Clinical Trial Protocol

Trial Title:	Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*) – a randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk.
EudraCT Number:	2012-005570-56
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Investigational Product:	Prolonged-release metformin
Protocol Version:	v5.0 18/03/2016

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1 Protocol Signatures:

I give my approval for the attached protocol entitled 'Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*) – a randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk' dated 18/03/2016(v5.0)

Chief Investigator

Name: Professor Simon Griffin

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*) – a randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk dated 18/03/2016 (v5.0) and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principle of Good Clinical Practice; as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name:

Signature: _____

Date: _____

2 Study Management Committee and Protocol Contributors

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Sponsor:	Cambridge University Hospitals NHS Foundation Trust and

	the University of Cambridge
Funder:	National Institute for Health Research – Health Technology Assessment Programme (09/01/48)

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4 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CEC	Clinical Events Committee
CI	Chief Investigator
CKD	Chronic kidney disease
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trials Authorisation
CVD	Cardiovascular Disease
DPP	Diabetes Prevention Programme
DSUR	Development Safety Update Report
DTU	Diabetes Trial Unit
eCRF	Electronic clinical research form
eGFR	Estimated Glomerular Filtration Rate
GP	General Practitioner
GCP	Good Clinical Practice
HDL	High-Density Lipoproteins
HDPE	High-Density Polyethylene
HES	Health Episode Statistics
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRB	Independent Review Board
ISF	Investigator Site File
LDL	Low-Density Lipoproteins
LFTs	Liver Function Tests
MI	Myocardial infarction
MRC	Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
NDH	Non-Diabetic Hyperglycaemia
NIMP	Non Investigational Medicinal Product
NRES	National Research Ethics Service
OC	Operational Committee
OGTT	Oral Glucose Tolerance Test
PI	Principal Investigator
PIC	Participant Information Centre
PIL	Participant Information Leaflet
PSSRU	Personal Social Services Research Unit
R&D	NHS Trust Research and Development Department
RA	Regulatory Agency
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source document verification
SmPC	Summary of Product Characteristics

SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TMF	Trial Master File
TSC	Trial Steering Committee
UKPDS	UK Prospective Diabetes Study
WHO	World health Organisation

5 Trial Synopsis

Title of clinical trial	Glucose Lowering In Non-diabetic hyperglycaemia Trial (*GLINT)* – a randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular disease (CVD) events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Eudract number for proposed trial	2012-005570-56
Medical condition or disease under investigation	Non-diabetic hyperglycaemia (NDH) (HbA_{1c} ≥36.6mmol/mol but <47.5mmol/mol) with an estimated 10-year CVD risk ≥20% (Framingham/QRISK2)
Purpose of clinical trial	To establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk
Primary objective	To evaluate the effect of adding metformin to the usual care of participants with NDH on a composite macrovascular endpoint (cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke)
Secondary objective (s)	To evaluate the effect of adding metformin to the usual care of participants with NDH on: •Each component of the primary composite endpoint •All-cause mortality •Incidence of non-melanoma cancer •Death due to a non-melanoma cancer cause •Incidence of physician-diagnosed type 2 diabetes •Participant satisfaction with treatment •Functional status •Health utility

Study Design	Multi-centre, randomised, double-blind, parallel group, pragmatic, primary prevention trial comparing the effect of prolonged-release metformin with placebo on a composite macrovascular outcome in people with non-diabetic hyperglycaemia (NDH) and high CVD risk in primary care
Study Endpoints	Primary Endpoint: Time to first confirmed event in the primary composite macrovascular endpoint (cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke). Secondary Endpoints: •Time from randomisation to the first confirmed event of the individual components of the primary composite endpoint *i.e.* cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke •Time to any cause of death (supplied by Office of National Statistics) •Time to first non-melanoma cancer (supplied by the National Cancer Registry) •Time to death due to a non-melanoma cancer cause according to primary / underlying cause of death on death certificate (supplied by the Office of National Statistics) •Incident type 2 diabetes mellitus (T2DM) (physician diagnosed) •Participant satisfaction with treatment (adapted DTSQ) •Functional status (SF-8) •Health utility (EuroQol EQ-5D)
Sample Size	The study will begin with a 250 participant feasibility phase. The feasibility phase aims to test the practicalities of different aspects of the study to confirm that it is possible to use this study model. If the analysis of the feasibility phase determines that this model is viable, the second phase of the study will commence and an additional 12,648 participants will be recruited; bringing the total sample size to 12,898. Analysis of the study efficacy will be conducted after 1,046 confirmed primary composite endpoint events have accrued.
Summary of eligibility criteria	Inclusion criteria: To be included in the study the participant must meet all of the following criteria: •Understand the study procedures, alternative treatments available, and

the risks involved with the study, and voluntarily agree to participate by providing written informed consent
- Age ≥ 40 years
- HbA_{1c} ≥36.6mmol/mol but <47.5mmol/mol; measured within one year prior to enrolment
- Estimated 10-year CVD risk ≥20% as assessed by the Framingham or QRISK2 scores; laboratory values used for the risk calculators should be collected no more than one year prior to enrolment.
- Estimated glomerular filtration rate (eGFR) ≥45ml/min as determined by the MDRD-4 method; measured within 6 months prior to enrolment
- Participant agrees to allow study staff to contact his or her General Practitioner and/or consultant to notify them of study participation and to obtain all medical records necessary for complete data ascertainment during the follow-up period (including recording of NHS number and access to Health Episode Statistics (HES))
- Participant agrees to be flagged with the Office for National Statistics and the National Cancer Registry for:
  - Time to first non-melanoma cancer diagnosis (supplied by National Cancer Registry)
  - Time to death due to a non-melanoma cancer cause according to primary/underlying cause of death on death certificate (supplied by the Office of National Statistics)

Exclusion criteria:

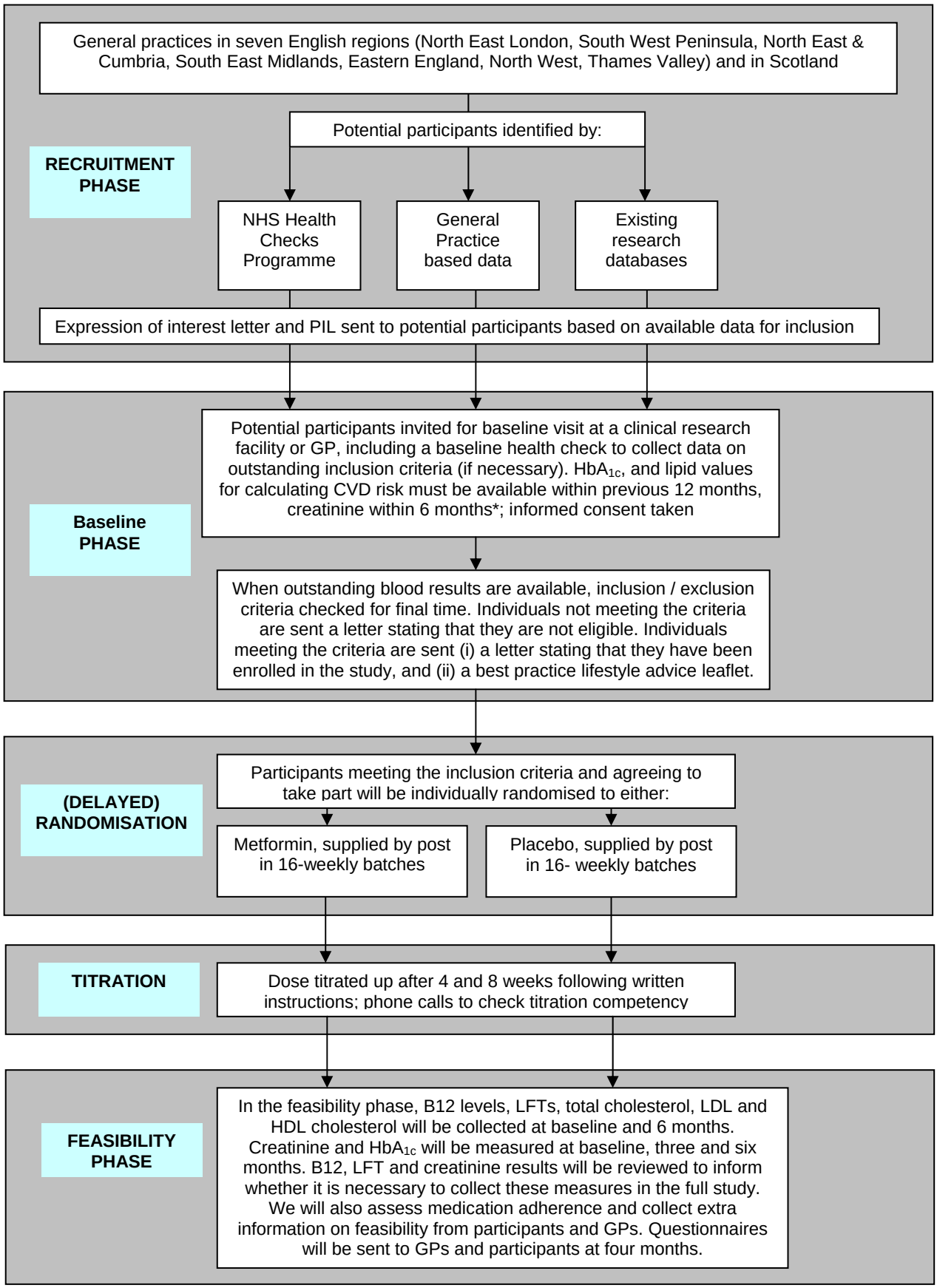
The participant may not enter the study if ANY of the following apply:
- Unable to provide written consent
- Prior history of physician-diagnosed T2DM.

