUCTION

1.1 BACKGROUND

Gestational Diabetes Mellitus (GDM) can be defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1].

The criteria for diagnosing GDM have historically been controversial. A multinational study looking at Hyperglycaemia and Pregnancy Outcome (HAPO) [2] looked at 23,000 women and identified the relationship between maternal glucose tolerance and neonatal outcomes. On the basis of this report the International Association of Diabetes and Pregnancy Study Group (IADPSG) published a consensus report [3] in 2010 highlighting the need for diagnosis and screening of diabetes in pregnancy; this was further supported by evidence from several trials published in 2008 [4] and 2009 [5].

The WHO and IADPSG have published different diagnostic criteria for the 75 g oral glucose tolerance test (OGTT); SIGN 116 [6] guideline recommends using the IADPSG criteria:

<table>
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<th>Blood glucose</th>
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<tr>
<td>Fasting</td>
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<tr>
<td>One hour after OGTT</td>
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<tr>
<td>Two hours after OGTT</td>
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GDM affects 3–10% of pregnancies [7], with a rising incidence in line with rising levels of obesity. There are several identifiable risk factors for GDM, a summary is listed below:

<table>
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<td>BMI &gt;30 kg/m²</td>
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<tr>
<td>Previous macrosomic baby weighing ≥4.5 kg</td>
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<tr>
<td>Previous GDM</td>
</tr>
<tr>
<td>Family origin with high prevalence of diabetes:</td>
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<tr>
<td>S. Asian (especially India, Pakistan or Bangladesh)</td>
</tr>
<tr>
<td>Black Caribbean</td>
</tr>
<tr>
<td>Middle Eastern (especially Saudi Arabia, UAE, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt)</td>
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These pregnancies are at risk of a number of maternal complications and adverse fetal outcomes including macrosomia, shoulder dystocia, stillbirth and neonatal
hypoglycaemia [9]. It has been demonstrated that with intervention, with the intent of achieving euglycaemia, there is a 67% lower risk of serious perinatal outcomes [10].

Current treatment modalities for GDM begin with modified diet and then progress onto medication in about 50% of cases. Traditionally, insulin was used as first-line therapy, but in the last decade certain oral anti-diabetes agents have increasingly been used as a first-line option.

In non-pregnant people with Type 2 diabetes there are several classes of oral anti-diabetes drugs available, of which two are of interest for this study.

- Glibenclamide is a second-generation oral sulfonylurea that increases insulin secretion. It is commonly used in the USA and is well tolerated.
- Metformin is a biguanide drug and has diverse mechanisms of action including a reduction in hepatic gluconeogenesis, increasing insulin sensitivity and insulin-mediated glucose uptake in peripheral tissue.

Langer et al [11] demonstrated in 2000 the safe use of glibenclamide compared to insulin in women with GDM, with similar outcomes in both treatment groups. Rowan et al [4] compared the use of metformin with insulin in pregnancy and found no difference in perinatal complications between the two groups. Following on from these two trials there have been several others comparing these agents individually with insulin. Both oral agents have become recognised forms of treatment of GDM, and NICE currently recommends treatment with either of these medications, leaving the choice up to the individual unit. In practice, metformin is widely used in the UK with glibenclamide the treatment of choice in the USA. If a woman does not achieve euglycaemia on single oral agent therapy the current management is to introduce insulin as second-line therapy. Rowan et al showed 46% of women starting on either metformin or glibenclamide will need additional insulin therapy during their pregnancy. Surprisingly, there has been no evaluation of the combination of glibenclamide and metformin, although in non-pregnant patients with Type 2 diabetes combined glibenclamide-metformin treatment is widely used as a strategy for avoiding or delaying commencement of insulin therapy.

1.2 RATIONALE FOR STUDY

With the rising incidence of GDM, the ability to manage the condition in a way that is most acceptable to the patient and also the most cost-effective develops greater significance.
Poor diabetes control in pregnancy has been shown to be associated with worse pregnancy outcomes with an increase in rates of maternal and perinatal complications although the risk of perinatal mortality is not increased [12].

Due to these increased risks, the importance of tight glycaemic control during pregnancy is strongly advocated. In fact, there is evidence from the HAPO trial that there is a linear relationship between hyperglycaemia and birthweight; even at glucose levels not normally considered abnormal for pregnancy.

Two randomised controlled trials (Langer and Rowan) have shown the safety and benefit of using metformin or glibenclamide with similar outcomes in GDM. Current standard practice involves diet advice, single-agent oral hypoglycaemic if necessary and if the patient still fails to achieve good glycaemic control then they are commenced on insulin therapy. The use of combination metformin and glibenclamide treatment is standard practice in Type 2 DM.

In terms of pharmacokinetics, metformin and glibenclamide act through different and potentially synergistic mechanisms to lower blood glucose. DeFronzo et al [13] showed in the non-pregnant population that a combination of the two anti-diabetes agents was more efficient at lowering blood glucose than either of the individual agents, although risks of hypoglycaemia may also be greater. Marre et al [14] examined the safety of combined therapy in patients who are no longer responding to monotherapy alone and showed the rates of hypoglycaemia in patients on dual combined therapy varied between 11–14% depending on dose, compared to 1–8% in the monotherapy groups. However, there was no increase in episodes of severe hypoglycaemia between the groups.

This feasibility trial will evaluate the use of dual oral anti-diabetes agents in GDM. Approximately 50% of GDM women on metformin in NHS Lothian need to proceed to insulin therapy during their pregnancy, causing not only inconvenience and anxiety for these women, but also discomfort of insulin injections, and costs associated with monitoring of insulin therapy.

