Are you at risk of having a heart attack or stroke?

You may be eligible to participate in a research study looking at treatment to prevent heart attack and stroke.

GLINT

1. Why have I been invited to take part in GLINT?

You have been invited because:

You have some or all of the following risk factors which put you at increased risk of having a heart attack or stroke:

- Aged 40 years old and above
- Higher than normal blood sugar (glucose) levels
- Other risk factors such as raised blood pressure, raised cholesterol or being overweight, which means that your risk of having a heart attack or stroke in the next ten years is over 20% (1 in 5 chance).

2. Is is possible to reduce the risk of having a heart attack or stroke?

This is a very important question with a very important answer – yes there is! The good news is that everyone at risk of having a heart attack or stroke can do things to keep healthy and reduce the risk of developing serious disease. Lifestyle changes are effective in reducing your risk. There are also a number of medications that can help reduce this risk. We already know that lowering blood pressure or blood cholesterol with medication reduces the risk of having a heart attack or stroke in the future.

3. What is the purpose of the GLINT study?

We want to test whether a medication to lower blood sugar (glucose) levels can also reduce the risk of experiencing a heart attack or stroke.

Metformin has been safely used as a first line tablet treatment for type 2 diabetes for several decades. Metformin works by decreasing blood sugar (glucose), and has been shown to reduce the risk of heart attacks and strokes by around 30% in people with type 2 diabetes. There is also some evidence that metformin may reduce the risk of some cancers

This study will test whether early treatment with metformin reduces the risk of developing heart attacks, strokes and cancer in people who do not have diabetes but have high blood sugar levels and above-average risk of heart attacks and strokes.

The study will take five to seven years to complete.

4. How is the GLINT study going to answer this question?

We are going to compare two different groups. Entry to these groups is random – you or the study team cannot choose which group you are and will not know which medication you will receive.

Everyone participating in the study returns to a follow up visit at three and six months after their first initial screening visit to monitor how they are getting on with the medication. We also write to you every year for the duration of the study (5 to 7 years) and ask you to complete a questionnaire.

Group 1 This group will receive placebo medication. A placebo is sometimes called the "dummy pill". Your medication will be sent to you in the post. Every 16 weeks you will receive a new package of your study medication via post for the duration of the study.
Group 2 This group will receive metformin. Your medication will be sent to you in the post. Every 16 weeks you will receive a new package of your study medication via post for the duration of the study.

Both groups will also receive a booklet including information about how to reduce your risk of developing a heart attack or stroke.

5. If you agree to participate in this study, you need to attend an initial screening visit.

At your first visit with the study team, you will have a blood test to measure the amount of sugar (glucose) and fat (cholesterol) in your blood, and the health of your kidneys and liver. We do this initial blood test to:

- Check that you DO NOT have diabetes
- Check that you DO have higher than normal blood sugar levels
- Check if your risk of having a heart attack or stroke in the next ten years is over 20%

If you meet these criteria you are eligible to enter the main study.

6. What does the main study involve? You will need to:

- Be able to attend three clinical visits over six months. The first lasts approximately 60 minutes and the 3 and 6 month visits last approximately 30 minutes each.
- Be able to regularly take the medication allocated to you for five to seven years.

7. Benefit of participating in GLINT

There is no guarantee that you will benefit from taking part in this study. However, all people taking part in the study receive information about reducing their risk of developing a heart attack or stroke. Your GP will also be given the results of your blood tests (such as blood glucose and cholesterol levels), and other measurements such as blood pressure. This will help them keep track of your health status and advice about other possible treatment.

Information collected as part of your participation in this study may benefit people like you with higher than normal levels of blood sugar (glucose).

8. What should I do if I want to participate in GLINT or learn more about the study?

If you wish to learn more about taking part in the study, please complete the reply slip and return this to the study team.

We will then send you a full Patient Information Sheet which aims to answer questions you may have about the study. You may wish to keep it for reference later. If you do not have a reply slip, or have anything you wish to ask the study team, please contact us and we will be happy to help.

You can contact the GLINT team on XXXX XXX XXXX during office hours (<<Local Office Hours>>) or email at: XXXXXX

PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

GLINT - Glucose Lowering in Non-diabetic hyperglycaemia Trial – 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

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why the research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this study and what will happen to you if you take part.
Section 2 gives you more detailed information about the conduct of the study.

Section 1: Purpose of the study and what will happen

1. What is the purpose of the study?

Diabetes is a chronic disease in which high glucose (sugar) levels in the blood increase the risk of serious health consequences such as heart attack and stroke which are cardiovascular diseases.