  NOTE: Participants with a history of gestational diabetes which resolved after pregnancy are permitted to enrol.
- Prior history of CVD, defined as:
  - myocardial infarction, surgical or percutaneous coronary revascularization procedure
  - Stroke (haemorrhagic or

	ischaemic) *NOTE: Participants with prior transient ischaemic attack or unstable angina are NOT excluded and may be enrolled* • Participant has a planned or anticipated coronary revascularization procedure within 6 months following enrolment *NOTE: Participants with previous peripheral revascularisation procedure are NOT excluded and may be enrolled* • Participant is breastfeeding or known to be pregnant • Participant is currently taking metformin (for any reason) or they have taken metformin in the last three months • History of cirrhosis of the liver or other significant hepatic impairment, as assessed by medical history • End-stage renal disease (CKD stage 3b or worse, eGFR<45ml/min) • In the investigator's opinion, participant has a medical history that indicates a life expectancy of <2 years or might limit the individual's ability to take the study treatments for the duration of the study. • Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study. Participant is enrolled in or has participated within 12 weeks prior to enrolment in another experimental protocol involving the use of an investigational drug or device or an intervention that would interfere with the conduct of the study
Investigational medicinal product and dosage	Prolonged-release metformin (Glucophage), tablet form 1500mg (3 x 500mg/day).
Comparator product(s)	Placebo tablet
Route(s) of administration	Oral
Maximum duration of treatment of a participant	Feasibility phase: Study duration is driven by the time required to recruit and follow 250 participants for at least a median of 6 months, anticipated duration is 30 months.

	Full study: duration is driven by the time to accumulate 1,046 confirmed events in the primary composite endpoint, anticipated duration is 5-7 years
Procedures:Recruitment	3 recruitment methods: •NHS Health Checks programme •Existing research databases held by GLINT investigators •Search of GP electronic records using risk scores to identify potential eligible individuals
Baseline	•Consent •Assessment of Eligibility •Blood sample taking •Clinical measures •Questionnaire
Treatment period	•Study medication •Annual questionnaire
End of study	•End of study questionnaire
Procedures for safety monitoring during study	100% source document verification (SDV) on first 5 participants at each site; outcome will determine further monitoring frequency. The IDMC will also monitor the safety of participants during the study
Criteria for withdrawal of participants on safety grounds	Protocol specified reasons for study medication discontinuation are: •An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures. Study drug can be resumed if the event resolves. •Development of chronic kidney disease (CKD stage 3b or worse, eGFR<45ml/min).

6 Study Flow Chart



ANNUAL FOLLOW-UP UNTIL END OF STUDY	All participants will be sent an annual questionnaire including questions on CVD, cancer and diabetes incidence; adverse events; medication adherence; SF8, EuroQol (EQ5D), treatment satisfaction; health service use in last 12 months; GPs will receive an annual questionnaire regarding vital status; CVD, cancer and diabetes incidence; adverse events; current medication; most recent eGFR value (if present)**

*Note that we do not plan to collect LFTs or B12 at baseline in the full study (following safety results from the feasibility phase); we do not plan to collect creatinine measures during study follow-up, (following safety results from the feasibility phase), although we will ask GPs to supply this value if available
** If eGFR < 45ml/min, study medication should be stopped

7 Background and rationale for study

Cardiovascular disease (CVD) is a major UK public health problem associated with substantial premature mortality, morbidity and financial cost (1). In the UK, population screening and risk factor reduction programmes are being implemented (2). High glucose levels are a risk factor for CVD (3). However, considerable uncertainty exists about the appropriate screening and treatment strategies for this risk factor. People with established T2DM are at increased CVD risk, but the degree to which that risk is modulated through glucose control is unclear. Observational studies show a consistent and continuous association between glycaemia and CVD risk, even below the diagnostic threshold for T2DM i.e. non-diabetic hyperglycaemia (NDH) (3-5). Despite this association, interventional trials have not consistently demonstrated reductions in CVD risk with intensive glucose control. The UK Prospective Diabetes Study (UKPDS), conducted in newly diagnosed diabetic patients, showed a reduced risk of myocardial infarction (RR 0.67, 95% CI 0.51 to 0.89) and all-cause mortality (RR 0.73, 95% CI 0.59 to 0.89) with metformin based treatment (6). In contrast, randomised trials of intensive control of hyperglycaemia, mainly involving agents other than metformin, in those with longstanding T2DM, have not demonstrated significant reductions in major cardiovascular event composites (7-9). Meta-analyses pooling all of the glucose-lowering trials in people with T2DM suggest a small, but statistically significant beneficial effect of intensive glucose control on CVD endpoints (10, 11). The hypothesis that tight glycaemic control is more important early in the course of T2DM or prior to its development, before macrovascular disease has developed, could unify these findings and is supported by subgroup analyses showing greater CVD effect in those with a shorter duration of T2DM (7-9).

The effect of glucose lowering on CVD mortality and events in people with NDH is unknown. This is an important gap in the current research base (12), particularly at a time when population-based programmes to identify those at high CVD risk are being undertaken. Non-diabetic hyperglycaemia affects 15-20% of the adult population and around 50% of all CVD events attributable to higher than normal glucose levels occur in this group (4). If a cheap and safe drug, such as metformin, were shown to reduce CVD risk, via reductions in glycaemia as well as other mechanisms (13), it would have important population health and economic benefits. There have previously been no primary CVD prevention trials evaluating metformin in people with NDH. The US Diabetes Prevention Programme (DPP) randomised approximately 1000 participants to metformin for diabetes prevention, but is under-powered to examine its impact on CVD events. We plan to quantify the effect of metformin compared to placebo on CVD risk in individuals with NDH using an individually-randomised controlled trial design.

Hyperglycaemia, insulin resistance and obesity are risk factors for malignancy (14). Recent observational data link metformin use to a 37% reduction in incidence of major

common cancers, including bowel, lung and breast (15), and this is supported by a body of evidence describing plausible mechanisms of action in addition to glucose-lowering (16). Among patients with T2DM use of metformin is associated with a halving of cancer mortality (17). However, these epidemiological data are limited by residual confounding and cannot establish causality. Indeed, a recent meta-analysis does not support the hypothesis that metformin lowers cancer risk by one-third (18). By randomising participants to metformin therapy, our study will also be able to evaluate the potential relationship between metformin and risk of cancer.

Previous T2DM prevention studies (19-25) have identified high risk individuals using an oral glucose tolerance test (OGTT). This method of identifying an at-risk population sub-group is challenging for practitioners and patients alike and is impractical within the context of a population-based CVD risk reduction programme. Our proposed study will assess the effect of metformin on outcomes among a high-risk group defined by a more pragmatic screening strategy utilising a non-fasted blood test (HbA_{1c}). A World Health Organisation (WHO) report endorsing the use of HbA_{1c} as an alternative test to the OGTT for defining T2DM has been published and is likely to impact on UK clinical practice (26). The cut-point for defining among asymptomatic non-pregnant individuals is HbA_{1c} ≥47.5mmol/mol (26, 27). The Expert Committee noted that the risk of T2DM and cardiovascular disease was elevated in people with NDH as defined by HbA_{1c}. The risk of progression to T2DM approximately doubles for each 0.5% increase in HbA_{1c}. The American Diabetes Association recommends the range 38.8 to 46.4mmol/mol to define those at high risk but acknowledges that 'the most appropriate level above which to initiate preventive interventions is likely to be somewhere in the range of 36.6–42.1mmol/mol' (27). Rather than define a new HbA_{1c} category equivalent to the OGTT-defined impaired glucose tolerance or impaired fasting glucose, the Expert Committee noted that it would be preferable to define a level of NDH at which the benefits of intervention outweigh the risks. Such an analysis requires long-term trials in people with NDH.

GLINT (Glucose Lowering in Non-diabetic hyperglycaemia Trial) is a pragmatic, placebo-controlled, double blinded trial which seeks to determine the impact of metformin on macrovascular outcomes in people with NDH over a median follow up period of five years. It will be run jointly by the University of Cambridge MRC Epidemiology Unit and the University of Oxford Diabetes Trials Unit (DTU). The study is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. GLINT is conducted in two phases (i) a feasibility phase and (ii) the extended study. The feasibility phase aims to address practicalities to validate the study model and minimise uncertainty concerning trial parameters, prior to commencement of the full study.

Funding for the feasibility phase, which will be carried out in two UK regions, is provided by the NIHR Health Technology Assessment programme. If successful, this will lead into the full study and recruitment will be expanded to a further six geographical regions in the UK.

The study duration is driven by the time to accumulate 1,046 confirmed events in the primary composite endpoint. Initially, 250 participants will be enrolled in the study. The enrolment of a further 12,648 individuals will depend on the outcome of assessment of data from the initial feasibility phase including demonstration of the feasibility of general practice and participant recruitment, the feasibility of randomisation and distribution of study medication, the acceptability of and adherence to the study medication among participants, the feasibility of adverse event reporting and outcome assessment and the safety of metformin and the proposed frequency of monitoring of

renal function and B12 levels. Demonstration of a treatment effect within the limited duration of follow-up in the feasibility phase is not an objective.

8 Study Design

8.1 Statement of design

GLINT is a multi-centre, randomised, double-blind, parallel group, pragmatic, primary prevention trial comparing the effect of prolonged release metformin with placebo on a macrovascular composite outcome in people with non-diabetic hyperglycaemia and high CVD risk in primary care.

8.2 Number of Centres

GLINT is a multi-centre pragmatic trial that will be conducted in eight regions across the UK.

8.3 Number of Participants

A total of 12,898 eligible individuals will be recruited, 250 in the initial feasibility phase, and a further 12,648 over approximately a two year period. Participants will be randomly allocated to treatment with either metformin prolonged-release tablets or placebo, and followed up for a median of approximately five years. The sample size calculation for the study can be found in section 15.3.

8.4 Study duration

The study will continue until 1,046 adjudicated primary endpoints have been accrued, or until the TSC determine a need to terminate the trial. All participants will receive study medication and annual questionnaires until study close-out. All participants that cease study medication will be followed up, if possible, for the full study period. All participants that withdraw from the study will have their vital status ascertained, if possible, at the end of the study.

8.5 Study objectives

8.5.1 Primary objective

The primary objective is to evaluate the effect of metformin in preventing major macrovascular events in participants with NDH.

Objective: To compare the impact of adding metformin versus placebo to the usual care of participants with NDH on major macrovascular outcomes as measured by the primary composite endpoint of CV mortality, nonfatal myocardial infarction or nonfatal stroke.

Hypothesis: Metformin is superior to placebo with regard to the risk of developing a confirmed event in the primary CVD composite endpoint.