The primary aim of this feasibility study is to determine recruitment rates to a randomised trial of glibenclamide compared with insulin (both in addition to maximum tolerated metformin) for the treatment of gestational diabetes mellitus. Secondary aims will be to compare glycaemic control in the two groups, evaluate acceptability and to collect information on a range of clinical outcomes to inform the design of a large definitive randomised trial.
2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine the number of women who are eligible who agree to be randomised to help inform upon the feasibility of a future, larger multicentre RCT.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary endpoint is the number (and corresponding throughput) of women who agree to be randomised.

Other key feasibility metrics

- Uptake rate — proportion of eligible women who agree to be randomised (clearly correlated to primary outcome but key to planning larger trial)
- Retention — proportion of participants randomised who remain in the study to provide outcomes
- Adherence — proportion of clinicians who adhere to the treatment regimen(s) and the protocol per se
- Safety — number of hypoglycaemic episodes needing treatment, any other adverse events and SUSARs

2.2.2 Secondary Endpoints

2.2.2.1 Glycaemic control

(Note: all biochemical measures of maternal glycaemic control will be recorded from regular downloads from the participant’s own glucose meter)

- Mean waking and post prandial blood glucose from randomisation to delivery
- Number and percentage of excursions in blood glucose below 3.5 mmol/l
- Number and percentage of excursions in blood glucose above or equal to 7.0 mmol/l at post-prandial test and above or equal to 5.5 mmol/l at fasting test
- Proportion of participants in the glibenclamide group who need insulin to maintain normoglycaemia
- Participant satisfaction with allocated treatment assessed by visual analogue scale
2.2.2.2 Clinical outcomes

- Change in maternal weight between booking, randomisation and 36 weeks (±1 week)
- Mode and gestation of delivery
- Delivery outcome (live birth/still birth/neonatal death/miscarriage)
- Birthweight and birthweight centile (adjusted for sex and gestation at birth)
- Incidence of neonatal hypoglycaemia (defined as any of the following: blood glucose <2.6 mmol/l) in first 2–4 hours of age, admission to neonatal unit for hypoglycaemia or treated with intravenous glucose or any other drug to increase blood glucose). NB if blood glucose is checked out with this 2-4hour timeframe, it will still be collected with the age (in hours) noted for when it was collected.

2.2.2.3 Other components of the primary outcome as in the MIG study including

- Delivery complications (shoulder dystocia, PPH, retained placenta)
- Apgar less than 7 at 5 minutes of age
- Neonatal complications (safety data) including
  - TTN
  - respiratory distress syndrome (need for at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during the first 24 hours after delivery)
  - hyaline membrane disease
  - jaundice
  - need for phototherapy
  - polycythaemia
- Birth trauma (injury to the baby at delivery, defined as mild if bruises or abrasions were present at birth but resolved before 6 weeks post-partum; or moderate or serious for other injuries including fractures, Erb’s palsy and brachial plexus injuries). This would be recorded as an AE

3 STUDY DESIGN

This initial feasibility study will be an open-label randomised-controlled trial aiming to recruit around 22 participants in each arm of the study (see flowchart).

Recruitment will take place over a 12 to 18 month time period, beginning in 2014. Participants will be recruited from the diabetes antenatal clinics within NHS Lothian and NHS
Greater Glasgow and Clyde. Participants will be followed up throughout their pregnancy (treatment phase) until their discharge following their delivery visit. If the participant and or their baby is discharged prior to being seen by a member of the research team then follow-up data will be collected from their notes and/or their baby’s notes up until the point of discharge.

3.1 INTERVENTION

The intervention will be glibenclamide therapy up to 20 mg daily in divided doses.

3.2 COMPARATOR

The comparator is insulin therapy (standard care), in a dose decided by the clinician. In our setting this is normally novorapid, insulatard, humalog or humulin I.

3.3 OTHER MEDICATIONS

Maximum tolerated metformin will be given to all women in the study. The standard care drugs (NIMPs) will be supplied by local pharmacies and the study intervention (IMP) provided by hospital pharmacies within the individual sites involved, depending on which antenatal clinic the patient attends. There will be over-labelling of glibenclamide but with the drug name and dose identifiable as this is an unblinded trial.

Blood glucose levels and episodes of hypoglycaemia will be monitored by the trial steering committee, who may consider early closure of the study if there are significant safety considerations.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Approximately forty-four women will be recruited in total, with between twenty and twenty-five being randomised into each arm of the study (1:1 allocation ratio). Participants will be recruited from the population of pregnant women with gestational diabetes on metformin therapy in NHS Lothian and NHS Greater Glasgow and Clyde. Recruitment will take place over twelve to eighteen months commencing 2014.

4.2 INCLUSION CRITERIA

Pregnant women in NHS Lothian and NHS Greater Glasgow and Clyde diagnosed with gestational diabetes mellitus between 16+0 and 36+0 weeks of gestation who attend either the
diabetes or metabolic antenatal clinics, and who are no longer achieving “adequate glycaemic control” on maximum tolerated dose metformin or 2 g metformin daily.