Metformin has been safely used as a first line tablet treatment for type 2 diabetes for several decades. Metformin works by decreasing blood sugar, and has been shown to reduce the risk of cardiovascular disease and premature death by around 30% in patients with type 2 diabetes. There is some evidence that metformin may also reduce the risk of some cancers in people with diabetes.

People who do not have diabetes but who have higher than normal blood sugar levels are at increased risk of heart attacks and strokes. This study will test whether early treatment with a well-established, safe and cheap drug (metformin) reduces the risk of developing cardiovascular disease and cancer in people who do not have diabetes but have high blood sugar levels and above-average risk of heart attacks and strokes. It will also test whether or not metformin reduces the risk of progression to diabetes.

2. Why have I been invited?

You have been invited to participate in this study because you have blood sugar levels that are slightly raised but below the level at which diabetes is diagnosed and are at increased risk of cardiovascular diseases. We believe that prolonged release metformin, a type of metformin that is slowly released into your bloodstream, may be a suitable treatment to reduce your blood sugar levels and your risk of developing diabetes, cardiovascular disease and cancer.

Initially, we plan to recruit 500 male and female participants aged 40 years or older who do not have diabetes but have raised blood sugar levels into a feasibility phase of the study. These participants will be recruited from the NHS Health Checks Programme, GP practices and databases held at our research centres. We hope to extend the study to involve approximately 13,000 participants from around Britain.

3. Do I have to take part?

No, participating in GLINT is completely voluntary.

If you decide to participate you are still free to change your mind and leave the study at any time without giving a reason.

If you choose not to participate or to leave the study, your future medical treatment and normal standard of care will not be affected in any way.

4. What will happen to me if I take part?

If you agree to participate in the study, you will be asked to sign an Informed Consent Form when you visit your local research facility or GP surgery, an example of which can be found at the end of this document, this demonstrates that you understand the nature of the study and what it involves for you. You will be given a copy of the signed consent form to take away for your records and to refer to later.

Treatment of patients with non-diabetic high sugar levels is usually limited to lifestyle advice about improving diet and increasing physical activity. Although we think metformin may be of additional benefit, we need to test whether or not this is true. This means that participants in the study will be randomly (by chance) allocated by a computer to one of two possible treatments. The two groups will be balanced and you will have a 50% chance of receiving metformin and an equal chance of receiving a placebo. A placebo is sometimes called the "dummy pill". It looks the same as metformin but does not contain any of the active ingredients and should have no effect on you.

Neither you nor the GLINT research team will know which treatment you are receiving during the study; however, your study doctor can find out if necessary.

This study will take place in two phases: (i) the feasibility phase (approximately 500 participants) and; (ii) the full study phase (approximately 13,000 participants including the participants from the feasibility phase). If you are enrolled during the feasibility phase, you will continue into the full study. The length of the feasibility phase will be approximately 12 months. We estimate the full study (including the feasibility phase) will take approximately 5-7 years.

For a brief overview of what will happen during the study please refer to the Schedule of Assessments in Table 1.

Table 1: Schedule of Assessments

	Visit 1 Baseline			*Visit 2*		*Visit 3*	*Annual questionnaire*	*End of study/early termination*
	Day 0	*Wk 4*	*Wk 8*	*Month 3*	*Month 4*	*Month 6*		
Informed Consent	X							
Collection of general health data	X							
Assessment of study eligibility	X							
Questionnaire	X							
Blood sample	X			X		X		
Phone call		X	X					
Postal questionnaire					X		X	X

Total time for visit	*60 mins*	*20 mins*	*20 mins*	*30 mins*	*40 mins*	*30 mins*	*40 mins*	*40 mins*

- ***Visit 1 (Baseline visit)***

This visit is anticipated to last one hour and will take place at your local research facility or GP surgery. During this visit we will discuss the study with you and you will have the opportunity to ask questions and to clarify anything that you are unsure of with a member of the GLINT team. If you are happy to take part in the study you will be asked to sign the Informed Consent Form.

After you have given consent to take part you will be asked a few questions about your health and lifestyle habits, and we will measure your weight, height and blood pressure. We may also take a sample of your blood to check your blood sugar and cholesterol levels and to check your kidney function. This blood sample will be equivalent to 2 teaspoons or 10 ml. (**Note:** these samples may not be required if these tests have been completed previously within our timeframe.. The purpose of all the assessments is to check if you meet all of the criteria for taking part and to provide your GP with information about your risk of cardiovascular disease to enable them to advise you appropriately.

If you are pregnant at the time of recruitment to the study, you will not be able to take part. However, metformin is used as a treatment for high blood sugar levels during pregnancy, so if you fall pregnant at any time during your participation in GLINT, you can remain in the study.