8.5.2 Secondary objectives

The secondary objectives are to evaluate the effect of metformin on:

- Time to event for each component of the primary composite endpoint
- All-cause mortality
- Time to non-melanoma cancer
- Death due to a non-melanoma cancer cause
- Time to incident physician-diagnosed T2DM
- Participant satisfaction with treatment (adapted DTSQ)
- Functional status (SF-8)

•Health utility (EuroQol EQ-5D)

8.5.3 Exploratory objectives

Additional objectives are to evaluate the effect of metformin treatment on:
•Time to confirmed hospital admission for congestive heart failure
•Time to confirmed hospitalisation for unstable angina
- Time to confirmed coronary, cerebrovascular or peripheral revascularization (e.g. coronary bypass graft, percutaneous intervention with balloon angioplasty or stent)
- Medical resource utilisation during the trial (e.g. hospitalisations, outpatient physician visits, medication use)

8.6 Study endpoints

8.6.1 Primary endpoint

Time from randomisation to the first confirmed CV event in the primary composite endpoint (CV mortality, nonfatal myocardial infarction or nonfatal stroke).

8.6.2 Secondary endpoint

- Time from randomisation to the first confirmed event of the individual components of the primary composite endpoint *i.e.* CV mortality, nonfatal myocardial infarction or nonfatal stroke.
- Time to any cause of death (supplied by Office of National Statistics)
- Time to first non-melanoma cancer diagnosis (supplied by National Cancer Registry)
- Time to death due to a non-melanoma cancer cause according to primary / underlying cause of death on death certificate (supplied by the Office of National Statistics)
- Physician diagnosed T2DM
- Participant satisfaction with treatment (adapted DTSQ) annually from randomisation and additionally at four months post-randomisation in the feasibility phase.
- Functional status (SF-8) annually from randomisation and additionally at four months post-randomisation in the feasibility phase.
- Health utility (EuroQol EQ-5D) annually from randomisation and additionally at four months post-randomisation in the feasibility phase.

8.6.3 Exploratory endpoints

•Time from randomisation to
  oConfirmed hospital admission for congestive heart failure
  oConfirmed hospitalisation for unstable angina
  oConfirmed coronary, cerebrovascular or peripheral revascularization
  - o Medical resource utilisation during the study (e.g. hospitalisations, outpatient physician visits, medication use) as measured by participant / GP questionnaires

9 Selection and withdrawal of participants

9.1 Inclusion Criteria

To be included in the study the participant must meet all of the following criteria:

- Understand the study procedures, alternative treatments available, and the risks involved with the study, and voluntarily agree to participate by providing written informed consent
- Age ≥ 40 years
- HbA_{1c} ≥36.6mmol/mol but <47.5mmol/mol; measured within one year prior to enrolment
- Estimated 10-year CVD risk ≥20% as assessed by the Framingham or QRISK2 scores; laboratory values used for the risk calculators should be collected no more than one year prior to enrolment.
- Estimated glomerular filtration rate (eGFR) ≥45ml/min as determined by the MDRD-4 method; measured within 6 months prior to enrolment
- Participant agrees to allow study staff to contact his or her General Practitioner and/or consultant to notify them of study participation and to obtain all medical records necessary for complete data ascertainment during the follow-up period (including recording of NHS number and access to Health Episode Statistics (HES))
- Participant agrees to be tagged for mortality with the Office for National Statistics and to be tagged for
  - Time to first non-melanoma cancer diagnosis (supplied by National Cancer Registry)
  - Death due to a non-melanoma cancer cause according to primary/underlying cause of death on death certificate (supplied by the Office of National Statistics)

9.2 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Unable to provide written consent
- Prior history of physician-diagnosed T2DM.
  NOTE: Participants with a history of gestational diabetes which resolved after pregnancy are permitted to enrol.
- Prior history of CVD, defined as:
  - myocardial infarction, surgical or percutaneous coronary revascularization procedure
  - Stroke (haemorrhagic or ischaemic)
    NOTE: Participants with prior transient ischaemic attack or unstable angina are NOT excluded and may be enrolled
- Participant has a planned or anticipated coronary revascularisation procedure within 6 months following enrolment
  NOTE: Participants with previous peripheral revascularisation procedure are NOT excluded and may be enrolled
- Participant is breastfeeding or known to be pregnant
- Participant is currently taking metformin (for any reason) or they have taken metformin in the last three months
- History of cirrhosis of the liver or other significant hepatic impairment, as assessed by medical history
- End-stage renal disease (CKD stage 3b or worse, eGFR<45ml/min)
- In the investigator's opinion, participant has a medical history that indicates a life expectancy of <2 years or might limit the individual's ability to take the study treatments for the duration of the study
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

- Participant is enrolled in or has participated within 12 weeks prior to enrolment in another experimental protocol involving the use of an investigational drug or device or an intervention that would interfere with the conduct of the study

9.3 Treatment Assignment, Randomisation Number and Method of Unblinding

A sequence of unique Randomisation Numbers will be generated for each study site by a nominated Oxford DTU statistician. This statistician (with no involvement otherwise in GLINT) will in strict confidence randomly assign treatment allocation codes for *metformin prolonged release tablets* or *placebo* 1:1 to each Randomisation Number, blocked within site. Prior to Trial Management System Database lock the Randomisation Numbers and their respective treatment allocation codes will be provided in strict confidence only to a nominated Oxford DTU senior applications programmer and to the IDMC independent statistician. The nominated programmer will store them in the encrypted Medication & Codebreak Database with access only being available for a single participant at a time and only to staff authorised to unblind assigned study medication as described in section 9.5.

A secure system will automatically produce medication distribution lists detailing which study medication packs should be sent to which participants. This system will identify from the Trial Management System Database which participants will be requiring titration or maintenance packs. It will then utilise the encrypted Medication & Codebreak Database to allocate the next available pack that has a Treatment Code which matches the Treatment Code allocated to the participant's Randomisation Number. Finally, it will access the encrypted Contact Database to acquire the participant contact details required for the mailing label.

Immediately after Trial Management System Database lock the Oxford DTU Informatics group will incorporate the treatment allocation codes into the Trial Management System Database so that unblinded data can be made available for analysis.

The Randomisation Numbers alone, *i.e.* without the treatment allocation codes, will be added to Trial Management System for allocation to participants eligible for randomisation.

9.4 Method of Blinding

The study uses a double-blind design, neither the participants nor GLINT personnel will know which treatment the participant is taking. The IMP will have the same visual appearance as the placebo.

9.5 Emergency Unblinding

The study phone line can be used to unblind participants to the randomised treatment assignment only if deemed clinically essential by those with responsibility for providing health care to the participant and the duty study clinician, that is to say in a situation in which the responsible clinician considers that the treatment received in the study needs to be identified in order to appropriately manage the participant's presenting condition. Drug identification information is to be unmasked ONLY if necessary for the welfare of the participant and will only be undertaken by those with appropriate delegated authority. All participants will be provided with a study contact card to present to any clinician that may treat them. The study card will have details of the 24 hour phone line (details of which will also be included on other key documents such as the Participant Information Leaflet). The 24 hour telephone number will be available during office hours, and by a study clinician outside of office hours, who will be able to unblind a participant if required. It is the responsibility of the Investigator or the team member

who completes the unblinding to promptly document and explain any unblinding to the Sponsor as per SOP.

The unblinding system is accessed electronically via the trial management system and can be accessed 24 hours a day. Any occurrence of an unblinding event will be recorded in the web-based electronic trial management system, which records the time, date and operator as well as the reason for unblinding, but not the allocated treatment. The study Sponsor will be informed of any unblinding occurrences. The data required to break the code are, however, stored in the separate encrypted Medication & Codebreak Database and only accessible to the site investigators or the 24 hour phone line team members.

The GLINT team at the MRC Epidemiology Unit, University of Cambridge will operate the phone line. The phone line will also be available to answer urgent clinical questions from sites concerning enrolled participants (adverse events, unblinding etc.) as well as questions to determine whether a particular participant qualifies for enrolment. Each site will have site-specific phone lines for participant queries to be manned during normal office hours.

9.6 Changes in participant study status

Optimally, all participants should remain on study treatment and follow up for the duration of the study. However, it is recognized that in rare instances a participant may temporarily or permanently discontinue study medication or participation in the study.

Discontinuations from the study occur only if the participant explicitly withdraws consent for all forms of follow up.

9.6.1 Discontinuation of study medication

Discontinuations from study treatment may occur for protocol-specified reasons (see below), due to the judgment of the primary investigator, or due to the participant's decision.

Protocol specified reasons for study drug discontinuation are:

- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures. Study drug can be resumed if the event resolves.
- Participant refuses follow up via participant annual questionnaire
- Development of chronic kidney disease (CKD stage 3b or worse, eGFR<45ml/min).
- Participant is temporarily not contactable

Participants are considered temporarily not contactable in the following situations:

- Telephone contacts are made at 4 and 8 weeks. Sites will make three attempts to call the participant during this period. After three failed call attempts the participant is lost to follow up and the drug supply is stopped.
- The participants are asked to complete and send a questionnaire at 4 months, then annually. Failure to return the questionnaire will result in a repeat issue of the questionnaire at 4 weeks after the due date and also at 8 weeks if required. Continued failure to return the questionnaire within another month results in an attempt to call the participant. After three failed call attempts the patient is lost to follow up and the drug supply is stopped.

For participants who fulfil the above criteria, attempts will be made annually to re-establish contact. If contact is re-established and the participant agrees, the drug will be re-started.

Note:
Participants who develop T2DM during the course of the study should be advised to continue taking study medication and their GP will be advised to consider adding either metformin, such that the daily dose does not exceed the permitted maximum, assuming the study medication is the active therapy (see Table 1), or an alternative glucose lowering drug if required.

GLINT study medication daily dose	Maximum additional daily amount of ***standard release metformin*** permitted	Maximum additional daily amount of ***prolonged release metformin*** permitted
500 mg (1 tablet)	2000 mg	1500 mg
1000 mg (2 tablets)	1500 mg	1000 mg
1500 mg (3 tablets)	1000 mg	500 mg

Table 1: Prescription of additional metformin for those developing T2DM during the study

Participants who become pregnant during the course of the study can continue taking study medication (28).