Inadequate glycaemic control is defined according to the SIGN 116 guideline as outlined below:

Table 3
More than two readings over a fortnight of:

<table>
<thead>
<tr>
<th></th>
<th>Blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>≥5.5 mmol/L</td>
</tr>
<tr>
<td>At ≤35 weeks of gestation 2 hour post prandial</td>
<td>≥7 mmol/L</td>
</tr>
<tr>
<td>At &gt;35 weeks of gestation 2 hour post prandial</td>
<td>≥8 mmol/L</td>
</tr>
<tr>
<td>Or a post prandial value at any time</td>
<td>≥9 mmol/L</td>
</tr>
</tbody>
</table>

4.3 EXCLUSION CRITERIA

- Women aged <16 or >50 years
- Pregnant women requiring insulin prior to 16 weeks of gestation
- Pregnant women <500 mg metformin daily
- Pregnant women with suspected Type 1 diabetes mellitus presenting in pregnancy
- Women with allergies to either glibenclamide or insulin or any of their excipients
- Women with any contraindications to sulfonylurea therapy
- Women unable to give written informed consent

4.4 CO-ENROLMENT

Participants who are enrolled in trials comprising of questionnaires/observation will be eligible for recruitment. However, any participants involved in any other CTIMP will not be eligible for recruitment. All the prospective participants will be questioned about any other trials they are involved in and this will be clearly recorded in their eCRF.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified at the antenatal clinics involved in the trial either when they are diagnosed with gestational diabetes or commenced on metformin therapy. During the initial diagnosis consultation, treatment options will be discussed including treatments in the event that monotherapy does not achieve adequate control. At this time they will be given a flyer about the study by their clinical care team. If they commence metformin treatment they will
be approached by a member of the research team with verbal and written information about the study. Women will not be formally recruited at this time; the purpose is to provide information and allow time for consideration. In the event that women no longer respond to metformin monotherapy, they will be approached for consent at the time that the need for additional therapy is identified.

5.2 CONSENTING PARTICIPANTS

As outlined above, participants will have been given both verbal and written information about the trial prior to being approached for recruitment and consenting. If they are deemed to no longer be responding to monotherapy by their clinician and are between 16\textsuperscript{th} and 36\textsuperscript{th} weeks of gestation then they will be offered the opportunity to participate in the study by a delegated research team member. If they agree to trial participation informed consent will be obtained, ensuring that the woman is aware that her participation or non-participation will not affect her medical care.

5.3 SCREENING FOR ELIGIBILITY

All women with GDM attending the selected sites outlined above who fail monotherapy and do not meet any of the exclusion criteria will be considered to be eligible (see eligibility check list in Appendix 2).

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Any women who are not recruited or deemed ineligible for the study will continue receiving care under the management of a clinician, as per current medical practice. Their care will not be affected due to non-trial participation.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Randomisation will be managed via a secure web-based randomisation facility hosted by the NPEU CTU, University of Oxford, with telephone back-up available at all times (24/7, 365 days a year). The randomisation program will use stratification to ensure balance between the groups with respect to trial site, BMI status (BMI <40 or ≥40) and multiplicity (singleton vs multiple pregnancy).

In order to randomise an eligible woman into the trial, minimal details regarding her booking visit/pregnancy will be required.
The Senior Trials Programmer at the NPEU CTU will write the randomisation program and hold the codes.

5.5.2 Treatment Allocation

At the initial clinic visit when treatment is started both intervention and standard care (insulin) will be supplied by the local pharmacies within the hospital where the participant is attending the clinic. Following this initial prescription, the study treatment (glibenclamide) will continue to be prescribed and dispensed through the hospital pharmacy. Further medication requirements for all NIMPs (metformin and insulin) will be supplied as per normal practice by the participants’ GPs and local community pharmacies.

There will be over-labelling of glibenclamide, but with the drug name and dose written on the box as this is an open label study. Participants will be able to collect their medication following their clinic appointment when they are randomised.

Participants will be provided with written instructions regarding their dosing and potential side effects of treatments. They will also receive detailed instructions on when to test their blood glucose and how to record it. They will have emergency contact numbers for the DSN as well as a member of the research team.

5.5.3 Withdrawal of Study Participants

Participants may withdraw from the study on request, or if their doctor believes it is inappropriate for them to continue. Women who, despite therapy with glibenclamide and metformin fail to achieve adequate glucose control despite maximal combined oral-agent therapy (as outlined in table 3 above), will be asked to stop glibenclamide and to start insulin under the guidance of their clinicians. Additionally, those not able to tolerate combined oral-agent therapy will be asked to stop glibenclamide and start insulin. Outcomes on these women will still be recorded.

5.5.3.1 Stopping rules:

The trial steering committee will monitor participants’ glucose readings, paying particular attention to number and frequency of episodes of hypoglycaemia. If it is deemed that there are too many incidences of hypoglycaemia in the intervention arm then the intervention could be withdrawn and the trial stopped prematurely.
6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 STUDY DRUG

6.1.1 Study Drug Identification
The study drug is glibenclamide in either a 2.5 mg or 5 mg tablet.

6.1.2 Study Drug Manufacturer
Due to contract variability in the participating hospitals, the manufacturer and Manufacturing Authorisation number of the IMP may vary. Working with local hospital pharmacies, we have identified a number of available SmPCs that may be applicable to this trial (see appendix 3). We have selected the original market holder’s (Aurobindo Pharma Limited, Marketing Authorisation numbers: PL 20532/0080 (5 mg) and PL 20532/0079 (2.5 mg)) SmPC for safety monitoring. We will collect information on the drug manufacturer on the IMP accountability logs and in the event escalated reporting is required we will be able to specify the exact manufacturer and medication used.