During the screening and baseline visit a member of the GLINT team will provide instructions on how and when to take the study medication in the event that you are enrolled into the study.

You will also be invited to provide an additional 20 ml (equivalent to 4 teaspoons) blood sample for use in future genetics and biomarker research. This research may find patterns that could tell us more about people at risk for diabetes and related issues such as heart disease and their treatment. It could indicate how a disease behaves or may help us identify the type of person who will respond best to certain treatment. This is an optional addition and if you choose not to provide this blood sample, this will have no effect on your participation in the GLINT study.

- ***Study medication***

Once all the results from this first visit are available we will assess whether you are eligible to participate or not. We will write to you to confirm your eligibility for GLINT. If eligible, you will be randomly allocated to receive either the metformin or the placebo. You will not know which medication you will receive. With the letter you will also receive the following:

- ✓ An emergency contact card. You should carry this card with you at all times (for example in a wallet or purse) because it details the name and the phone number of the study site to be contacted in case of an emergency.
- ✓ A leaflet with information on changes that you could make to your lifestyle in order to reduce your risk of cardiovascular disease.

Approximately one week later you will receive the following:

- ✓ Your first batch of study medication in the post. This will include a study treatment leaflet with instructions on how and when to take the medication.

We will also write to your GP and enclose your test results. Every 16 weeks you will receive a new package of your study medication via post for the duration of the study (5-7 years).

If you are not eligible for GLINT, we will inform you of this and also your GP of the clinical results. Should you wish to discuss your results please contact your GP. Any samples we have collected as part of the research will be destroyed.

Please note: if any results we obtain during the study are found to be abnormal we will inform your GP.

- ***Phone call at 4 and 8 weeks***

These phone calls are expected to take approximately 20 minutes. A member of the GLINT team will call you approximately 4 and 8 weeks after your first visit to discuss how you are getting on with taking the study medication, whether you have experienced any side effects from the study medication or if you're having any problems taking part in the study. During the phone call you will discuss what dose of medication to take going forward.

- ***Visit 2 (3 months after visit 1)***

This visit to your local research facility or GP surgery is expected to take approximately 30 minutes. A 10 ml blood sample equivalent to 2 teaspoons will be taken at this visit. This is to check your sugar levels and the function of your kidneys. A member of the GLINT team will also ask if you have experienced any side-effects from the study medication. Please bring along any unused study medication that you have with you to this appointment.

- ***Questionnaire (4 months after visit 1)***

You will receive a questionnaire approximately 4 months after your first visit. We anticipate that the questionnaire will take 40 minutes to complete. We ask that you complete and return the questionnaire in the freepost envelope provided.

At the same time, your GP will receive a brief questionnaire asking about your current health.

- ***Visit 3 (6 months after visit 1)***

This visit to your local research facility or GP surgery will take approximately 30 minutes. A 10 ml blood sample equivalent to 2 teaspoons will be taken at this visit. This is to check your sugar and cholesterol levels and the function of your kidneys. A member of the GLINT team will again ask if you have experienced any side effects with the study medication. Please bring along any unused study medication that you have with you to this appointment.

- ***Questionnaire (annually after visit 1)***

You will receive a further questionnaire annually on the anniversary of your enrolment in the study for approximately 5 to 7 years. We anticipate that the questionnaire will take 40 minutes to complete. We ask that you complete and return the questionnaire in the freepost envelope provided. If you report any side-effects, you may be contacted by your local site to gather follow up information.

Your GP will receive a brief questionnaire asking about your current health approximately every year. We can also follow your progress by using three national registries, the Office of National Statistics, the National Cancer Registry and the Health Episode Statistics registry, to find out if you develop cardiovascular disease or cancer.

5. What will I have to do?

You should tell the study team if you feel unwell or different in anyway. If you have any concerns please either contact your study doctor using the contact numbers at the end of this information sheet, or your GP.

You should discuss your participation in this study with any private medical, protection or life insurance provider you use, as failure to notify them may affect or invalidate your cover.

In order for the GLINT team to maintain contact, we ask that you inform us of any changes in contact details (i.e. address or telephone contact details). This information is important to ensure we are sending the study medication to the right address.

Study medication

You will receive all study medication by post. Each tablet contains 500 mg of study medication. In the first 4 weeks, you will take 1 tablet every day. In weeks 5 to 8, you will take 2 tablets each day. From week 9 onwards, you will take 3 tablets each day. You can choose at what times of the day you take the tablets, for example all three at breakfast or dinner or one in the morning and two in the evening and so on. It may help you to remember if you take your tablets at the same time each day and possible side effects may be reduced if you take the tablets with food. You will receive a study treatment leaflet with your first batch of medication. You should use this to record the date you started taking your tablets and dates when you increase to 2 tablets and then 3 tablets a day.