Participants who experience a possible CVD event during the study will be encouraged to continue taking study medication as long as there are no contraindications.

9.6.2 Staged withdrawal from study

Each participant has the right to withdraw their consent to participate at any time by informing the GLINT team in person, by telephone or in writing. However, it is expected that the investigator will make every effort to understand the participant's barriers to participation and provide reassurance, counselling, education, or other mitigation strategies as necessary.

Participants can opt to discontinue any or all of the following:

- Study medication
- Follow up via participant questionnaires
- Follow up by GP questionnaires
- Registry follow up

Withdrawal of consent is defined as an explicit withdrawal from all forms of follow up.

Any information already provided, results from tests already performed on the participant or their samples will continue to be used in the study. We will document the reasons for withdrawn consent, the attempts by the investigator to mitigate those concerns, and the methods permitted for vital status ascertainment (e.g. contact GP and ONS/NHS tagging) on the Trial Management System Database.

10 Study Treatments

10.1 Dosage schedules

10.1.1 Route of Administration and Maximum dosage allowed

Metformin comes in prolonged release tablet form for oral administration. The maximum dosage of the study medication will be 1500mg per day.

Participants that have moderate renal impairment (chronic kidney disease stage 3a estimated glomerular filtration rate [eGFR] 45-59 ml/min/1.73m^2) recorded during their participation will be recommended a maximum daily dose of 1000mg metformin prolonged release/placebo.

10.1.2 Maximum duration of treatment of a participant

This is an event driven study and the maximum duration of treatment of a participant is anticipated to be approximately 7 years.

10.1.3 Procedures for monitoring participant compliance

Participants will be instructed to bring all unused or part-used medication and packaging to both the three and six month visits, during the feasibility phase only, so that adherence can be assessed. The study medication will be returned to the participants at those visits. In addition, the four-month questionnaire in the feasibility phase and the annual questionnaire in the full study will include questions which assess compliance with study medication. Data on compliance with study medication will be reviewed during the interim analysis conducted during the feasibility phase of the study.

10.2 Presentation of the drug

One prolonged release tablet contains 500mg metformin hydrochloride corresponding to 390 mg metformin base. It is a white to off-white, capsule-shaped, biconvex tablet, debossed on one side with '500'. The placebo will be created in the image of the active product.

10.3 Known drug reactions & interaction with other therapies

Metformin is a longstanding first-line treatment for T2DM with an excellent safety record. It has also been used in at least 31 trials with 4,570 individuals at risk of developing T2DM followed for 8,267 person-years [23]. In these trials metformin has been associated with substantial beneficial effects on CVD risk factors and risk of T2DM. Refer to Section 12.2 for known drug reactions.

Therapy with metformin should be temporarily discontinued if participants become acutely ill or undergo procedures requiring general anaesthesia or use of iodine containing contrast dye. Metformin must be discontinued 48 hours prior to or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal. Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and the risk of lactic acidosis.

Alcohol consumption can increase the risk of lactic acidosis, a very rare adverse effect. In the information sheet, participants are therefore advised to avoid drinking lots of

alcohol, both regularly and in short episodes. Participants will be advised not to exceed the Government recommendations; these are 21-28 units of alcohol per week for men and 14-21 units of alcohol per week for women.

Precaution is required when combining metformin with medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and sympathomimetics). Precaution is also required when combining metformin with diuretics, especially loop diuretics. They may increase the risk of lactic acidosis due to their potential to decrease renal function.

10.4 Dosage modifications

During the treatment period, randomised participants will receive study medication by post in 16-weekly batches. For the first batch following randomisation, individuals will be advised to take 1 tablet/day (500mg metformin prolonged release/placebo) for four weeks, titrating up to 2 tablets/day for weeks 5 to 8, and 3 tablets/day thereafter. Participants will receive a phone call four and eight weeks after randomisation to confirm titration competency. Participants will have contact details of their local research team and the emergency telephone number should they have any queries or experience any serious side effects. Any participants who cannot tolerate 1500mg/day will be advised to take the highest tolerated dose, this will be determined during the titration calls and at the 3 and 6 month visits. Participants will be expected to continue taking study medication for the duration of the study.

Participants that have moderate renal impairment (chronic kidney disease stage 3a estimated glomerular filtration rate [eGFR] 45-59 ml/min/1.73m^2) recorded during their participation will be recommended a maximum daily dose of 1000mg metformin prolonged release/placebo.

During the feasibility phase, research staff will telephone the first 10 participants recruited in each site to enquire as to receipt of the study drug. The DTU will use information from these calls to monitor for any critical failures in the drug delivery process and if they occur will devise an action plan to address underlying causes.

Following completion of the feasibility phase, participants will not be asked to attend any further research visits / health assessments beyond the baseline visit, and will be followed up by post.

If the participant experiences episodes of hypoglycaemia, they will be advised to down-titrate their dose. If they continue to experience hypoglycaemic episodes they will be advised to discontinue the study medication.

10.5 Legal status of the drug

Merck Serono Ltd (Bedfont Cross, Stanwell Road, Feltham, Middlesex TW14 8NX) are the marketing authorisation holders of Metformin SR 500mg prolonged release tablets (marketing authorisation number PL 11648/0054). Glucophage SR is currently licensed for use in the treatment of type 2 diabetes mellitus in adults when dietary management and exercise alone does not result in adequate glycaemic control.

The study is being carried out under a Clinical Trial Authorisation. The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the study.

10.6 Drug storage and supply

Investigational materials for the feasibility phase will be provided by Merck Serono as Metformin prolonged release 500mg tablets and matching placebo.

The IMP will be packaged in HDPE bottles with dosing instructions and posted directly to the participants in 16-weekly batches by the drug packager. The IMP does not require any special storage conditions.

10.7 Concomitant therapy

Concomitant medications will be used at the discretion of the participant's usual care provider, who will be informed of the participant's enrolment in the study and the use of blinded study medication. Open label use of metformin is contraindicated during the study except for those participants who develop T2DM during the study where up to a maximum of 1g/day (Table 1) can be prescribed in conjunction with continued study medication.

Any current prescribed medication, other than the study medication, will be recorded at the baseline visit following information from the participant. This information will be updated following receipt of annual questionnaires sent to the participant's GP.

11 Procedures and assessments

A study flow diagram and schedule of procedures to be performed during the study is found in section 6 and Appendix 1. The intent of this large, pragmatic trial is to use routine clinical information whenever possible as an efficient strategy for protocol implementation and endpoint ascertainment.

11.1 Recruitment

Participants will be recruited via one of three complementary routes: (i) the NHS Health Checks programme; (ii) individuals participating in existing research databases held by GLINT investigators; and (iii) search of GP electronic records using risk scores to identify potentially eligible individuals.

Potential participants will be sent information about the study. They will be invited to attend a local clinical research facility or to return to their participating study practice to discuss the study and undergo eligibility assessments performed by a suitably trained and qualified member of the research team or NIHR clinical research network nurses.

11.2 Baseline visit (Visit 1)

Suitably qualified and delegated members of the study team will undertake the process of seeking informed consent from individuals who are eligible to take part in the study.

Baseline visits will last approximately one hour following standard operating procedures undertaken by trained staff. A unique participant ID number will be allocated to all individuals considered for enrolment. The following data will be collected:

1. Written informed consent
2. Socio-demographic data: age, gender, ethnicity
3. Medical history (including diabetes, CVD, cancer)
4. Biochemistry: Outstanding blood values (if not available in past 12 months), total cholesterol, LDL and HDL cholesterol, triglycerides, HbA_{1c}, creatinine (if not available in past 6 months)
5. Blood pressure (3 measures to be recorded)
6. Modelled ten-year cardiovascular risk (QRISK2 / Framingham)
7. Clinical variables: height, weight

8. Questionnaire including self-reported morbidity (CVD, cancer, T2DM), health service use in the past 12 months, and health utility (EuroQol EQ5D).
9. In addition, with consent, we will centrally store a sample of whole blood for DNA analysis, and a serum and plasma sample for biomarker analysis.

NOTE:
During the feasibility phase, additional baseline assessments are collected as described in Section 11.3.2. Baseline biochemical values should be used to assess eligibility during the feasibility phase. If baseline laboratory values reduce the CVD risk calculation to <20% and/or the HbA_{1c} <36.6mmol/mol, the participant remains eligible based on the prior risk calculation. However, if eGFR is <45ml/min or HbA_{1c} is ≥47.5mmol/mol, the participant is ineligible.

If consent is given but the participant is not eligible to take part in GLINT (following receipt of biochemistry results from the baseline visit), research samples of whole blood and serum will be destroyed. Participants will be informed that they are not eligible for GLINT. Their GP will receive the clinical results and will be informed that their patient consented to take part in the study but was not eligible following the baseline visit. Travel expenses will be reimbursed according to local site policy.

Participants meeting the eligibility criteria will be randomised *i.e.* assigned to the next in sequence Randomisation Number. For participants requiring outstanding blood test values, randomisation will be delayed until all information necessary to assess eligibility is available. A duration of approximately fourteen working days will be allowed between attendance at a baseline visit and when participants are notified whether they have been included in the study or not (following assessment of outstanding blood tests). They will be randomised to metformin or placebo which they will receive by post direct from the IMP packagers in 16-weekly batches.

Participants who have been randomised will receive a best practice leaflet describing the benefits of lifestyle changes for CVD risk reduction and their GP will be sent a letter informing them that the participant has been enrolled in the GLINT. This letter sent to the GP will include the results of the baseline CVD risk assessment, information about the safety and tolerability of metformin, and what to do should the participant develop T2DM.