6.1.3 Marketing Authorisation Holder
Appendix 3 lists all possible MA numbers.

6.1.4 Labelling
Pharmacy in Edinburgh Royal Infirmary
51 Little France Crescent
Old Dalkeith Road
Edinburgh
EH16 4SA

Pharmacy in Western General Hospital Edinburgh
Crewe Road South
Edinburgh
EH4 2XU

Pharmacy in Glasgow Royal Infirmary
84 Castle Street
Glasgow
G4 0SF
Pharmacy at Southern General Hospital
1345 Govan Rd
Glasgow
Lanarkshire
G51 4TF

The Investigational Medicinal Product (IMP) (glibenclamide) will be over-labelled in the local hospital pharmacies (para 6.1.4). See supplemental documents for an example of the over-labeling. This is an unblinded trial so the labeling will contain the medication’s name, dose and instructions as well as labeling it as a trial medication.

Each participant will be prescribed sufficient glibenclamide for one week at maximum dose initially. Following this first week they will be given appropriate amounts as required.

6.1.5 Storage

Glibenclamide should be stored in its original blister packs at a temperature of no more than 25°C as per the SmPC.

6.1.6 Summary of Product Characteristics

A link to the relevant Summaries of Product Characteristics (SmPC) is given in Appendix 1. Note, that the NICE guidelines on Diabetes in Pregnancy endorse the use of this drug in pregnancy.

6.2 DOSING REGIME

Participants will be commenced on glibenclamide, in addition to their previous metformin dose, at the time of randomisation if allocated to the intervention arm of the trial.

They will commence on 2.5 mg glibenclamide once or twice daily as decided by their clinician and increased up to 10 mg twice daily. Whilst the SmPC states that the maximum dose of glibenclamide is 15 mg daily, it is felt that due to the changes in metabolism, protein binding and body composition in pregnancy, a higher maximum dose of 20 mg daily is more suitable in the treatment of GDM. Herbert et al [15] have demonstrated that concentration-time profiles for non-pregnant women receiving 1.25–10 mg twice daily were comparable to those in pregnant women receiving 1.25–23.75 mg twice daily. We note that the large studies on the use of glibenclamide in pregnancy have used up to 20 mg per day (in divided doses) [11,16]. Additionally, the 2013 Practice Bulletin on Gestational Diabetes from the American College of Obstetricians and Gynecologists suggests that “The usual dosage of
glyburide is 2.5–20 mg daily in divided doses, although pharmacokinetic studies during pregnancy indicate daily doses up to 30 mg may be necessary to achieve adequate control" [15,16]. Of note, none of the six referees of the grant application related to this protocol have commented adversely on the dose of glibenclamide (reports available on request).

The dose will alter according to the clinician’s recommendations, following a strict dosing algorithm drawn up prior to the study commencing, either during telephone consultations or during clinic visits. Women will be phoned two to five days after initially starting on glibenclamide or after any dose increase, with up titration of treatment if any episode of hyperglycaemia occurs (see 4.2 for definitions of hyperglycaemia). Similarly, if hypoglycaemia occurs, the dose will be down titrated. If necessary the dose can be down-titrated to 0mg and then up titrated again (this is a clinical decision made by the clinical care team) without the participant needing to exit/re-enter the study. There are no safety implications regarding this beyond those which apply to all patients commencing or up titrating their treatment. As with any other changes in dose, this will all be captured in the eCRF. It is anticipated that maximum doses of glibenclamide will be reached within 2 weeks after starting glibenclamide.

Once control of diabetes is achieved, women will continue with glibenclamide treatment, in combination with their previous dose of metformin, either until delivery (after which all diabetes medication will stop) or if they fail to achieve adequate glycaemic control with dual oral therapy at which time they will stop glibenclamide, and convert to insulin under their clinician’s guidance.

If hyperglycaemia, as defined by SIGN and outlined in table 3, is still present after two weeks from the time that glibenclamide was started, then glibenclamide will be stopped and the participant converted to insulin treatment.

6.3 DOSE CHANGES

Dose changes will be guided by the treatment algorithm which will be drawn up on commencement of the study and managed by the participant in consultation with the clinical team (diabetologist, obstetrician, midwife and diabetes specialist nurse).

6.4 PARTICIPANT IMP COMPLIANCE

In an open-label study there is always the concern that participants in the standard care arm will be lost to follow-up. However, these participants will be attending regular clinic appointments at least alternate weekly throughout their pregnancies; therefore we believe it
will be difficult for them to be lost to follow-up providing the investigators approach them during these clinic visits.

6.5 OVERDOSE

Hypoglycaemia is a theoretical risk of combination therapy, particular in overdosage. It should be treated urgently in the conscious patient with oral glucose. If the patient is comatose the glucose should be administered by intravenous infusion. Alternatively glucagon administered in a dose of 1 mg subcutaneously or intramuscularly may be used. The participant should be observed over several days in case hypoglycaemia recurs. If severe hypoglycaemia has occurred fetal wellbeing should be checked.

6.6 NON-INVESTIGATIONAL MEDICINAL PRODUCT

There are five NIMPs associated with this trial; all of the details for these drugs are outlined below.