It is important that you take the study medication as directed by the GLINT team. When you come to your clinic visits, you will need to bring the carton(s) containing unused medication bottles. At the end of the study, you will be asked to take any unused medication to your local pharmacy for disposal.

X-ray investigations and surgical procedures

If you need to have an X-ray examination involving the injection of a dye, tell the doctor that you take metformin as you may need to stop taking it for a few days afterwards (usually 48 hours).

Please notify all doctors that you're taking the study medication if you are going to have an operation under general anaesthetic, as you may need to stop taking metformin for a couple of days before and after the procedure (usually 48 hours before and 48 hours after) or until your kidney function has been found to be normal.

6. What is the drug being tested?

Metformin (Glucophage SR®) is licensed and has been commonly prescribed as the first treatment for patients with type 2 diabetes in order to lower their blood sugar levels. It is not yet licensed or used in people like you who have not been diagnosed with diabetes but have higher than normal blood sugar levels.

7. What are the side effects of the drug being tested?

Very common (more than 1 in 10 patients)

Gastrointestinal disorders such as nausea, vomiting, diarrhoea, stomach ache and loss of appetite. These undesirable effects occur most frequently when people begin taking

metformin and resolve spontaneously in most cases. A slow increase of the dose may reduce the risk of gastrointestinal side-effects.

Common (between 1 in 10 and 1 in 100 patients)
Taste disturbance.
Very rare (less than 1 in 10,000 patients)
Skin rashes including redness, itching and hives.

Lactic acidosis
Lactic acidosis (too much acid in the blood) is a very rare but serious complication that can occur due to metformin accumulation in the body. Reported cases were mainly found in patients with diabetes who had significant kidney problems, which is why we will test your kidney function at the start of the study and after 3 and 6 months to make sure that your kidneys are working well. People with severe kidney disease will not be able to take part in this study.

If you develop kidney disease during the study, please inform your study team using the telephone number given in Section 21 of this information sheet. Symptoms include unexpected weight loss, feeling weak or tired, muscle pains, very fast breathing which you cannot stop, stomach pains, feeling cold or dizzy, or developing a slow / irregular heartbeat. If you experience any of these symptoms please report them to your GP and the GLINT team immediately.

Alcohol consumption can increase the risk of lactic acidosis. It is recommended that you avoid drinking excessive amounts of alcohol, both regularly and in short episodes. Government recommendations should not be exceeded; these are 21-28 units of alcohol per week for men and 14-21 units of alcohol per week for women.

Hypoglycaemia
Another serious but rare side effect of metformin is hypoglycaemia, or a decrease in the sugar content of the blood. This is more likely if people who are taking metformin miss a meal. People feel anxious, may feel shaky, have palpitations and a fast heartbeat, experience sweating, feel hungry but may also feel sick or vomit, their speech may begin to slur. Hypoglycaemia requires prompt treatment, usually involving eating or drinking something containing sugar; otherwise this condition may lead to loss of consciousness, if symptoms persist medical attention should be sought. If you experience any of these symptoms please report them to your GP as soon as possible.

Vitamin B12 deficiency
Vitamin B12 is essential for the normal functioning of the brain and nervous system, and also for the formation of blood. Long-term metformin use has been associated with vitamin B12 deficiency, which is why we will test your vitamin B12 level at the start of the study and after 6 months to make sure that it is normal. Vitamin B12 deficiency can lead to nerve damage (neuropathy) affecting various parts of the body, although metformin has not been associated with nerve damage. People with neuropathy may lose sensation in the skin of their feet. People may also experience weakening of muscles which may lead to an increase in risk of bone fractures as the muscles cannot support the bones. The action of the stomach, intestine, bladder, penis or sometimes the heart, can also be affected in those who are vitamin B12 deficient. As a result people may have altered bowel movements, such as intermittent diarrhoea or constipation. Other symptoms can include feeling sick, vomiting, stomach bloating, discomfort and unintentional weight loss. Some people may have low blood pressure with symptoms like dizziness, weakness, visual impairment or possibly a loss of consciousness that most frequently occurs when getting out of bed in the morning.

8. What are the possible disadvantages and risks of taking part?

The risks of participating in this study are minimal. If you choose to be involved in GLINT we will invite you to attend a recruitment visit to assess your eligibility, and if eligible, visits at three and six months. Possible side effects of the medication are listed above. There are risks of taking blood samples which may include some discomfort and/or bruising at the site where blood is taken. Light headedness may occur in some individuals during blood taking but this is resolved by resting for a short period.