11.3 Study assessments

11.3.1 Approximate timing of assessments

Week 4: Phone call
Phone call from their local site at week four after randomisation to confirm:
- Titration competency
- Adverse events

Week 8: Phone call
Phone call from their local site at week eight after randomisation to confirm:
- Titration competency
- Adverse events

3 month: Visit 2 (feasibility only)
- HbA_{1c}
- Creatinine
- Medication count

- Adverse events
- Titration competency

6 month: Visit 3 (feasibility only)

- HbA_{1c}
- Creatinine
- B12 levels, LFTs, total cholesterol, LDL and HDL cholesterol
- Medication count
- Adverse events
- Titration competency

GP/participant questionnaire Mail Out (Issued after 4 months, annually and at end of study)

Participant questionnaire

- Self reported morbidity (CVD, cancer, T2DM)
- Medication adherence
- Health service use in past 12 months
- EuroQoL EQ-5D
- Treatment satisfaction/SF-8
- Self-Adverse events

GP questionnaire

- Vital status i.e. alive or dead
- Morbidity (CVD, cancer, T2DM)
- Current prescribed medication
- Adverse events
- Whether participant has become pregnant

Participants and GPs will be instructed to return the completed questionnaires to the DTU in freepost envelopes. If necessary, reminders will be sent after 4 and 8 weeks for the annual questionnaire. Participants will be contacted by phone if they do not respond to the reminders. Annual questionnaires will not be sent within 4 weeks of the end of study questionnaires being issued.

Participants and GPs will be reminded about the potential risks of taking metformin when they receive their four month questionnaire in the feasibility phase and the annual questionnaire in the full study.

When a participant or GP indicates that a primary or secondary endpoint has occurred following receipt of the annual questionnaire, information on this event will be collected immediately. We will also use information from the Office for National Statistics, the Cancer Registry and Health Episode Statistics to assess whether participants have experienced a study endpoint.

11.3.2 Additional Information

•B12 levels, LFTs, total cholesterol, LDL and HDL cholesterol will be collected at baseline and 6 months. B12 and LFT results will be reviewed following the feasibility phase to inform a decision on whether it is necessary to include these measures in the full study.

- HbA_{1c} and serum creatinine will be collected at baseline, 3 months, and 6 months. Baseline HbA_{1c} and serum creatinine should be used for assessment of eligibility. Creatinine results will be reviewed following the feasibility phase to inform a decision whether it is necessary to centrally monitor renal function in the full study.
- Feedback about study participation, including how to optimise medication adherence, will be sought through the invitation of a subset of volunteers to participate in focus groups.
- We will use information received from the Office for National Statistics, the National Cancer Registry and Health Episode Statistics to assess clinical primary and secondary outcomes. Any events found will be added manually to the GLINT Trial Management System Database.

All participants in the feasibility phase of the study will continue into the full study and receive scheduled assessments as described in Appendix 1.

11.4 End of Study Participation

Provision of study medication will not be continued beyond the study period. After the study ends, participants should follow up with their usual care physician to determine appropriate future treatment. Participants' GPs will be made aware of their involvement in the study from the point of consent. Participants will receive an "end of study" newsletter after the end of the study. If the study finishes early, participants will receive a final annual questionnaire in addition to the "end of study" newsletter.

11.5 Schedule of Assessments

Please see Appendix 1.

12 Assessment of Safety

Oxford DTU are hosting the trial management system which will collect the information to facilitate safety reporting to the Sponsor at the agreed interval described in sections 12.5 and 12.6.

12.1 Definitions

12.1.1 Adverse event (AE)

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

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse events will be recorded from the point of informed consent, regardless of whether the participant has received a medicinal product and evaluated at local study centres by a member of the study team with appropriate clinical expertise. This includes evaluation of its seriousness, expectedness and causality.

12.1.2 Adverse Reaction to an IMP (AR)

All untoward and unintended responses to an investigational medicinal product

related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3Unexpected adverse reaction

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

When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant/event outcome or action criteria.

12.1.4Serious adverse event (SAE) or serious adverse reaction (SAR)

Any untoward event or medical occurrence that at any dose:

- Results in death,
- Is life-threatening, (**NOTE**: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events deemed significant by the investigator. **NOTE**: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

12.1.5Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information.

12.2 Reference Safety Information

For this study the Reference Safety Information is: Section 4.0 of the SmPC for Glucophage prolonged release metformin (http://www.medicines.org.uk/EMC/medicine/20952/SPC)

12.2.1Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

The common side effects of metformin include GI upset and diarrhoea. Hypoglycaemia does occur rarely and lactic acidosis is a very rare but serious adverse effect.

Evidence from participants with NDH in the DPP suggests that hypoglycaemia is not expected and serious adverse effects will be very rare [18]. GLINT participants will be

advised about the symptoms suggestive of hypoglycaemia (such as tachycardia, palpitations, shakiness, sweating, inability to concentrate, dizziness, hunger, blurred vision, obvious impairment of motor function, confusion or inappropriate behaviour which reverse after intake of carbohydrates) and how to respond. Serious hypoglycaemia (requiring the assistance of another person) will be regarded as a serious adverse event triggering the safety reporting mechanism described in section 11.5 below. Each participant will be issued with a card indicating that he/she is participating in a research study. This card will indicate the name and the phone number of the investigational site to be contacted in case of an emergency, including any episode of suspected hypoglycaemia requiring the assistance of another person. The card will also specify temporary interruption of treatment with study medication if participants undergo general anaesthesia or investigation with iodine-containing X-ray contrast media, and if participants are at risk of tissue hypoxia or sudden deterioration in renal function, for example due to severe dehydration or infection, shock, sepsis, acute heart or respiratory failure, hepatic impairment and recent myocardial infarction.

An extremely rare but potentially serious side-effect of metformin is lactic acidosis. The risk of lactic acidosis is increased among people with chronic kidney disease (CKD stage 3b or worse). Consequently, we will exclude individuals with eGFR<45ml/min and measure creatinine at baseline, three and six months in the feasibility phase. Participants' GPs will be reminded of contraindications to metformin and this rare side effect and the need to discontinue study medication in these eventualities (i) when they are informed that their participant has entered the study; (ii) at the four month questionnaire phase in the feasibility phase; and (iii) annually thereafter when receiving their questionnaire. Written reminders detailing the action to be taken by participants in the event of a severe illness, including renal failure, will be sent to participants at four month questionnaire phase in the feasibility phase and every twelve months when they receive their annual questionnaire. Any participant who develops chronic kidney disease (CKD stage 3b or worse, eGFR<45ml/min) during the study will not be offered further metformin/placebo. The mechanism for reporting and responding to potential adverse events is shown in the safety reporting section 12.4 and 12.5 below.

Chronic metformin use has been associated with Vitamin B12 deficiency [24]. Severe B12 deficiency can result in neuropathic symptoms that can be mistaken for diabetic neuropathy. However, the strength of this association has varied in epidemiologic studies and the clinical significance of mild B12 deficiency syndromes is unclear. The GLINT feasibility phase will measure B12 levels at baseline and 6 month visits. If a participant has a B12 level < 200 pg/ml the results will be reviewed by a study clinician and their GP contacted if necessary. The results will be reviewed following the feasibility phase to inform a decision whether it is necessary to continue monitoring B12 levels in the full study.

12.3 Expected Adverse Events / Serious Adverse Events (AE / SAE)

Expected events, which may or may not fulfil the criteria for serious are listed in Appendix 2 (Modified safety reporting). Any events, that occur, that meet serious criteria, which are not listed in Appendix 2, will also be collected and reported.

12.4 Recording and evaluation of adverse events

Non-serious Adverse Events
AEs will only be recorded if they result in cessation of the drug and the event is considered related to the drug.

The following information will be recorded: description of event, date of onset, dosage and any required changes, assessment of seriousness, assessment of expectedness, relevant medical history, concomitant medications, causality assessment and resolution/outcome.

Serious Adverse Events All events that fulfil the criteria for serious will be collected and reported, however those detailed in Appendix 2 will be subject to a modified safety reporting plan. These events include (1) Primary and secondary study endpoints, (2) Other cardiovascular events of interest (that may be associated with the primary CV endpoints and are included among items that will be sent for review by the CEC), (3) other non-cardiovascular events of interest (e.g. incident cancer, incident T2DM), (4) known common toxicities of metformin.

Any SAE which is not listed in appendix 2 will be recorded using the AE/SAE eCRF.

12.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be study drug related
Definitely, Probable and Possible causalities are considered to be study drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the study and meets the criteria for reporting or recording in the appropriate section of the CRF.

12.4.3 Recording of adverse events

Adverse events and adverse reactions may be recorded either in the participants medical notes, directly into the eCRF (which is considered source data) or via a questionnaire.

12.5 Reporting serious adverse events

All serious adverse events are recorded in the eCRF through one of three paths:

- Direct participant contact with their study centre
  Participants will be instructed to contact their study centre if they have any serious illness, a hypoglycaemic event that required the assistance of another person, are admitted to hospital for any reason, or discontinue their drug. Study centre staff will conduct a telephone interview to establish the participant's status and record any relevant clinical and safety data. If the centre staff have any concerns about the participant's status they will instruct the participant to contact their GP.
- Questionnaires (Month 4 & Annually thereafter)
  The participant will receive an annual questionnaire that includes questions to capture safety and all relevant clinical data. This is returned by post to the DTU. Participants' GPs will also complete a similar questionnaire, which will also be mailed to the DTU, along with any relevant supporting documentation. Should any further data be required in addition to the questionnaires, the study staff will contact the participant and/or the participant's GP.
- Registry reports (*e.g.* HES)
  Periodic reports will be sourced from national registries/databases. Identified SAEs will be entered to the trial database by Cambridge study team.

The Cambridge study team receive immediate notification by email that an SAE has been recorded in the trial eCRF and will ensure the event is reported within the appropriate timelines (see appendix 2 – Modified safety reporting).

In the event that a participant contacts the study staff and immediate eCRF data entry is not possible an SAE form can be faxed or emailed to the Cambridge study team to ensure reporting timelines can be met.

For serious adverse events reported via direct participant contact to site staff, the 24 hour clock starts at the time of contact. The site will enter the event via the eCRF immediately.

For serious adverse events identified by questionnaires and national registries/databases the 24 hour clock starts at the time data review identifies a reportable event

12.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned study, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 12. 2 for the Reference Safety Information to be used in this study.
All SUSARS will be reported in an expedited manner.

12.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator.
The Chief Investigator must report all the relevant safety information previously

described, to the:
- Sponsor,
- Competent authorities in the concerned member states (eg MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.6.1 When to report?