6.6.1 Drug Identification

1) Metformin 500 mg film-coated tablet
2) NovoRapid FlexPen 100 U/ml solution for injection for pre-filled pen
3) Insulatard InnoLet 100 iu/ml suspension for injection in pre-filled pen.
4) Humalog 100U/ml Kwikpen
5) Humulin 1 100iu/ml Kwikpen

6.6.2 Drug Manufacturer

1) Merck Serono
   Merck Santé s.a.s.
   Centre de Production
2, rue du Pressoir Vert
45400 SEMOY
FRANCE
2) and 3) Novo Nordisk Limited
Broadfield Park
Brighton Road
Crawley
West Sussex
RH11 9RT
UK

4) and 5) Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL
UK

6.6.3 Marketing Authorisation holder

1) Lipha Pharmaceuticals Limited. MA no: PL 03759/0012-0013
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX
UK

2) Novo Nordisk A/S. MA no: EU/1/99/119/009
Novo Alle
DK-2880 Bagsvaerd
Denmark

3) Novo Nordisk A/S. MA no: EU/1/02/233/011
Novo Alle
DK-2880 Bagsvaerd
Denmark

4) Eli Lilly Nederland. MA no: EU/1/96/007/031
6.6.4 Labelling and Packaging

The labelling and packaging for the NIMPs will be the manufacturer’s original labelling and packaging.

6.6.5 Storage

2) and 3) Specific instructions as advised by the manufacturer are: Before opening: store in refrigerator (2°–8°C). Do not freeze. During use and when carried as a spare (by the participants): store below 25°C for a maximum of six weeks. Do not refrigerate and do not freeze. Keep the pencap on InnoLet in order to protect from light.

6.6.6 SmPC

The Summary of Product Characteristics (SmPC) is given in Appendix 1.

6.6.7 Dosing Regimen

1) The participants will already be either on the maximum dose of metformin (2 g daily) or on their maximum tolerated dose at point of entry into the study. This will not alter after commencing their IMP.

2) and 3) Participants randomised into the control arm of the study will continue with their previous metformin dose and commence insulin as per standard care.

6.6.8 Overdose

1) Hypoglycaemia has not been seen with metformin hydrochloride at doses of up to 85 g (maximum dose in this study is 2 g), although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to
lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

2) and 3) A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if doses significantly greater than the participant’s requirements are administered:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the participant with diabetes always carries sugar-containing products.

Severe hypoglycaemic episodes, where the participant has become unconscious, can be treated with glucagon (0.5–1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the participant does not respond to glucagon within 10–15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the participant in order to prevent a relapse.

6.7 PROHIBITED MEDICATIONS/MEDICATIONS TO BE AWARE OF INTERACTIONS

- For participants in intervention arm (i.e. taking glibenclamide)
  - Hypoglycaemic effect is increased by the use of: antifungal medication, sulphonamides, anti-inflammatory agents (e.g. phenylbutazone, salicylates) dicoumarin anticoagulants and heparin, lipid regulating agents, some antidepressants, ACE-inhibitors, H2-blockers including ranitidine. These medications are not prohibited but may necessitate dose reduction.
  - Hypoglycaemic effects may be diminished by rifampacan, thiazide diuretics and beta-blockers necessitating dose increase.
  - Beta blockers can mask the symptoms of hypoglycaemia.
  - Alcohol may interact with glibenclamide provoking facial flushing and has a variable effect on blood sugars. Pregnant women should avoid alcohol in any case, so this is unlikely to be a significant issue during this trial.

- For participants in standard care arm (i.e. on insulin)
  - The following substances may reduce the participant’s insulin requirement: monoamine oxidase inhibitors (MAOI), beta-blockers, ACE inhibitors, salicylates, anabolic steroids and sulphonamides.
o The following substances may increase the participant's insulin requirement: thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, danazol.

o Beta blockers may mask the symptoms of hypoglycaemia.

o Alcohol may intensify or reduce the hypoglycaemic effect of insulin. Pregnant women should avoid alcohol in any case, so this is unlikely to be a significant issue during this trial.
## 7 STUDY ASSESSMENTS

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>Information</th>
<th>Consent and Randomisation</th>
<th>Subsequent Clinic Visits (no predetermined no.)</th>
<th>Labour/delivery/neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Short) Participant Information Leaflet (PIL)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended PIL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMH and obstetric history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, weight and BMI</td>
<td>X</td>
<td>X (weight and BMI checked at 36 ±1 week)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>OGTT blood glucose levels at diagnosis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose readings for the previous week</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP dispensed</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review treatment dose and type</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Review of hypoglycaemic and hyperglycaemic episodes</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Review of AEs/SAEs</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Review of side effects</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Review of pregnancy complications</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Participant satisfaction, visual analogue scale</td>
<td>X (between 38 and 40 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labour / delivery information</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby weight, adjusted birth centile calculation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unused drug/packaging returned</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby blood glucose at 2 to 4hr of age (or as soon as measured following delivery with age in hours noted) and any episodes of hypoglycaemia</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other neonatal and biochemical outcomes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.1 SAFETY ASSESSMENTS

Safety will be assessed at each routine clinic visit and documented as noted in section 10.

7.2 STUDY ASSESSMENTS

See table 5 of study assessments for summary.

7.2.1 Information Visit

During the initial diagnosis consultation with their clinician the woman will discuss treatment options in the event that monotherapy does not achieve adequate control. At this time they will be given both verbal and written information about the study regarding the trial (in the form of the study flyer), i.e. this comprises the initial approach that coming directly from a member of the patient’s clinical care team.

Soon after commencing metformin the patient will be approached by a member of the research team with more detailed verbal and written (PIL) information about the study.

7.2.2 Recruitment and Randomisation Visit (between 16 and 36 weeks gestation)

If the woman is deemed to have failed monotherapy according to the criteria above, and she meets the eligibility criteria (see Eligibility Checklist Appendix 2), she will be offered the opportunity to participate in the study by a delegated research team member.