9. What are the possible benefits of taking part?

There is no guarantee that you will benefit from taking part in this study. However, information collected as part of your participation in this study may benefit people like you with higher than normal blood sugar levels. You will have your risk of cardiovascular disease assessed and will receive advice about how this risk can be reduced.

10. What are the alternatives for treatment?

There is no standard drug treatment for people whose blood sugar levels are higher than normal but lower than the level at which diabetes is diagnosed. Changes in lifestyle (e.g. improved diet and increased exercise) have been shown to be beneficial for people with higher than normal blood sugar levels. Metformin (Glucophage SR®) is being tested in this study in the hope that it will lower blood sugar levels and help in the prevention of heart disease, stroke and cancer.

11. What happens when the study stops?

After the study has finished you will not continue to receive study medication. Your GP will decide if you need any treatment after the study is finished. At the end of the study you will receive a newsletter to inform you of the study findings.

12. Expenses & Payment?

You will not receive any payment for participating in this study. <<Local text regarding reimbursing parking and mileage expenses>>

Section 2: Study Conduct

13. What if new information becomes available?

Sometimes during the course of a study, new information becomes available which might affect your decision to continue participating in this study. The GLINT team will contact you to discuss the new information so that you can decide whether you wish to continue participating in the study. If you still wish to continue on the study, you will be asked to sign a new Informed Consent Form.

The study Sponsor (Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge), the regulatory authority (Medicines and Healthcare products Regulatory Authority, MHRA) or the study doctor may decide to stop the study at any time. If that happens we will tell you why the study has been stopped and arrange for appropriate care and treatment for you.

14. What if I decide I no longer wish to participate in the study?

You are free to withdraw your participation in this study at any time without giving a reason, by telling the GLINT team. If you no longer wish to take the study medication at any time during the study, we would still like you to remain in the study and complete the annual questionnaire until the study finishes.

If you no longer wish to continue completing the questionnaires we would like to continue following your progress through information from the national registries.

Your decision to stop taking part in this study will not affect the standard of care you receive. Any information already provided or results from tests already performed on you or your samples will continue to be used in the study.

The study doctor may also choose to withdraw you from the study if they feel it is in your best interest or if you have been unable to comply with the requirements of the study. Reasons for study withdrawal could include:

- You have experienced a serious side effect
- You are unable to complete the visits, study documentation or take the study medication as required
- The study doctor feels you no longer appear to benefit from the treatment.

If you have experienced any serious side effects during the course of the study which require you to discontinue the study medication or to withdraw from the study, your study doctor or your GP will follow up with you regarding your progress until the side effect has been stabilised or resolved.

15. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to your study doctor who will do their best to answer your questions.In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Addenbrookes Hospital or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Patient Advice and Liaison Service (PALS) at your hospital.

16. Will my taking part in this study be kept confidential?

All information collected about you as a result of your participation in GLINT will be kept securely and strictly confidential. You may ask to see your personal information at any time.

In order for your study medication and questionnaires to be posted to you, we will collect and store your contact details. These details will be accessible by authorised members of the GLINT team and the authorised personnel at the drug packaging and distribution company. This information will be stored separately from your study data.

In order to access your information in the national registries, we will collect and store your NHS number. This number will only be accessible by authorised staff associated with the study.

We will need to inform your GP of your participation in this study so that any medical decisions made by your GP account for any treatment you are receiving as part of this study.

Authorised staff, who work for or with the sponsor of the study, the hospital Research and Development Department or the Regulatory Agency responsible for drug research may require access to your personal information and/or medical records to verify the data for this study and ensure that it is being conducted in accordance with UK law. All information will be treated in the strictest confidence during the review process.

17. What will happen to my samples?

Blood samples taken to assess your health will be sent to the local NHS laboratory. The samples will be destroyed after analysis by the local laboratory.

If you agree to provide a sample of blood for future research, your sample will be stored at a central facility indefinitely for research into the causes and treatment of diabetes, other related diseases, genetic and/or biomarker research. To protect your confidentiality, samples taken from you for this part of the research will be labelled with a unique code assigned to you upon entering this study. Persons handling your samples will not be able to link this code back to you.
If you give your consent to participate in GLINT and subsequently are not eligible, the blood samples for future research collected will not be stored. If you withdraw from the study, any information and stored blood samples already provided or results from tests already performed will continue to be used in GLINT.