12.6.1.1 Fatal or life-threatening SUSARs

All parties listed in 12.6.1 must be notified as soon as possible but no later than **7 calendar days** after the GLINT team has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

12.6.1.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 11.7.1 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

12.6.2 How to report?

12.6.2.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product,
b) an identifiable subject (e.g. participant code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,

and, when available and applicable:
- a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's protocol code number)
- a unique case identification (i.e. sponsor's case identification number).

12.6.2.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

12.6.2.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority

should be adhered to.

12.7 Pregnancy Reporting

The occurrence of pregnancy in participants during the study should be reported to the Chief Investigator and the Sponsor within 14 days of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

13 Evaluation of Results (Definitions and response / evaluation of endpoints)

Study endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. These definitions will be provided in an endpoint ascertainment manual for the Clinical Events Classification Committee (CEC). Participants and their GPs will be surveyed annually regarding procedures and hospitalisations which have taken place between study contacts. We may also conduct electronic READ code searches in participant GP records to search for relevant clinical outcomes. Medical records pertaining to hospitalisations and procedures of interest will be obtained and thoroughly reviewed in order to determine whether an event of significance has occurred. HES data will also be accessed to provide evidence for potential endpoints. This information will be collated and anonymised in an 'endpoint pack' and sent to the CEC for review.

Events included in the primary composite outcome, all-cause mortality, hospitalisations for heart failure and unstable angina, and coronary, cerebrovascular or peripheral revascularisations will be adjudicated by the CEC blinded to study treatment.

14 Storage and Analysis of Samples

Samples will be collected for immediate and future biomarker measurements. Fresh blood samples will be sent to local NHS clinical biochemistry laboratories for the measurement of standard clinical blood tests. Additional research samples will be collected and stored for genetic and other biomarker work. The research samples will be stored in a -80^{o}C freezer. All samples will be logged into a central database and will be stored at either access controlled local sites or in an off-site Human Tissue Authority licenced facility. All stored samples will be link anonymised.

15 Statistics

15.1 Statistical methods

Analysis of primary endpoint in the full study
The primary endpoint is a time-to-event variable indicating whether or not each participant experienced any of the following events as verified by the study endpoint committee: CV mortality, non-fatal myocardial infarction or non-fatal stroke. The number and percentage of individuals experiencing the endpoint will be presented, by randomised group, along with the median and inter-quartile range of the time to event/censoring. The cumulative incidence of the endpoint, by randomised group, will be estimated using the method described by Gooley [25] and plotted.

A Cox regression model, with time since randomisation as the underlying timescale, will be used to estimate the hazard ratio, 95% confidence interval and p-value for the comparison of the metformin group with the placebo group. The assumption of proportional hazards will be tested by including a parameter for randomised group x time interaction in the Cox regression model, as well as by checking Schoenfeld

residuals, and using 2 standard graphical checks which will be described in the Statistical Analysis Plan. If these tests and graphical checks provide strong evidence against the proportional hazards assumption, then alternative modelling approaches will be considered; these will be outlined in the Statistical Analysis Plan.

Each of the individual components of the primary endpoint, i.e. CV mortality, non-fatal MI, and non-fatal stroke will be analysed separately using the same method described above, although no p-values will be calculated in these analyses.

For the analysis of the primary efficacy endpoint in the full study, a 2-sided p-value < 5% will be considered statistically significant.

Analysis of secondary and exploratory endpoints in full study
Secondary and exploratory endpoints defined in section 8.6.2 and 8.6.3 will be analysed using the same approach described for the primary endpoint, giving hazard ratios and 95% confidence intervals; however, no p-values will be calculated in these analyses. Where no "time to event" data are available, binomial regression will be used.

15.2 Interim analyses

The analysis of the feasibility phase will be descriptive; no p-values will be calculated. The analysis will be conducted after 250 participants have been randomised. The interim analysis will include presentation of the following information, separately by randomised group:

- Number and percentage of individuals recruited via each of the 3 recruitment strategies.
- Summaries of baseline characteristics of recruited participants; these summaries will be means and standard deviations for continuous variables with a reasonably symmetric distribution, medians and interquartile ranges for continuous variables with a skewed distribution, and frequencies and percentages for categorical variables.
- Baseline estimate of future cardiovascular risk using Framingham risk equations
- Compliance with study medication.
- Creatinine and HbA_{1c} values at 0, 3 and 6 months; B12 and LFT values at 0 and 6 months

Success of the feasibility phase, e.g. examination of the parameters outlined above, will determine if we proceed to the full study (subject to appropriate funding). It is anticipated that the full study will commence no more than 2.5 years (30 months) after the start of the feasibility phase. This allows sufficient time for analysis to test the model is viable and to roll out the study to the additional regions.

15.3 Number of participants to be enrolled

For the feasibility phase: It is not appropriate to estimate power in a feasibility phase when the aims are to assess study feasibility rather than to demonstrate a treatment effect. However, it is possible to determine the precision with which certain parameters can be estimated, based on a sample size of 250 individuals:

Expected recruitment rate via vascular checks programme: based on data from ADDITION-Leicester, this was 20%. With 250 individuals the 95% confidence interval around an estimate of 20% would be from 15% to 26%. However, this trial required an OGTT, so may be an underestimate of what could be expected in GLINT (which does not require fasting or an OGTT). If instead the recruitment rate were 50%, the 95% confidence interval around this estimate would be from 44% to 56%.

Expected recruitment rate directly from participating general practices: based on data from ADDITION-Cambridge, this was 74%. With 250 individuals the 95% confidence interval around an estimate of 74% would be from 68% to 79%.

Expected modelled risk: based on data from EPIC-Norfolk, this was 2.2% per year. With 250 individuals the 95% confidence interval around an estimate of 2.2% would be from 0.9% to 5.2%.

Expected adherence to IMP: based on data from the DPP, this was 80%. With 250 individuals the 95% confidence interval around an estimate of 80% would be from 74% to 85%.

For the full study: EPIC-Norfolk data suggests that 10% of individuals screened by the NHS checks programme will have a CVD risk >20%, an HbA_{1c} of 36.6 and 47.5mmol/mol, and an annual CVD event rate of 2.2%. We have considered the estimated event rate in our study in light of currently declining CVD rates. The estimate from EPIC-Norfolk is relatively low as the Standardised Mortality Ratio in this region is 94 and the cohort appears to exhibit the 'healthy volunteer effect'. As GLINT will recruit a significant proportion of people from black and minority ethnic groups and individuals from a part of the UK with higher CVD event rates (for example Scotland for the full study and East Midlands for the feasibility study), we believe our estimate is conservative and protects this study from a low event rate due to a secular decline in CVD. If 25% agree to participate, and 16% are lost to follow-up, we require 1,046 confirmed primary events to detect a treatment difference. We therefore need 515,920 individuals to be screened and 12,898 participants randomised to detect a 17% CVD relative risk reduction (85% power, p=0.05). Treatment effect is estimated from observed CVD risk reductions in T2DM (15-30% [6, 26, 27]) and expected CVD risk reductions (9-13%) due to changes in HbA_{1c}, BMI, lipids, and blood pressure among people with non-diabetic hyperglycaemia.[23] A lesser treatment effect might become unattractive from clinical and health economic perspectives. For example, a relative risk reduction of less than 17% would mean that more than 59 individuals would need to be treated for 5-years to prevent one CVD event.

15.4 Criteria for the premature termination of the study

The stopping guideline to be included in the IDMC charter will detail when they might recommend premature termination of the study to the Trial Steering Committee. The IDMC charter will be filed in the TMF. The specific roles of the IDMC is to perform an interim review of the study's progress including updated figures on recruitment, data quality, adherence to protocol treatment and follow-up, and main outcomes and safety data.

15.5 Procedure to account for missing or spurious data

In the analysis of the efficacy endpoints of the full study, participants who are lost to follow-up will be censored at their last known follow-up time.

15.6 Procedures for reporting any deviation(s) from the original statistical plan

A Statistical Analysis Plan describing the details of the proposed analyses of the full study will be written and reviewed by members of the MRC Biostatistics Hub in Trials Methodology Research based in Cambridge as well as the TSC, before publication on the study and ISRCTN websites prior to unblinding. Any subsequent deviations from this plan will be reported in the publication describing the results from the study.

15.7 Inclusion in the analysis

The primary analysis of this endpoint will be based on an intention to treat population, which includes all participants in the group to which they were randomised. A secondary analysis will be performed in a per-protocol population which will be defined prior to Trial Management System Database lock.

15.8 Health economic analysis

The economic evaluation will be conducted from the health care perspective in the first instance. To assess resource use in primary care, outpatient settings, hospitalisations, and prescribed regular and occasional-use medications, participants and GPs will be sent annual postal questionnaires. Medication use will also be collected at baseline. Unit costs will be applied to the reported resource use volumes, using unit costs obtained from standard national sources including Department of Health Reference Costs, the British National Formulary and Personal Social Services Research Unit (PPSRU) Costs.

Effectiveness will be measured by 1) the primary endpoint of cardiovascular mortality or morbidity, non-fatal myocardial infarction or stroke; and 2) quality adjusted life years. These will be measured and reported over the 5 years of the follow-up period and extrapolated in a long-term (lifetime) analysis. Incremental cost-effectiveness will be reported for each measure of effectiveness and for each time horizon.

Mean costs and effects, mean differences between the study groups, and incremental cost-effectiveness ratios and net benefit statistics will be reported. Parametric and non-parametric measures of uncertainty around each of these will be reported as appropriate. Results will be also presented in the form of cost-effectiveness planes and cost-effectiveness acceptability curves showing the probabilities that treatment with metformin is cost-effective compared with placebo at a range of willingness to pay thresholds. Sensitivity analyses will be undertaken to explore the effect on the results of different discount rates, future drug prices, and factors that may affect the generalisability of the study results.

The precise form of the extrapolation model will be explored during the feasibility phase and the early phases of the full study if it proceeds. Several well-validated models are available for cardiovascular disease and for diagnosed T2DM, including the UKPDS Outcomes Model 39 but not for people with non-diabetic hyperglycaemia, and model estimation and development will be required to link the GLINT population into existing disease models, and into existing screening models to inform decisions about population-based screening for CVD risk and individuals at high risk of developing T2DM.

15.9 Definition of the end of the study

The end of the full study will be the date when the final participant and GP questionnaires have been received for data entry. The date of the last point of contact will be the date of censor for participants who do not return a questionnaire.