If the woman agrees to trial participation then the trial will be discussed with her and informed consent gained, ensuring that she is aware that their participation or non-participation will not affect her medical care. The original consent form(s) will be stored in the Investigator Site File (ISF) file, a copy is given to the participant, a copy added to the medical notes and a copy faxed to the Trial Office 0131 242 2686.

During this visit a maternal weight, height and BMI will be recorded. NB, gestation at time of recruitment will be checked by the randomisation program by inputting the EDD which has been calculated through an online program at the time of the booking scan. Manual gestation-wheels will not be used at any time in this trial.

Following consent the participants will be randomised using the web-based randomisation program and then treatment will be commenced in that same visit. Participants randomised to the intervention arm will be able to collect their over-labelled medication from pharmacy following their clinic appointment. Participants randomised to standard care (insulin) will be given their insulin by the diabetes specialist nurses in clinic, as per standard care.
Participants will be provided with written instructions regarding their dosing and potential side effects of both treatments. They will also receive detailed instructions on when to test their blood glucose and manner of recording it. They will have emergency contact numbers for the DSN as well as a member of the research team.

### 7.2.3 Subsequent Visits

The majority of subsequent visits will take place during the participant’s routine diabetic/metabolic antenatal clinic visit, as decided by their clinician. The participant may also consult the clinical team (e.g. the diabetes specialist nurse and/or a midwife or clinical research fellow) by phone between formal visits. The longest interval between visits will be two weeks. Whilst doses of either the intervention or control drugs are being adjusted, women will be in touch with a diabetes specialist nurse at least once a week.

Information will be gathered regarding participants' blood glucose readings including the number and proportion of excursions in blood glucose out-with the acceptable range (para 4.2, table 3), side effects, adverse events and pregnancy complications. Glucomen LX blood glucose meters will be used. Using the Diasend hardware the data will be extracted from the meters at each clinic visit and downloaded into an Excel spreadsheet.

Information will also be recorded from the medical notes as and when required, particularly if the decision to alter therapy is made.

Due to individual variation and frequent dose changes, participants will not be asked to bring in their medications for compliance checking as this would prove too difficult to ascertain.

Participants will be asked to complete a participant-satisfaction questionnaire at least once during their pregnancy. The timing will depend upon the gestation at randomisation, however it should be completed between 36 and 40 weeks of gestation.
7.2.4 Labour/delivery visit and neonatal assessments

Admission for delivery will not be a formal study visit and will not be recorded as an SAE. Information on pregnancy and delivery complications will be collected. Adverse events (AEs) will be recorded in the patient notes, serious adverse events (SAEs) will be recorded on the SAE form (see section 10). Information will be obtained on the maternal outcomes of delivery, including mode of delivery, indication for delivery method, date and gestation of delivery, and blood loss. Delivery outcome (live birth, still birth, and early neonatal death[^1]) will also be collected and recorded by local investigators. Adverse events and pregnancy complications will be reviewed where possible at this visit and unused study medication returned for disposal. Data regarding maternal and neonatal information can be collected from the notes following discharge however only up until the point of discharge. (i.e. anything written in the notes that occurs following discharge will not be collected). If the participant has been discharged prior to a research team member reviewing them and downloading their blood glucose meter then their meter will be collected from them at home as a part of standard postnatal care, by their usual clinical care team.

Cord blood will be collected where possible for analysis of biochemical markers i.e. c-peptide. Cord blood should be stored in K-EDTA tubes at 4°C for no more than 24 hours before transport to the laboratory. In the laboratory, the sample should be spun, supernatant plasma extracted and stored at -20°C until analysis. Analysis of c-peptide will be done either in batches as the study progresses or at the end of the study. The c-peptide analysis will be exploratory but has been added as an additional study endpoint. Stability at room temperature for 24 hours is demonstrated [17]. All cord blood collected in Glasgow will be transferred to Edinburgh by the end of the study for analysis and will be stored in the Edinburgh Reproductive Tissue Bio Bank (ERTBB).

[^1]: This refers to the death of a neonate within 7 days of a live birth
Participants recruited from the Edinburgh study sites will be approached about donating placental tissue in addition to cord blood. All samples will be stored in the ERTBB under the governance of the SAHSC bio resource.

Outcome data regarding the neonate will be collected including the birthweight, adjusted birthweight centile, trauma, blood glucose of the neonate at 2–4 hours of age and any incidence of neonatal hypoglycaemia within the first 48 hours of life. If the neonatal blood glucose is not checked within the 2-4 hours of age the information on neonatal blood glucose will still be collected and a note made of age (in hours) that this was collected at.

8 DATA COLLECTION

Data will be collected from the participant’s clinical record; considered to be source data. Data on the participant’s blood glucose readings will be directly downloaded during each clinic visit from the meter into an Excel spreadsheet. Information will be extracted from their clinical record into the electronic case report form (eCRF). Data will be collected as it becomes available i.e. at or shortly after each participant visit. Data will be collected by the local investigators. Standardised participant-satisfaction questionnaires will be utilised.

9 STATISTICS ANALYSIS

9.1 SAMPLE SIZE AND POWER

A formal power calculation is not considered necessary or appropriate for a feasibility study: the primary outcome in this feasibility study is recruitment rate. This, together with data on glycaemic control and participant acceptability will be used to determine whether a large randomised trial is warranted and feasible. The remaining outcomes will be used either as safety markers, or to inform the design of a large randomised trial.

9.2 STATISTICAL ANALYSIS

9.2.1 Analysis of feasibility metrics

The primary outcome is the number of women who agree to be randomised; this will be reported across both arms of the trial. Other key feasibility metrics collected regarding retention, adherence and safety will be reported as proportions with 95% confidence intervals (CI) to illustrate the range of compatible values in relation to the number recruited.
9.2.2 Primary Analysis population

Women will be analysed in the groups to which they are randomly assigned, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat (ITT) population).