18. What will happen to the results of the study?

The results of the study will be anonymous and you will not be able to be identified from any of the data produced. When the results of this study are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. The GLINT funding provider, National Institute of Health Research, and the medication suppliers, Merck Serono, will receive the study results.

If you would like to obtain a copy of the published results please contact the GLINT research team directly who will be able to arrange this for you.

19. Who is organising (sponsoring) and funding the study?

This study is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study is being funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme. The study drug metformin (Glucophage SR®) and placebo will be supplied by Merck Serono.

20. Who has reviewed this study?

All research studies are reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES East of England Cambridge South Committee. The study has also been reviewed and approved by the Medicine and Healthcare products Regulatory Authority (MHRA).

21. Further information and contact details

If you or someone on your behalf needs to make contact with the study team please contact the GLINT team using the number below during office hours (<<Local Office Hours>>):

Name, Study coordinator Tel: XXXXX XXXXXX

In the event that we miss your call or if you call outside of normal office hours there is an answer phone on this number and if you leave a message we will respond to you at the earliest opportunity.

Please note: In an emergency outside of office hours please use XXXX XXXXXXX and await instruction.

TO BE PRINTED ON HEADED PAPER

INFORMED CONSENT FORM

GLINT - Glucose Lowering in Non-diabetic hyperglycaemia Trial

Principal Investigator:

Participant Number: XXXXXXX

If you agree with each sentence below, please initial the box

		INITIALS	
1	I have read and understood the Participant Information Sheet version 2.1, dated 13/05/2014 for the above study and I confirm that the study procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.		
2	I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.		
3	I understand that sections of my medical notes or information related directly to my participation in this study may be looked at by responsible individuals from the sponsor, regulatory authorities and research personnel where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records.		
4	I understand that information held and maintained by the Health and Social Care Information Centre and other central UK NHS bodies may be used to help contact me and provide information about my health status.		
5	I understand that my GP to be informed of my participation in this study, for my test results to be forwarded to them, and for them to provide GLINT research team with information about my health (to include questionnaires and access to GP clinical databases).		
6	I understand that my NHS number will be stored to allow access to my information through the Office of National Statistics and the National Cancer Registry.		
7	I understand that the GLINT research team may close the study or stop my participation in it at any time.		
8	I agree that information gathered about me can be looked after and stored by the GLINT research team and may be used in future projects.		
9	I agree to participate in this study.		
10Optional	I agree to be re-approached to consider participating in possible future studies on the basis of information gained from GLINT.	Yes	No
11Optional	I agree to give an additional optional blood sample to be used for future genetic and biomarker research. However, I understand that if I do not meet the randomisation criteria that my blood samples will be destroyed.	Yes	No

_____	_____	_____
Name of participant	Signature	Date

_____	_____	_____
Name of person taking consent	Signature	Date

Time of Consent (24hr clock) _____:_____

One copy for the participant, one copy for the study team, one copy to be retained in medical records where available.

{ TO BE PRINTED ON LOCAL HEADED PAPER}

GLINT
Glucose Lowering in Non-diabetic hyperglycaemia Trial

{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL PHONE NUMBER}
{LOCAL EMAIL ADDRESS}

<<Title>> <<FirstName>> <<Surname>>
<<Address Line 1>>
<<Address Line 2>>
<<Town>>
<<Postocde>>

<<Date>>

New trial: GLINT – Glucose Lowering in Non-diabetic hyperglycaemia Trial

Dear <<Title>> <<Surname>>

The <<LOCAL SITE NAME>> is currently recruiting participants for GLINT. When you participated in the xxxx Study you consented to being recontacted with information on new research studies that you may wish to consider participating in.

Diabetes is a chronic disease in which high glucose (sugar) levels in the blood increase the risk of serious health consequences such as heart attack and stroke which are cardiovascular diseases. There is evidence that damage caused by high glucose levels starts below the level at which people are diagnosed with diabetes. Metformin, a tablet treatment for diabetes, reduces the risk of heart attack, stroke and premature death. It can also prevent the development of diabetes in people whose blood glucose is raised but below the level at which diabetes is diagnosed. We would like to test whether metformin can also reduce the risk of heart attack, stroke and premature death in people with higher than normal blood glucose levels but below the level at which diabetes is diagnosed.

Results from the tests that you completed as part of your participation in the xxxx Study indicate that your blood glucose levels were in the range that would qualify you for inclusion in this trial.

To help you decide if you wish to be involved we have enclosed an information leaflet which explains why we are doing the trial and what it involves.