16 Data handling and record keeping

16.1 Trial Master File

The Trial Master File (TMF) will be located at the MRC Epidemiology Unit, Cambridge Biomedical Campus in Cambridge and the other investigator sites will have Investigator Site Files (ISF). All essential documents to demonstrate the compliance of the study and study personnel with the conditions and principles of GCP and all applicable regulatory requirements will be stored in the Trial Master Files.

16.2 Source Data

Study data will include data collected as part of the NHS Health Checks programme, data held in the existing research registries and data held in the databases of participating general practices. These source data will be entered into the eCRF by the research team at each site. For any data acquired that is entered directly into the eCRF, the eCRF will be considered as the source data. Consent forms and any outstanding tests required to confirm eligibility will be completed at the recruitment site. Data from annual questionnaires sent to participants and GPs will be entered into the eCRF by the study personnel at the DTU. Further data on potential CVD events will be collected by the study coordinators from GP and hospital records where necessary. These may include, but are not limited to, discharge summaries, ECGs, laboratory results, clinical charts, pharmacy records, and correspondence (collected from medical notes).

All documents will be stored safely in confidential conditions. Where possible, on study - specific documents, the participant will be referred to by the study participant number, not by name. However, for some documents e.g. signed consent, participant and GP questionnaires, repeat prescription forms, the participant will be referred to by their name.

16.3 Data Protection & Patient Confidentiality

Local databases will be used to identify and recruit potential participants. Thereafter participants will be randomised and all study data will be entered into a Trial Management System Database using InferMed Macro software and validation procedures. Participants will be identified throughout by a study specific unique Participant ID number. A separate encrypted participant Contact Database will be used to store participant names, addresses, NHS numbers and other identifying details required for drug distribution. Access to the participant Contact Database will be restricted to the secure computer system used to facilitate distribution of the study medication, and Informatics personnel not otherwise involved in GLINT who can amend the details where changes are required.

Local sites will store source data for each participant. This will be labelled with the participant's study number, initials and date of birth. Data will include the original signed and dated consent form, the results of any laboratory tests or procedures carried out and any additional documentation obtained to support events reported in the annual questionnaires.

The eCRF will also be considered source data for any data obtained from the participant during the baseline visits that is immediately entered onto the eCRF. Table 2 lists what data and the source from where it is to be obtained.

Data	**Source**
Consent	Consent form
Medical screening	eCRF
Socio-demographic	eCRF
Height	eCRF
Weight	eCRF
BMI	eCRF
BP	eCRF
Qualifying labs	Source database

Lab results	Biochemistry output (varying at different sites)
Drug accountability	eCRF/questionnaire (depending on time point in study)
Drug satisfaction	Participant Questionnaire
Participant reported CV events	Participant Questionnaire
Participant reported cancer events	Participant Questionnaire
Participant reported diabetes	Participant Questionnaire
EQ5D	Participant Questionnaire
SF8	Participant Questionnaire
HERC	Participant Questionnaire
GP reported events	GP Questionnaire
Pregnancy	GP Questionnaire
Medication list	eCRF
AE/SAE form	eCRF or paper CRF

Table 2: Source of data

Source documents for other data points will be kept in local coordinating centres and entered onto the eCRF by the study coordinator. The DTU will send out the annual questionnaires to the participants and their GPs and enter the data on receipt of the completed documents.

GLINT staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant ID number on the CRF and Trial Management System Database. Consent forms, GP questionnaires and participant questionnaires will contain participant names. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.
All investigators and study site staff involved in this study must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

17 Study Committees

17.1 Trial Steering Committee

The GLINT Trial Steering Committee (TSC) will have responsibility for the oversight of the study (Figure 1). The TSC will consist of nine individuals, comprising three senior independent academic representatives who are experts in their field (one of whom will chair the committee), four GLINT PIs, one lay representative and a Sponsor representative. A TSC charter will delineate operating procedures. The TSC is the main decision-making body for GLINT and is charged with the overall scientific, professional, and operational conduct of the study. The primary functions of the TSC are to:

1. Review and approve the study protocol and all protocol amendments.
2. Supervise the conduct of the study in accordance with its responsibilities described in the study protocol.
3. Review and approve the Statistical Analysis Plan.
4. Oversee all study subcommittees, including but not limited to:
    - Clinical endpoint committee
    - Data monitoring and ethics committee

- Operational committee

5. Review and consider recommendations from the IDMC
6. The TSC will determine the time to terminate the study, based on recommendations from the IDMC and other available information. The TSC may also find it necessary to terminate the study under certain circumstances, including but not limited to the following reasons:

- Animal, human or toxicological test results, in the reasonable determination of the TSC, support termination of the study
- Ethical or participant safety issues occur that the TSC feels support termination of the study
- Extraordinary scientific, regulatory or other events that negatively impact the rationale for the study such that the TSC agrees it is appropriate to terminate the study

7. Review all sub-study requests and approve where appropriate.
8. Consider, authorise as appropriate and prioritise requests for access to GLINT study data and genetic samples for academic or other collaborations. After the TSC disbands, the MRC Epidemiology Unit, DTU and the sponsor will assume this responsibility.
9. Approve the communication strategy on how to best communicate information about the progress of the study.
10. Ensure accurate, uniform, timely, and high quality reporting of the full study and all approved sub-studies.
11. All members of the TSC will have access, in confidence to the draft manuscript describing the primary results paper.

17.2 Operational Committee

The OC is composed of Centre Leads selected by the TSC from investigators in each centre with appropriate clinical trial experience. The OC will be co-chaired by representatives from the MRC Epidemiology Unit and the DTU. The primary role of the OC is to serve as the interface between the TSC and the study sites. Committee members will be instrumental in serving as ambassadors of the study to encourage recruitment as well as ensure study compliance by working with study personnel and mediating in centre-specific issues. The committee will provide a means of transmitting any identified needs, concerns, or suggestions from the sites to the TSC and assist in disseminating clinical or operational information to the sites. The functions and operating procedures of the OC are delineated in a charter. Specific functions of the OC will include the following:

1. All members will serve as advocates for the study.
2. Centre Leads will:
    - Communicate with investigators in their respective centres to review centre-specific progress reports, including but not limited to recruitment/retention of participants, event reporting and data collection, and communication between sites and usual care providers.
    - Communicate with investigators in their respective centres to review and attempt to resolve any operational issues raised by their centre
3. Committee Co-Chairs will:
    - Compile centre-specific performance metrics for presentation to the TSC
    - Liaise with Centre Leads, academic coordinating centres (MRC Epidemiology Unit and DTU project teams), and sponsor to implement study policies.

17.3 Independent Data Monitoring Committee

The IDMC will be composed of five senior academic individuals, including the IDMC Chair. There will be at least one member with expertise for each of cardiology, endocrinology, and oncology, and an Independent Statistician (not affiliated to the MRC

Epidemiology Unit, DTU, or the Sponsor) and a Sponsor representative. All of these individuals will have long-standing experience in the operational, medical, and biostatistical aspects of clinical trials. The MRC Epidemiology Unit senior statistician assigned to GLINT will oversee the provision of interim masked data sets for use by the IDMC and the MRC Epidemiology / DTU study coordinating centres. DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the IDMC, using treatment codes provided in advance by the Informatics Group at the DTU. During the Open Session of the IDMC meetings, representatives of the TSC may present updates on the study status or the safety profile of metformin, but will not be privy to discussions of the unmasked data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the IDMC while the study is ongoing.

During the feasibility phase, the IDMC will meet after 250 participants have been recruited, and will report to the TSC before the full study commences. Thereafter, the IDMC will meet every six months during the full study.

The IDMC will be responsible for the interests of the participants and, to this end, will undertake regular reviews of the safety data (including SAEs). The IDMC will have access to an agreed subset of the study data as listed in the IDMC charter (updated as necessary during the study) in an unblinded fashion throughout the study duration. In addition, the IDMC will evaluate interim analyses of the data every six months, or on an ad hoc basis if needed, to determine if it believes either the study should be terminated early because the metformin arm (with respect to the placebo arm) demonstrates (a) clear inferiority, i.e., it is not in participant's best interest to continue taking blinded therapy; or (b) clear superiority, i.e., it is not in participant's best interest to continue taking blinded placebo. If the IDMC finds it necessary to recommend actions regarding interruption of the study or changes to the protocol based on medical rationale that would make it unethical to continue the study in its present form, those recommendations will be forwarded to the TSC. The details of the IDMC's functions and the early stopping rules will be delineated in a separate IDMC charter.

17.4 Clinical Events Committee (CEC)

The events which constitute the principal endpoints of this study will be adjudicated by an independent CEC, coordinated through the MRC Epidemiology Unit, which will include at least two clinically qualified members. The specific endpoints to be adjudicated include: CV mortality, nonfatal myocardial infarction, nonfatal stroke, all-cause mortality, hospital admission for congestive heart failure, hospitalisation for unstable angina; coronary, cerebrovascular or peripheral revascularization. Clinicians will review study data and efficacy endpoints using pre-specified criteria and definitions. The CEC will be blinded to the assigned study drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.