9.2.3 Analysis of clinical outcome measures

The following methods will be used throughout for the analysis of glycaemic control measurements, secondary clinical outcomes and participant acceptability.

Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables. All comparative analyses will be performed unadjusted for stratification factors at randomisation, given the small sample size. For binary/dichotomous outcomes, risk ratios plus 95% CIs will be presented. For continuous outcomes, results will be presented as differences in means (plus 95% CIs) or differences in medians (plus 95% CIs). Analysis of time to event outcomes will use survival analysis techniques.

Information regarding the variance of glycaemic control outcome measures and event rates for other clinical outcomes will be used to inform the sample size for the future main trial.

Statistical analysis will be performed by an NPEU statistician co-applicant who has been integral to the study design, contributing to the trial protocol, developing the data collection forms and specifying the corresponding study databases.

10 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AEs) that occur after joining the trial must be reported in the patient notes. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present
at the last visit must be followed up until resolution of the event or the end of trial, whichever is sooner.

10.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An adverse reaction (AR) is any untoward or unintended response to an IMP which is related to any dose administered to that participant.

A serious adverse event (SAE), serious adverse reaction (SAR) is any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.
- results in any other significant medical event not meeting the criteria above.

* Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP and NIMPs in the Summary of Product Characteristics (SmPC).

10.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until stopping the IMP or discharge following delivery of the baby, whichever is later.

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication.
regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified by support departments e.g. laboratories, the labour ward, antenatal or the postnatal ward or the neonatal ward.

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

All adverse medical events reported by the participant should be noted in the participant’s hospital notes, together with a note of the date of starting, the duration, and any medical treatment received.

The clinician will assess **ALL** reported SAEs. Some adverse events are expected and will not therefore be reported as SAEs **but** will be recorded in the eCRF and presented to the DMC, as part of the ongoing safety review.

For this study the following events are **NOT** considered SAEs:

- Pregnancy is not considered an AE or SAE, as it is part of the inclusion criteria
- Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. This includes pregnancy. However, **complications occurring during such hospitalisation will be AE/SAEs.**
- The following are also not considered SAEs
  - Miscarriage
  - Preterm labour
  - Preterm prelabour spontaneous rupture of membranes
  - Preterm delivery in maternal interest
  - Preterm delivery in fetal interest
  - Hospitalisation for pregnancy induced hypertension
  - Hospitalisation for “maternal discomfort”
  - Hospitalisation for “rest”
 Hospitalisation for “observation” or “monitoring” for which the women is admitted for a period of less than 12 hours
- Delivery complications such as caesarean section or post-partum haemorrhage
- Admission of the baby to the neonatal unit for a period of up to 14 days.
- Maternal hypoglycaemia

**NOTE:**
- Maternal hypoglycaemia is not an adverse event but we will collect in real time the incidence of hypoglycaemia in each group.
- Maternal hyperglycaemia is the condition under treatment and is not an adverse event. However, a blood glucose of ≥20mmol/L (confirmed by two consecutive readings) will be considered an SAE and therefore subject to expedited reporting.

### 10.4 ASSESSMENT OF AEs AND SAEs

As this is an unblinded feasibility trial, seriousness, causality, severity and expectedness will be assessed.

The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate. If there is a disagreement between the investigator and the CI assessments then both can be presented stating the reason for the disagreement.

#### 10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

#### 10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

**Unrelated:** where an event is not considered to be related to the IMP.

**Possibly Related:** The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in Section 4.8 of the Summary of Product Characteristics [refer to Appendix 1 for the date of most recent revision].
Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC. The event may be classed as either:

**Expected**: the AR is consistent with the toxicity of the IMP listed in the SmPC.

**Unexpected**: the AR is not consistent with the toxicity in the SmPC.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the eCRF or SAE form 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**: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office immediately or within 24 hours. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.
The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow-up information will be retained by the Investigator in the Investigator Site File (ISF). ACCORD will let the trial manager have a copy of SAEs so that the information can also be included on the study database.

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report will be submitted to the regulatory competent authority and main REC listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow-up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.
11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), a Trial Manager and a clinical research fellow.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the eCRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

11.2 TRIAL STEERING COMMITTEE

The trial will be overseen by a Trial Steering Committee (TSC) consisting of an independent chair and at least two other independent members. Committee members will be deemed to be independent if they are not involved in trial recruitment and are not employed by any organisation directly involved in the trial conduct.

Representatives from relevant Patient/Public Involvement groups, the Chief Investigator, other Investigators/co-applicants will be joined by observers from the NPEU CTU. The CSO programme manager will be invited to attend all TSC meetings.

The role of the TSC is to provide the overall supervision of the trial. The TSC should monitor the progress of the trial and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or unfeasibility.

11.3 DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC), independent of the applicants and of the TSC, will review the progress of the trial and provide advice on the conduct of the trial to the TSC and (via the TSC) to the funder. The committee will periodically review trial progress and feasibility metrics as well as secondary outcomes. The content and timings of the DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.
11.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.5 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

11.6 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, and any relevant amendments.
12.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – the current REC approved Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant’s medical notes.

12.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator’s responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.
12.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the eCRF at each Investigator Site.

12.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator’s Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

12.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Access to collated participant data will be restricted to those clinicians treating the participants.
Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.
13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study is defined as 6 weeks or discharge from hospital (whichever is sooner) after delivery of the baby (last visit) of the last participant.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) 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 REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow-up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

13.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

When the participant delivers her infant, the drug will stop being administered.