We would be grateful if you could return the enclosed reply slip in the freepost envelope, indicating whether or not you would be interested in learning more about the trial. Your decision does not affect your participation in other studies and no further action will be taken for the GLINT trial without your agreement.

Please do not hesitate to contact us if you require any further information. Our Freephone number is 0800 XXXXXXX there is an answer phone on this number and, if you leave a message, we will get back to you promptly (**Note:** the office is manned during normal office hours Monday-Friday 9am-5pm). Thank you for taking the time to read this letter.

Yours sincerely

Professor Simon Griffin
GLINT Chief Investigator

The GLINT trial

Participant Trial Number	«FullID»
Title	«Title»
Forenames	«ForeNames»
Surname	«Surname»
Address 1	«Addr1»
Address 2	«Addr2»
Town	«Town»
County	«County»
Postcode	«PostCode»

- I confirm that the above details are correct.
- Please amend my details as indicated above. (delete as applicable)

If you wish to take part **please complete your telephone details below** as we will contact you by telephone to arrange an appointment.

HOME TELEPHONE	……
WORK TELEPHONE	……
MOBILE TELEPHONE	……
E-mail	……

Please indicate when it is a convenient time for us to **call you**: (Please tick)

Morning		**Afternoon**		**Evening (6-8p.m.)**	
Any further information you wish to provide …					

I do/do not wish to take part in the GLINT trial. (delete as applicable)

…… ……..
Signature Date

Please complete this reply slip and return it to the <<Local Research Facility>> in the enclosed freepost envelope.

{ TO BE PRINTED ON LOCAL HEADED PAPER}

GLINT
Glucose Lowering in Non-diabetic hyperglycaemia Trial

{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL ADDRESS}
{LOCAL PHONE NUMBER}
{LOCAL EMAIL ADDRESS}

<<Doctor>> <<Firstname>> <<Surname>>
<<Surgery Address Line 1>>
<<Surgery Address Line 2>>
<<Surgery Town>>
<<Surgery Postcode>>

<<DATE>>

Dear <<Doctor>> <<Surname>>

RE: *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*

Patient Name and DOB

Your patient has agreed to participate in the above clinical trial at *(Local site name).* This study is to compare the impact of adding metformin versus placebo to the usual care of patients who have high modelled cardiovascular risk (≥20% over 10 years) and blood glucose levels that are raised but below the diagnostic threshold for diabetes on death due to cardiovascular disease, nonfatal heart attack and nonfatal stroke. This is a double-blinded, placebo controlled randomised trial using metformin (Glucophage XR®) in people with non-diabetic hyperglycaemia (HbA1c 5.5-6.4%, 37-47mmol/mol).

Participants will be required to take 500mg metformin prolonged release (Glucophage XR)/placebo with a starting dose of 1 tablet/day (500mg Metformin/placebo) for 4 weeks, titrating up to 2 tablets/day (1000mg Metformin/placebo) for weeks 5 to 8 and then up to the maximum dose of 3 tablets/day (1500mg Metformin/placebo) for the remainder of the trial. Currently, funding is available for the feasibility phase of 500 participants which we estimate will run for eighteen months. This may be extended into the full trial which will then run for a further 5 years to recruit an additional 12,500 participants.

Study participants who develop diabetes after being randomised to GLINT study medication (metformin prolonged release or placebo) may be prescribed additional metformin at your discretion. If study participants begin metformin, the GLINT study medication assignment will not be unblinded except in exceptional situations or clinical emergencies. Therefore, you should assume that your patient is receiving active metformin in the study medication and use the table below to determine the maximum amount of additional metformin to prescribe.

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

We will send a postal questionnaire to you at 4 months post enrolment and annually thereafter. We wish to gather information on incidences of CVD, cancer and diabetes, and current prescribed medication. We do not anticipate this to take up too much of your time. Your efforts will assist the trial in obtaining the information it requires to determine whether giving metformin to those at risk of developing diabetes prevents its onset and also reduces the number of CVD, nonfatal heart attack, nonfatal stroke and cancer events.

The main side effects to be aware of are detailed in the Participant Information Sheet which you will find enclosed in this letter.

Contraindications
One potential side effect of metformin is a reduction in plasma Vitamin B12 levels. As a precaution during the feasibility study we are measuring B12 levels at baseline and six months.
The contraindications to metformin are listed below.

- Hypersensitivity to metformin or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (eGFR <30ml/min).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

Patients are advised to discontinue the study medication (1) prior to receiving iodinated contrast media in radiologic studies and not to restart it until 48 hours after the procedure and renal function has been found to be normal, and (2) 48 hours prior to elective surgery under general, spinal or peridural anaesthesia and not to restart it earlier than 48 hours following the surgery.