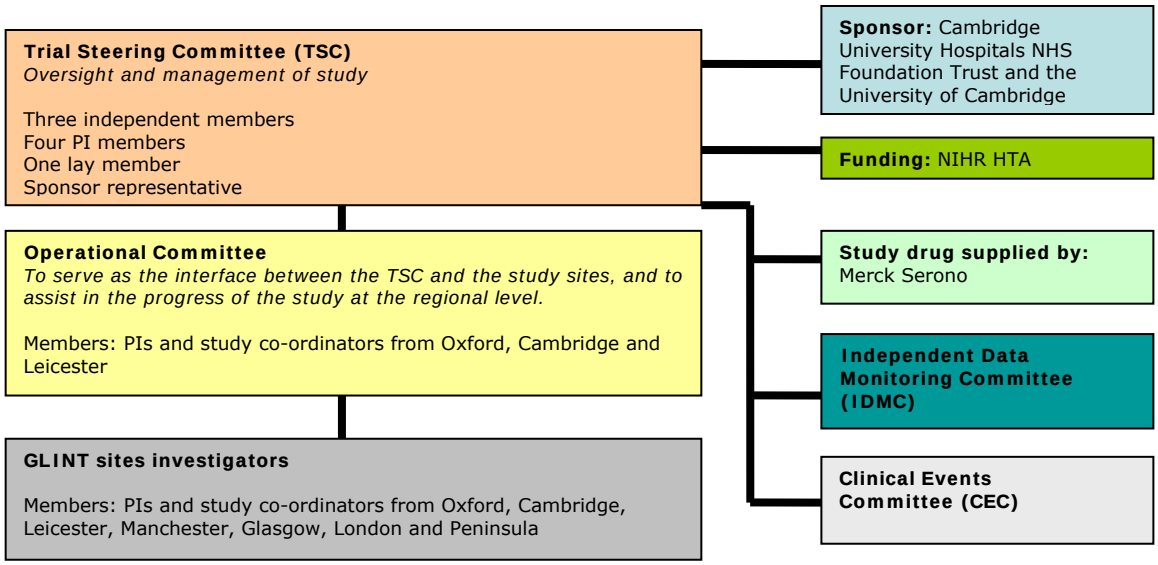


Figure 1: GLINT governance structure

18 Ethical & Regulatory considerations

The conduct of the study will be monitored by a steering committee including independent members and a lay member. See also Section 17 above, which outlines IDMC responsibilities during the full study.

18.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that each study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with their participation. The informed consent form used for this study and any change made during the course of this study, must be prospectively approved by the REC. The investigator will retain the original of each participants signed informed consent form.

For the purposes of this study we will only include participants with a good written and verbal understanding of the English language.

We will ask all potential participants to provide written informed consent in order to be recruited to the study, and to allow access to information contained in medical records for responsible members of the GLINT team. In addition, we will request informed consent to monitor participants' vital status (dead/alive) and collect information on potential endpoints using data from ONS and the Information Services Division of the Scottish Government, the National Cancer Registry, HES, from their GP, the NHS tracking system, and share contact details with authorised third parties for the dispatch of study medication.

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks

involved in taking part. The details of the study will verbally communicated to the participants during the informed consent procedure by a trained member of staff. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be sent an information sheet and consent form at least one week in advance of their recruitment visit to consider the study information. They will be given an opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The staff member taking consent will ensure that the participant has read and understood the information sheet prior to taking consent. We will not include people with an impaired ability to give consent to the study.

Written informed consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed informed consent will be given to the participants. The original signed form will be retained at the study site.

Consent will also be sought from study participants to store whole blood samples for future DNA analyses and a serum sample for biomarker analyses. All samples will be stored by the MRC Epidemiology Unit, University of Cambridge.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the study will be communicated to the participant as soon as possible by the required means (i.e. phone, email or post) details may also be communicated on the study website.

18.2 Ethical committee review

The protocol, informed consent form, participant information leaflet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA), and host institution(s) for written approval.

Before the start of the study or implementation of any amendment we will obtain approval of the study protocol, protocol amendments, informed consent forms and other relevant documents e.g. advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.3 Regulatory Compliance

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

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the REC and/or MHRA approval has been obtained. Participants would be notified in writing in the event of an urgent safety measure.

18.5 Peer Review

The study protocol was reviewed by the funders of the study – the National Institute for Health research HTA programme.

18.6 Declaration of Helsinki and Good Clinical Practice

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.7 GCP Training

All GLINT staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with your Trust's policy.

19 Sponsorship, Financial and Insurance

The study will be sponsored by the Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study will be funded by National Institute for Health Research – Health Technology Assessment Programme (09/01/48).

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the study caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the study, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

20 Monitoring, Audit & Inspection

The investigator must make all study documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the study documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the study. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the study. Throughout the course of the study, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Monitoring will be performed according to GCP. It is planned to do 100% SDV on the first 5 participants at any site. The frequency of any additional on-site monitoring will be informed by the data quality found at site and risk assessment undertaken by the sponsor. If data quality is not an issue, further on-site visits will be performed on an annual basis. To optimise resources, GLINT personnel from one site will conduct the on-site monitoring visits at another site. If there are issues with data quality the site in question will be required to complete a remedial action plan and will be re-monitored after an additional five participants.

Additional data monitoring will be carried out through data checks generated automatically through the Trial Management System Database e.g. validation data item checks which will be addressed by the study coordinators at site. Resolution of questionnaire data queries generated by the Trial Management System Database will be managed by coordinating centre clinicians/ study coordinators.

Monitoring reports will be reviewed in accordance with Sponsor SOPs.

21 Protocol Compliance and Breaches of GCP

GLINT will be conducted in accordance with the current approved protocol, with the conditions and principles of GCP, relevant regulations and standard operating procedures. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect 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".

In the event that a serious breach is suspected the Sponsor should be informed within 24 hours.

22 Publications policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, and any other publications arising from the study. PIs will have final sign off on press releases. Authors will acknowledge that the study was "Funded by the NIHR Health Technology Assessment Programme". Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

GLINT participants will be informed of the outcome of the study via a newsletter.

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24 Appendices

24.1 Appendix 1 Schedule of procedures

	Recruitment	Visit 1 Baseline (day 0) [2]	4 wks	8 wks	Visit 2 3 month visit*	4 month mail-out*	Visit 3 6 month visit*	Annual GP / participant questionnaire [6]	End of study / early termination
Demographic information (DOB, sex, ethnicity)	X	X							
Medical history information (including diabetes, CVD, cancer)	X	X							
Biochemistry: HbA_{1c}, TC, LDL, HDL, triglycerides		X (if value n/a in past 12 months)			X		X		
Biochemistry: Creatinine		X (if value n/a in past 6 months)			X		X		
Blood pressure		X							
Modelled ten-year cardiovascular risk (QRISK2/Framingham)		X (if value n/a in past 12 months)							
Anthropometry: height, weight		X							
Informed consent and stored blood sample authorisation		X							
Randomisation		X [3]							
If consent obtained, a whole blood sample will be taken for storage for future DNA analysis, and a serum and plasma sample for biomarker analyses		X							
Letter / lifestyle booklet / emergency card sent to participant if inclusion criteria met; letter sent to GP informing them individual is in study		X							
Drug dispensation		X [4,5]							
Phone call to check titration competency and adverse events			X	X					
Feasibility phase									
HbA_{1c}, creatinine		X [7]			X		X		
B12 levels, LFTs, total cholesterol, LDL and HDL cholesterol		X [7]					X		

	Recruitment	Visit 1 Baseline (day 0) [2]	4 wks	8 wks	Visit 2 3 month visit*	4 month mail-out*	Visit 3 6 month visit*	Annual GP / participant questionnaire [6]	End of study / early termination
Medication count					X		X		
Questionnaire sent to participant / GP						X			
Participant questionnaire									
Self-reported morbidity (CVD, cancer, T2DM)		X				X		X	X
Medication adherence						X		X	X
Health service use in past 12 months (adapted from HERC questionnaire)		X				X		X	X
EuroQol EQ-5D		X				X		X	X
Treatment satisfaction / SF-8						X		X	X
Adverse events / side-effects					X	X	X	X	X
GP questionnaire									
Vital status						X		X	X
Morbidity (CVD, cancer, T2DM)						X		X	X
Current prescribed medication						X		X	X
Adverse events						X		X	X
Whether participant has become pregnant						X		X	X
Endpoint ascertainment									
ONS/national registry tagging for ICD-10 coded mortality		X							
National cancer registry tagging		X							
Hospital Episode Statistics		X							

[1] Potential recruiting routes: Individual is flagged by NHS Health Checks as (potentially) meeting inclusion criteria; Individual is identified by research database as (potentially) meeting inclusion criteria; Individual is identified by GP records as (potentially) meeting inclusion criteria
[2] Visits 1 and 2 may be, but are not required, to be performed on the same day
[3] Randomisation may be delayed up to 14 working days if complete data to assess eligibility is not available at visit 1.
[4] Participant receives batch of metformin / placebo every 16 weeks
[5] Participants who terminate study medication will continue to be observed and sent annual questionnaires according to their planned schedule for the remainder of the study.
[6] Reminders about postal questionnaires to be sent 4 and 8 weeks after initial posting; annual questionnaires to continue until study closeout
[7] During the feasibility phase, these measures will be taken for all participants at the recruitment visit
*these measures will only be taken in the feasibility phase of the study

24.2 Appendix 2 Modified Safety Reporting

All SAEs listed below are exempted from routine SAE reporting. However they will be assessed for relatedness to the study drug and if the event is considered related and not expected *i.e.* it is a SUSAR it will be reported in an expedited manner.

All SAEs not listed below will be reported as per standard guidelines and processes. In addition a quarterly line listing of these SAEs will be submitted to the sponsor.

1.Primary and secondary study endpoints
These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification (CEC) charter:
-Cardiovascular (CV) death e.g. fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention
-Non-fatal MI
-Acute coronary syndrome
-Non-fatal CVA
-CHF requiring hospitalization
-Unstable angina requiring hospitalization
-All cause mortality

2.Other Cardiovascular Events of Interest
-Atrial fibrillation/Atrial flutter
-Ventricular fibrillation/tachycardia requiring intervention
-Deep Vein Thrombosis (DVT)
-Pulmonary embolism
-Percutaneous Coronary Intervention (PCI) – (including non-serious events)
-Coronary Artery Bypass Graft (CABG)
-Coronary catheterization
-Stress test (including non-serious events)
-Abdominal aortic aneurysm/repair
-Carotid endarterectomy/ carotid angioplasty and/or stenting
- Any hospitalization due to cardiovascular events (i.e., whether or not the hospitalisation was for an obvious study endpoint)
-Shock/hypotension
-Accelerated or malignant hypertension/hypertensive urgency
-Transient Ischemic Attack (TIA)
-Syncope
-Renal artery angioplasty and/or stenting
-Other arterial angioplasty and/or stenting

3.Non-cardiovascular events of interest
Any non-melanoma incident cancer
Any non-melanoma recurrent cancer
Death due to cancer (any non-melanoma type)
Physician diagnosed T2DM

4.Known adverse reactions of metformin
-GI upset / diarrhoea
-Hypoglycaemia

Appendix 2 Modified Safety Reporting Flowchart