13.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer of the IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

14.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion). A summary will be sent to participants.

14.3 PEER REVIEW

The project has been peer reviewed by the Diabetes Research Network “Diabetes and Pregnancy” group chaired by Prof David R McCance, Belfast.
15 REFERENCES


APPENDIX 1: SUMMARY OF PRODUCT CHARACTERISTICS

The original market holder's (Aurobindo Pharma Limited, MA number: PL 20532/0080 (5 mg, date of last revision 04/07/2011) and PL 20532/0079 (2.5 mg, date of last revision 04/07/2011)) SmPCs will be used for safety monitoring purposes.

The manufacturer may change the SmPCs for this study as new information becomes available. The study will therefore adopt the manufacturer's current SmPC. The study team will monitor and review changes to the SmPC and consider the impact on the study and revise documents if required.

The SmPCs for Glibenclamide are published on the MHRA website at:

5 mg:
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm?prodName=GLIBENCLAMIDE%205MG%20TABLETS&subsName=GLIBENCLAMIDE&pageID=SecondLevel
(note, the disclaimer has to be ticked prior to full access)

2.5 mg:
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm?prodName=GLIBENCLAMIDE%202.5%20MG%20TABLETS\nBP&subsName=GLIBENCLAMIDE&pageID=SecondLevel
(note, the disclaimer has to be ticked prior to full access)

The SmPC for the NIMPS are all from the medicines.org website and are listed below.

1) Metformin: (last updated 15/04/2013)
http://www.medicines.org.uk/emc/medicine/23244/SPC

2) Novorapid: (last updated 22/08/2012)
http://www.medicines.org.uk/emc/medicine/25033/SPC/NovoRapid+100+U+ml+in+a+vial%2c+NovoRapid+Penfill+100+U+ml%2c+NovoRapid+FlexPen+100+U+ml%2c+NovoRapid+FlexTouch+100+U+ml/

3) Insulatard Innolet: (last update 13/12/2012)
http://www.medicines.org.uk/emc/medicine/3512/SPC/Insulatard+100+IU+ml%2c+Insulatard+Penfill+100+IU+ml%2c+Insulatard+InnoLet+100+IU+ml/

4) Humalog 100U/ml Kwikpen (last updated 02/12/2013)
http://www.medicines.org.uk/emc/medicine/9314/SPC/Humalog+100U+ml,+solution+for+injection+in+vial,++Humalog+100U+ml,+solution+for+injection+in+Cartridge,++Humalog+KwikPen+100U+ml,+solution+for+injection/#ORIGINAL

5) Humulin 100iu/ml Kwikpen (last updated 06/08/2012)

http://www.medicines.org.uk/emc/medicine/3425/SPC/Humulin+Vials%2c+Cartridges+and+KwikPens
APPENDIX 2: ELIGIBILITY CHECKLIST

Is the woman aged ≥16 years and ≤50 years old?

Has the woman been diagnosed with gestational diabetes mellitus as per the SIGN 116 guidelines?

Has the woman been taking metformin (minimum of 500mg and maximum 2g daily) but has not achieved good glycaemic control (as per table)?

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Fasting</th>
<th>≥5.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs post prandial at &lt;35 weeks of gestation</td>
<td>≥7 mmol/L</td>
<td></td>
</tr>
<tr>
<td>2 hrs post prandial at &gt;35 weeks of gestation</td>
<td>≥8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Postprandial value at any time</td>
<td>≥9 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Is the woman <16th or >36th weeks of gestation?

Does the woman have suspected type 1 diabetes presenting in pregnancy?

Does the woman have any allergies to either glibenclamide, insulin or any of their excipients?

Does the woman have any contraindications to sulphonylurea therapy?

Has the woman given written informed consent?

ELIGIBLE FOR RANDOMISATION
## APPENDIX 3: INVESTIGATIONAL MEDICINAL PRODUCT DETAILS

<table>
<thead>
<tr>
<th>Drug Identification</th>
<th>Drug Manufacturer and Marketing Authorisation Holder</th>
<th>Date of last update</th>
<th>Marketing Authorisation no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide, 2.5 mg and 5 mg tablets</td>
<td>TEVA UK Limited Brampton Road, Hampden Park Eastbourne, East Sussex BN22 9AG</td>
<td>20/03/2013</td>
<td>PL 00289/0047 PL 00289/0048</td>
</tr>
<tr>
<td>Glibenclamide 2.5 mg and 5 mg tablets BP,</td>
<td>Aurobindo Pharma Limited Ares Odyssey Business Park West End Road South Ruislip HA4 6QD</td>
<td>04/07/2011</td>
<td>PL 20532/0079 PL 20532/0080</td>
</tr>
<tr>
<td>Liamid 2.5 mg and 5 mg tablets,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliken 2.5 mg and 5 mg tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide 2.5 mg and 5 mg tablets</td>
<td>Medreich Plc Warwick House Plane Tree Crescent Feltham TW13 7HF</td>
<td>12/06/2013</td>
<td>PL 21880/0113 PL 21880/0114</td>
</tr>
<tr>
<td>Glibenclamide 2.5 mg and 5 mg tablets</td>
<td>Wockhardt UK Limited Ash Road North Wrexham Industrial Estate Wrexham LL13 9UF</td>
<td>15/10/2012</td>
<td>PL 29831/0102 PL 29831/0101</td>
</tr>
</tbody>
</table>