If you have any queries or require further information please contact the GLINT Trial Team on Freephone 0800 XXXXXX *(***Note:** the office is manned during normal office hours Mon-Fri 9am-5pm) or via email **XXXXX@XXXXXX.XXX.XX.XX***.*

Yours sincerely

GLINT Trial Team

Encs: Participant Information Sheet, version *(1.0)* dated *(05Nov2013)*

GLINT

Glucose Lowering in Non-diabetic hyperglycaemia Trial

STUDY TREATMENT INFORMATION

This leaflet contains important information relating to your GLINT study treatment. Please read all of the information contained in this leaflet carefully. If you have any questions about your study treatment, please call your local GLINT site.

Please keep this information in a safe place for future reference.

Draft v1.0 Maintenance 05 November 2013

1. Study medication will be sent to you via the post. Please check that each pack of medication you receive has arrived undamaged (the seals along the edge of the box should still be intact). If a treatment pack arrives damaged, or appears to have been tampered with, please contact the GLINT drug supply team on 01865 857267

2. It may help you remember if you take the treatment at the same time each day.

3. If you forget to take a tablet at your usual time, you may still take it later the same day. However, if you miss a whole day or more, do not make up the missed tablets. Continue with the treatment for the next appropriate day.

4. You should receive your next supply of medication before your existing supply is finished. It will contain 12 bottles of tablets which is sufficient for 16 weeks of treatment. You should finish all of the medication from your existing supply before starting the next batch of medication.

5. If you reach the end of your medication before receiving your next supply, or if you lose the study medication, please contact the GLINT drug supply team on 01865 857267

6. Keep the medication out of the reach and sight of children, and store it in a dry place away from excessive heat, cold or moisture.

7. If you are anticipating surgery requiring general, spinal or peridural anaesthetic or an investigation with iodine-containing X-ray contrast media, you should stop the study tablets 48 hours prior to the procedure and resume as soon as your doctor approves.

8. If you develop kidney failure you may need to stop taking this medication. Please contact your local GLINT trial site.

9. If you experience minor symptoms that you believe may be related to the study tablets, you could try discontinuing them for a few days and then try taking them again. If you experience major symptoms or feel that you must stop the tablets altogether, then please telephone your GLINT trial site.

10. If you are prescribed any of the following drugs by your own doctor, please telephone your local GLINT trial site.

Drug Names	**Brand Names**	**Brand Names**
Metformin	Actoplus MET	Glucophage
	Actoplus MET XR	Glucovance
	Apo-Metformin	Glumetza
	AvandaMet	Jentadueto
	Bolamyn SR	Janumet
	Competact	Janumet XR
	Diabex	Metaglip
	Diaformin	Obimet
	Dianben	PrandiMet
	Eucreas	Riomet
	Fortamet	

Weeks 1-12

The tables below can be used as a reminder of the number of tablets to take each day during the first 12 weeks of the trial. Put a cross in the box(es) each day after you have taken your tablet(s). Enter the date when you first started the study medication and when you increased to two and then three tablets per day.

Take one tablet a day with food for 4 weeks (weeks 1 to 4).
START DATE:

Mon	Tues	Wed	Thurs	Fri	Sat	Sun

Take up to two tablets a day with food for 4 weeks (weeks 5 to 8) unless otherwise instructed. ***START DATE:***

Mon	Tues	Wed	Thurs	Fri	Sat	Sun

Take up to three tablets a day with food for 4 weeks (weeks 9 to 12) unless otherwise instructed. ***START DATE:***

Mon	Tues	Wed	Thurs	Fri	Sat	Sun

GLINT

Glucose Lowering in Non-diabetic hyperglycaemia Trial

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Draft 1.0 Titration 05 November 2013

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2. The first carton of medication that you will receive will contain 9 bottles of tablets which will provide 16 weeks of treatment. You should aim to gradually increase the number of tablets that you are taking until you are taking the full study dose as instructed by your GLINT trial site:

   Weeks 1, 2, 3 and 4 - Take one tablet a day
   Weeks 5, 6, 7 and 8 – Take two tablets a day
   Week 9 onwards – Take three tablets a day

3. It may help you remember if you take the treatment at the same time each day.

4. If you forget to take a tablet at your usual time, you may still take it later the same day. However, if you miss a whole day or more, do not make up the missed tablets. Continue with the treatment for the next appropriate day.

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	Bolamyn SR	Janumet
	Competact	Janumet XR
	Diabex	Metaglip
	Diaformin	Obimet
	Dianben	PrandiMet
	Eucreas	Riomet
	Fortamet	