Clinical trial results:
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.

Summary

EudraCT number	2012-005570-56
Trial protocol	GB
Global end of trial date	05 November 2016

Results information

Result version number	v1 (current)
This version publication date	26 November 2017
First version publication date	26 November 2017

Trial information

Trial identification

Sponsor protocol code	GLINT

Additional study identifiers

ISRCTN number	ISRCTN34875079
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	R&D Number: A093318, EudraCT: 2012-005570-56, REC reference: 13/EE/0415

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Sponsor organisation address	Addenbrooke’s Hospital, R&D Department, Box 277, CAMBRIDGE, United Kingdom, CB2 0QQ
Public contact	Carrie Bayliss, Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, +44 1223348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, +44 1223348158, cctu@addenbrookes.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2016
Global end of trial reached?	Yes
Global end of trial date	05 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

People who do not have diabetes but who have higher than normal blood sugar levels are at an increased risk of cardiovascular disease (e.g. heart attack or stroke). This study will test whether early treatment with a well-established, safe and cheap drug (metformin) reduces the risk of developing cardiovascular disease in people who do not have diabetes but have high blood sugar levels and above-average risk of heart attacks and strokes.
The feasibility trial aimed to assess the feasibility of the Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT) and to estimate key parameters that would inform design of the full trial, including: recruitment strategy, randomisation, electronic data capture, drug distribution by post, retention, adherence to study medication, safety monitoring and remote collection of outcome data.

Protection of trial subjects:

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). Creatinine was therefore measured at baseline, three and six months. Participants with eGFR 45-59 ml/min/1.73m2 were recommended a maximum daily dose of 1000mg metformin prolonged release/placebo. Individuals with eGFR<45ml/min were excluded from the trial.
Chronic metformin use has been associated with Vitamin B12 deficiency. B12 levels were measured at baseline and 6 months. If a participant had a B12 level < 200 pg/ml the results were reviewed by a study clinician.
GLINT participants were advised about the symptoms suggestive of hypoglycaemia and how to respond.
A Trial Steering Committee (TSC) provided overall supervision for the trial, to ensure it was conducted in accordance with the protocol and GCP and to provide advice through its independent Chair. An Independent Data Monitoring Committee (IDMC) reviewed an agreed subset of the study data on regular intervals to ensure the rights and safety of trial participants were protected. Any recommendations were forwarded to the TSC.

Background therapy:

Prolonged-release metformin (Glucophage SR): 500 mg oral tablet, up to three tablets per day, administered orally until the end of treatment phase.
Placebo: matched oral tablet, up to three tablets per day, administered orally until the end of treatment phase.

Evidence for comparator:

The placebo product visually matches the metformin tablet.

The placebo product is manufactured using commonly used and recognised tablet excipients that are also employed in the active tablets and are packed into high-density polyethylene (HDPE) bottles.

Actual start date of recruitment	03 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 249
Worldwide total number of subjects	249
EEA total number of subjects	249

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	184
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Participants were identified from 31 GP practices across Cambridgeshire and Leicestershire. 10 GP surgeries had the facilities to undertake the consent and baseline measures. Participants from the other 21 GP's were invited to a clinical research facility to undertake the consent and baseline measures after being screened for eligibility.

Pre-assignment

Screening details:

Participants were assessed for eligibility to participate in the study at an initial visit to their GP or clinical research facility. Inclusion criteria includes but is not limited to:
- Age ≥ 40 years
- Specific biochemistry ranges
- Agreement to obtaining medical records

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The placebo tablets had the same appearance as the trial IMP. Neither the participants nor the GLINT personnel will know which treatment the participant is taking.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental

Arm description:

Participant's who received Metformin drug

Arm type	Experimental
Investigational medicinal product name	Prolonged-release metformin
Investigational medicinal product code	PL 116487/0054
Other name	Glucophage SR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received their dosage of drugs through the post packaged in high-density polyethylene in 16 week batches. Upon receipt of their first batch, participants were advised to take one table (500mg) a day for four weeks, titrating up to two tablets/day for weeks five to eight and then three tablets/day thereafter. Any participant who could not tolerate 1500mg/day were advised to take the highest tolerated dose.

Arm title	Control

Arm description:

Participants receive placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Up to three tablets a day as tolerated

Number of subjects in period 1	Experimental	Control
Started	125	124
Baseline	125	124
Three month study follow-up	107	113
Four month questionnaire	105	112
Six month study follow-up	104	109
One year questionnaire	109	115
End of study questionnaire	95	92
Completed	95	92
Not completed	30	32
Consent withdrawn by subject	1	-
Did not return end of study questionnaire	29	32

Baseline characteristics

Reporting groups	
Reporting group title	Experimental
Reporting group description:	
Participant's who received Metformin drug	
Reporting group title	Control
Reporting group description:	
Participants receive placebo	

Reporting group values	Experimental	Control	Total
Number of subjects	125	124	249
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	27	61
From 65-84 years	88	96	184
85 years and over	3	1	4
Not recorded	0	0	0
Age continuous			
Units: years			
arithmetic mean	69.9	70.1	
standard deviation	± 7.2	± 6.2	-
Gender categorical			
Units: Subjects			
Female	17	13	30
Male	108	111	219

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: Participant's who received Metformin drug	
Reporting group title	Control
Reporting group description: Participants receive placebo	

Primary: The time required to recruit and follow 250 participants for at least a median of 6 months

End point title	The time required to recruit and follow 250 participants for at least a median of 6 months
End point description:	
End point type	Primary
End point timeframe: Recruitment was closed in November 2015, data collection was closed 28th October 2016	

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[1]	124[2]		
Units: Months				
number (not applicable)	125	124		

Notes:

[1] - All participants were included in analysis

[2] - All participants were included in analysis

Statistical analyses

Statistical analysis title	Overall Statistical Analysis
Statistical analysis description: Descriptive statistics were used to analyse results by randomised group, no p-values were calculated	
Comparison groups	Experimental v Control
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0 [4]
Method	Descriptive
Parameter estimate	Descriptive

Notes:

[3] - Descriptive

[4] - No p values were calculated

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the start of IMP dosing. Information was collected via three routes: GP and Participant questionnaires, direct contact with participants and GP's.
AEs were only recorded when they resulted in cessation of the drug

Adverse event reporting additional description:

Serious Adverse Events (SAEs) SAEs were collected over the same time period as stated above, and were subject to a modified safety reporting plan.

A listing of serious adverse events has been uploaded.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control

Reporting group description: -

Serious adverse events	Experimental	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 125 (17.60%)	13 / 124 (10.48%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured rib			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental drug overdose			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Laparoscopic Heller's cardiomyotomy and fundoplication			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar decompression surgery			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip replacement			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate surgery			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Knee replacement			
subjects affected / exposed	2 / 125 (1.60%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparoscopic cholecystectomy			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total Knee Replacement			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallstones			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Phimosis			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
withdrawal from alcohol			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus A infection			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Experimental	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 125 (15.20%)	10 / 124 (8.06%)	
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	
occurrences (all)	1	1	
Tired & confused			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Tiredness and not feeling right			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Gastritis reported by GP. Discharge summary indicates pulmonary embolism.			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Light headed, breathless, tiredness and flatulence.			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Thirst and dry mouth			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Tiredness and loss of appetite			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Unobtainable			
subjects affected / exposed	2 / 125 (1.60%)	0 / 124 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Faecal soiling			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Nausea and loss of appetite			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Constipation and dry skin			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Stomach upset (no diarrhoea), light headedness and dizziness			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 125 (0.00%)	2 / 124 (1.61%)	
occurrences (all)	0	2	
Diarrhoea			

subjects affected / exposed	2 / 125 (1.60%)	0 / 124 (0.00%)	
occurrences (all)	2	0	
Constipation and headache			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
GI upset			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Indigestion and belching			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Loose stools and bloating			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Loose stools, gastric upset and extreme flatulence			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Nausea and diarrhoea			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Taste disturbance and bloated stomach			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle pain in both arms			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2014	Change of Sponsor from sole sponsored by the University of Cambridge to being joint sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.
10 November 2014	1) Criteria for withdrawal of participants on safety grounds. Updated reasons for discontinuation of study medication 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). 2) Clarification of primary and secondary outcomes for the full trial (did not affect feasibility phase) 3) New wording for emergency unblinding and study discontinuation 4) New procedures for study management in line with the change of Sponsor
13 April 2016	Sample size for feasibility phase changed from 500 to 250

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of study due to limited funding only allowing the feasibility phase to be carried out

Notes: