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Master of science thesis

"A protocol for an observational study for metformin hydrochloride for treating type II diabetes mellitus."

«Πρωτόκολλο μελέτης παρατήρησης της υδροχλωρικής μετφορμίνης για τη θεραπεία του σακχαρώδους διαβήτη τύπου ΙΙ.»

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ABBREVIATIONS AND DEFINITIONS OF TERMS

A.E.(s)	Adverse Event(s)
ADA	American Diabetes Association
BUN	Blood Urea Nitrogen
CIs	Confidence Intervals
CRF	Case Report Form
DMC	Data Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FPG	Fasting Plasma Glucose
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HEENT	Head, Eyes, Ears, Nose and Throat
IRB	Institutional Review Board
LDL	Low-density lipoprotein
ME	Monitoring Entity
NIMH	National Institute of Mental Health
OCR	Office of Clinical Research
PHI	Protected Health Information
PI	Principal Investigator
S.A.E.	Serious Adverse Event(s)
S.E.	Standard Error
SD	Standard Deviation
SGOT/AST	Serum glutamic oxaloacetic transaminase /aspartate aminotransferase
SGPT/ALT	Serum glutamic-pyruvic transaminase and alanine transaminase
T2DM	Type 2 diabetes mellitus
WBC	White Blood Cell Count
WHO	World Health Organization

ABSTRACT

Context:

Diabetes is a global health issue in terms of prevalence, healthcare cost, and overall complications. The world prevalence of diabetes among adults (aged 20 to 79 years) is expected to be 6.4%, affecting 285 million adults in 2010 and will increase to 7.7% and 439 million adults by 2030 (Shaw 2010). With the rise in global epidemic, diabetes is also a major cause of mortality and morbidity. The total number of excess deaths attributable to diabetes worldwide was estimated to be 3.96 million in the age group 20 to 79 years, 6.8% of total (all ages) mortality. Diabetes is a considerable cause of premature mortality, a situation that is likely to worsen, particularly in low and middle-income countries as diabetes prevalence increases (Roglic 2010). Thus, diabetes imposes a significant socio-economic burden globally.[1]

Type 2 diabetes primarily develops from pathogenic defects in the mechanisms of insulin secretion and hepatic and peripheral insulin action. The consequent disruption of normal glucose metabolism involves a number of organ systems and is ultimately manifested in fasting and daytime hyperglycemia. Chronically elevated blood glucose concentrations determine the progression of the disease by further exacerbating insulin resistance and causing b-cell exhaustion in addition to decreasing their responsiveness to glucose. The b-cell secretory dysfunction is characterized by the lack of the early phase of glucose-induced insulin secretion and the insufficient and delayed late phase of secretion. Glycemic levels in patients with type 2 diabetes are directly related to the risk of developing microvascular and macrovascular complications, the main cause of the morbidity and mortality associated with this disease. The goal of treatment is to decrease the risk and delay the progression of these complications by improving glycemic control. Current oral antidiabetic agents, used as monotherapy or in combination, include traditional insulin secretagogues, insulin sensitizers and inhibitors of carbohydrate absorption.[2] A number of medical organizations have developed guidelines or recommendations for treatment of type 2 diabetes mellitus (T2DM). Most people with T2DM are initially recommended to reduce calorie intake and increase physical activity in order to improve glycaemic control (ADA-American Diabetes Association 2016). However, in order to achieve and maintain specific glycaemic targets, the majority of people with T2DM will require pharmacological glucose-lowering interventions.

[1] Raval AD, Chovatiya K, Bhavsar AB, PatelMH. Dapagliflozin for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD009001. DOI: 10.1002/14651858.CD009001.

[2] Daniel Porte, Jr. "Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications", Diabetes Metab Res Rev 2001; 17: 181–188, DOI: 10.1002 / dmrr.197

Metformin is currently the first-line glucose-lowering drug for people with T2DM because of its postulated benefits including absence of weight gain, or even weight loss, and lack of hypoglycaemia (Inzucchi 2012; Nathan 2009). If behavioral interventions like diet and exercise and maximum tolerated doses of one oral glucose-lowering drug fail to achieve the glycaemic target, other glucose-lowering drugs are often added (ADA 2016). As T2DM is a progressive condition, a substantial proportion of people with T2DM will, with time, require insulin. Some guidelines recommend to continue metformin in this situation (ADA 2016).[3]

Objectives: To assess the efficacy of metformin hydrochloride therapy for adults with type 2 diabetes mellitus.

Study Design:

Prospective, open-label, observational study.

Participants/Eligibility Criteria/Screening Period:

Participants: Patients aged ≥ 20 to <75 years with diagnosed type 2 diabetes mellitus.

Eligibility criteria:

- Patients to be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the trial.
- Patients should have no hepatic, cardiovascular or pulmonary impairment.

Screening Period: The study will include a 12-week screening period (visits every 4 weeks, including evaluations of eligibility, glycated haemoglobin [HbA1c].

Study Interventions and Measures:

Metformin is an anti-hyperglycemic agent that has been used with increasing frequency over the past several years, especially in obese or overweight patients with type 2 diabetes whose blood glucose levels cannot be controlled non-pharmacologically.[4] Metformin is a biguanide antihyperglycaemic agent that suppresses the release of glucose from the liver and improves insulin sensitivity in peripheral tissues. Additionally, it suppresses intestinal absorption of glucose. These pharmacological actions produce a blood glucose-lowering effect.[5]

[3] Madsen KS, Kähler P, Kähler LK, Madsbad S, Metzendorf MI, Richter B, Hemmingsen B. Metformin and sulphonylurea (second- or third-generation) combination therapy for adults with type 2 diabetesmellitus. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012368. DOI: 10.1002/14651858.CD012368.

[4] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD002967. DOI: 10.1002/14651858.CD002967.pub4.

[5] Kaku K, Sumino S, Katou M, Nishiyama Y and Kinugawa Y. Randomized, double-blind, phase III study to evaluate the efficacy and safety of oncedaily treatment with alogliptin and metformin hydrochloride in Japanese patients with type 2 diabetes, Diabetes Obes Metab, 2017;19(3):463–467.

PROTOCOL SYNOPSIS

Study Title	**"A protocol for an observational study for metformin hydrochloride for treating type II diabetes mellitus."**
Funder	Department of "Diabetes and Endocrinology" of "Evangelismos" Hospital.
Study Objective(s)	**Primary** To assess the efficacy of metformin hydrochloride therapy for adults with type 2 diabetes mellitus. The efficacy of the drug is determined by the difference in HbA1c before and after drug administration in the clinic. **Secondary** Change before and after drug administration in the clinic, in: • Fasting Plasma Glucose (FPG); • Fasting insulin; • Fasting glucagon; • Body weight; • Safety and tolerability of metformin based on Adverse Events. Degree of compliance with the treatment: will be calculated by dividing the actual number of od administrations by the planned number and results will be defined as: ➢ Excellent (100%); ➢ Very good (90-99%); ➢ Good (80-89%) and ➢ Poor (<80%).
Study Design	The trial will be an open-label prospective observational study in which approximately 110 patients (*see chapter 5.5 Sample Size and Power*) aged ≥ 20 to <75 years with diagnosed type 2 diabetes mellitus will take part. Those who will agree to participate in the study will be requested to systematically complete report forms at each visit.
Subject Population key criteria for	**Inclusion Criteria** 1. Patients aged ≥ 20 to <75 years with diagnosed type 2

Inclusion and Exclusion:	diabetes mellitus. 2. Patients to be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the trial. **Exclusion Criteria** 1. Patients should have no hepatic, cardiovascular or pulmonary impairment.
Number Of Subjects	An average difference in HbA1c of Δ=1,4% will be considered as clinically significant. For the purpose of the study, it will be considered that the standard deviation from last visit to baseline is around s=4%. Therefore, in order to detect a significant difference at p-value=0,05 with a power of 90% (which is considered sufficient for our study) the subjects needed to be recruited are ≥ 86 based on the below formula: $n \geq 2\left(\frac{s}{\Delta}\right)^2 (1.96+1.28)^2$ The goal of the study is to recruit approximately 110 subjects that will take part in the study.
Study Duration	A 24-week treatment period with metformin 500mg once daily.
Study Phases **Screening** **Study Treatment**	Screening for eligibility and obtaining consent: The study will include a 12-week screening period (*visits every 4 weeks, including evaluations of eligibility, HbA1c*). At week -4 HbA1c level should be ≥6.9% and <10.5% and no more than 10% difference in HbA1c level between week −8 and −4. At week 0 the eligibility of each patient was evaluated. From patients who are eligible for the study those that they agree to participate should complete and sign a consent form prior the beginning of the screening period. Observation Period: A 24-week treatment period.
Efficacy Evaluations	Mean change in HbA1c levels from baseline to the end of the treatment period (week 24).
Safety Evaluations	All Adverse Events (A.E.), Serious Adverse Events (S.A.E.) and all symptoms that follow drug administration should be recorded and the relevance to the drug should be determined by the doctor.
Statistical and Analytic Plan	Primary endpoint: A paired t- test will be utilized to determine the difference between mean HbA1c from baseline to the end of the treatment period (week 24). Main secondary endpoints: A paired t- test will be utilized to

determine the difference between mean for

1. Fasting Plasma Glucose (FPG))
2. Fasting insulin levels and
3. Body weight

from baseline to the end of the treatment period (week 24).

DATA AND SAFETY MONITORING PLAN

The Monitoring Entity (ME) will include the following expertise in the relevant:

- PI (Principal Investigator)→ Dr. _____ Head of Diabetes and Endocrinology Department;
- Data Monitoring Committee (DMC) →Mr._____, Bioethics and patients advocates; Dr. _____, senior researcher in diabetes; Mr._____, Biostatistician;
- Biostatistician→ Mr._____ Manager of the Biomedical Department;
- Independent Medical Monitor → Dr. _____ Team leader of the Diabetes and Endocrinology Department.[67]

TABLE 1: SCHEDULE OF STUDY PROCEDURES

	Screening Period				Observation Study Visits							Interim Analysis		
Study Phase	Week -4	Week -3	Week -2	Week -1	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 20
HbA1c Level	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fasting Plasma Glucose (FPG)					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fasting Insulin Levels					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Body Weight					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Compliance rate					✓	✓	✓	✓	✓	✓	✓			
Informed Consent/Assent	✓													
Review Inclusion/Exclusion Criteria	✓	✓	✓	✓										
Laboratory Data (HDL, LDL Creatinine etc.)					✓							✓	✓	✓
Demographics/Medical History	✓													
Physical Examination	✓													
Vital Signs: BP, HR, RR	✓													
Height and Weight	✓													
Pregnancy Test	✓													
Prior/Concomitant Medications	✓													
Clinical Laboratory Evaluation	✓													
Adverse Event Assessment					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[6] Stanford University HRPP Guidance, Data and Safety Monitoring, GUI-P20.

[7] Data Monitoring Committees in Clinical Trials: A Practical Perspective. Susan S Ellenberg, Thomas R Fleming, David L DeMets Copyright ® 2002 John Wiley & Sons, Ltd. Print ISBN: 0-471-48986-7

1 BACKGROUND INFORMATION

1.1 Introduction

Diabetes mellitus is a metabolic disorder resulting from a defecting insulin secretion, insulin action, or both. The consequence of this insulin disorder is the presence of chronic hyperglycaemia, which conditions disturbances on carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease (*e.g. myocardial infarction, cerebrovascular events*).

Diabetes mellitus is one of the most common chronic diseases in developing and developed countries. In 2000 the worldwide prevalence of diabetes (for all age groups) was 2.8%; in 2011 the global prevalence in the adult population was 8.3%. In 2030 is expected a prevalence of 4.4% (for all age groups) and will affect an estimate of 366 million people (Whiting 2011; Wild 2004). People with type 1 and type 2 diabetes are frequently admitted for hospital care. It is expected that in the course of a year, 25% to 30% will be hospitalized (Moss 1999).[8]

Metformin is currently the first-line glucose-lowering drug for people with T2DM because of its postulated benefits including absence of weight gain, or even weight loss, and lack of hypoglycaemia (Inzucchi 2012; Nathan 2009). If behavioral interventions like diet and exercise and maximum tolerated doses of one oral glucose-lowering drug fail to achieve the glycaemic target, other glucose-lowering drugs are often added (ADA 2016). As T2DM is a progressive condition, a substantial proportion of people with T2DM will, with time, require insulin. Some guidelines recommend continuing metformin in this situation (ADA 2016).

Metformin is an anti-hyperglycemic agent that has been used with increasing frequency over the past several years, especially in obese or overweight patients with type 2 diabetes whose blood glucose levels cannot be controlled non-pharmacologically. Metformin is a biguanide antihyperglycaemic agent that suppresses the release of glucose from the liver and improves insulin sensitivity in peripheral tissues. Additionally, it suppresses intestinal absorption of glucose. These pharmacological actions produce a blood glucose-lowering effect.

1.2 Compliance Statement

This will be conducted in full accordance with all applicable “Evangelismos” Hospital of Athens Research Policies and Procedures and all applicable governmental laws and regulations and will be in compliance with the protocol and ethical principles of the Declaration of Helsinki and the International Conference of Harmonisation Tripartite Guidelines for Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or

[8] Colunga-Lozano LE, Hernandez AV, Delgado-Figueroa N, Gonzalez-Padilla DA, Roman Y, Cuello-García CA.Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus.Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD011296.DOI: 10.1002/14651858.CD011296.www.cochranelibrary.com

others in accordance with “Evangelismos” Hospital of Athens Institutional Review Board (IRB) Policies and Procedures and all governmental requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Objective (or Aim)

The primary objective of the study is to assess the efficacy of metformin hydrochloride therapy for adults (≥ 20 to <75 years) with type 2 diabetes mellitus. The efficacy of the drug is determined by the difference in glycated haemoglobin [HbA1c] before (i.e. week 0) and after drug administration (i.e. week 24) in the clinic.

2.2 Secondary Objectives (or Aim)

The secondary objectives are to determine changes before (i.e. week 0) and after drug administration (i.e. week 24) in the clinic, in:

- Fasting Plasma Glucose (FPG);
- Fasting insulin;
- Fasting glucagon;
- Body weight;
- Safety and tolerability of metformin based on Adverse Events.

Degree of compliance with the treatment: will be calculated by dividing the actual number of administrations by the planned number and results will be defined as:

- Excellent (100%);
- Very good (90-99%);
- Good (80-89%) and
- Poor (<80%).

3 INVESTIGATIONAL PLAN

This is a protocol concerning a prospective open label observational study that will be conducted in “Evangelismos” Hospital of Athens. The study will include a 12-week screening period and a 24-week treatment period.

3.1 General Schema of Study Design

Prior to the initiation of the screening period, all subjects should provide a receipt of informed consent, and following that, a study Patient Enrollment Form will be completed at the site (i.e. “Evangelismos” Hospital) for enrollment into the study. This form, the signed consent form and information from existing data and records, will be securely sent to the Hospital’s Data Center. The Data Center Registration Form will be completed and a Study Number will be assigned at the Hospital’s Data Center.

Screening period will start from 1st October 2017 and will last for 12 weeks, ending 24th of December 2017.

All subjects will be evaluated by the Principal Investigator and Biostatistician during the 12-week screening period. Patients aged ≥ 20 to <75 years will be eligible for enrolment in the 12-week screening period if they were diagnosed with type 2 diabetes and have no hepatic, cardiovascular or pulmonary impairment.

On completion of the screening period, patients will be included in the treatment if they meet the following criteria: HbA1c level ≥6.9% and <10.5% at week −4 (*8 weeks after the start of the screening period*); no more than 10% difference in HbA1c level between week −8 and −4. Patients who have evident renal impairment will be excluded before the treatment period.

TABLE 2: DIABETES DIAGNOSTIC CRITERIA

HbA1c	mmol/mol	%
Normal	Below 42 mmol/mol	Below 6.0%
Prediabetes	42 to 47 mmol/mol	6.0% to 6.4%
Diabetes	48 mmol/mol or over	6.5% or over

The sample size of the study, will be 110 subjects. The rationale of the sample size is the following:

An average difference in HbA1c of Δ=1,4% will be considered as clinically significant.

For the purpose of the study, it will be considered that the standard deviation from last visit to baseline is around s=4%.

Therefore, in order to detect a significant difference at p-value=0,05 with a power of 90% (which is considered sufficient for our study) the subjects needed to be recruited are ≥ 86 based on the below formula:

$$n \geq 2\left(\frac{s}{\Delta}\right)^2 (1.96+1.28)^2$$

The administration of metformin hydrochloride will be provided orally via a capsule of 500mg once-daily, after breakfast throughout the 24-week treatment period. Observational study visits will be performed every 2 weeks (starting from week 0).

Treatment period will start on the 1st of January 2018 and will last for 24 weeks (i.e. 11th of June 2018).

All symptoms that will follow drug administration will be recorded, and the relevance to the drug will be determined by the doctors.

Furthermore, in order to calculate the compliance of the of the patients (*i.e. the extent to which they adhere to the protocol*) all patients will be asked regarding the number of drugs

left when they visit the clinic. The calculation will be performed by dividing the actual number of administrations by the planned number and will be scored by using the following scale:

- Excellent (100%);
- Very good (90-99%);
- Good (80-89%) and
- Poor (<80%).

3.2 Study Duration, Enrollment and Number of Sites

Screening period will start from 1st October 2017 and will last for 12 weeks, ending 24th of December 2017.

Enrollment in the study will start after the screening period from the 26th until the 31st of December 2017.

Treatment period will start on the 1st of January 2018 and will last for 24 weeks (i.e. until 11th of June 2018).

The site in which the study will be performed is "Evangelismos" Hospital of Athens.

3.3 Total Number of Subjects Projected

3.3.1 Duration of Study Participation

Study duration per subject will be up to 84 days for the screening period and up to 168 days for the treatment period.

3.3.2 Total Number of Subjects Projected

Recruitment will stop when approximately 150 subjects agree to participate. It is expected that approximately 130 subjects will be enrolled to produce 110 evaluable subjects.

3.4 Study Population

3.4.1 Inclusion Criteria

Inclusion Criteria

1. Patients aged ≥ 20 to <75 years with diagnosed type 2 diabetes mellitus.

2. Patients to be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the trial.

3.4.2 Exclusion Criteria

Patients should have no

1. hepatic;
2. cardiovascular or
3. pulmonary impairment;

4. Subjects treated with metformin before the study initiation.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

In general, all visits will contain similar activities in terms of preparation for the visit, greeting the participant, reviewing self-administered forms, performing the various activities of the visit, providing the participant with appropriate materials before he/she leaves, and scheduling the next visit. Since the visits contain many different activities and the participant will most likely be seen by different staff, it is helpful to have one person oversee the participant's progress through each screening visit. It is useful to have a visit-specific checklist for following the participant through the various activities and ensuring that the participant will completes them. [9]

The screening visits will be 4, starting from week -12 until week -1. In more detail, the visits will be:

- 1st visit in week -12;
- 2nd visit in week -8;
- 3rd visit in week -4;
- 4th visit in week -1.

During these visits, the relevant data should be collected:

- Inform consent form and medical record review of the subjects (*1st visit*) and in each visit the appropriate information should be collected.
- HbA1c levels;
- Information regarding hepatic, cardiovascular or pulmonary impairment.

Subjects will be eligible for enrolment if:

1. HbA1c level is ≥6.9% and <10.5% at week -4;
2. no more than 10% difference in HbA1c level between week -8 and -4;
3. No hepatic, cardiovascular or pulmonary impairment.

4.2 Observational Period - "24-week Treatment Period with metformin hydrochloride".

4.2.1 Visit 1

In the 1st visit, the following baseline characteristics of the patients will be collected:

[9] Women's Health Initiative (WHI), Volume 2, Section 4 – Screening, ClinicalTrials.gov Identifier: NCT00000611

General Characteristics:

- Male (%)
- Female (%)
- Caucasian (%)
- Age (mean, SD)
- Diabetes duration (median, IQR)
- Weight (median, IQR)
- Blood pressure (mean, SD), diastolic
- Current smoker (%)
- Ex-smoker (%)

Clinical history:

- Prior cardiovascular disease (%)
- Stroke (%)
- Angina (%)
- Peripheral vascular disease (%)
- Coronary revascularization (%)
- Hypertension (%)
- Microvascular disease (%)

Laboratory data:

- Total cholesterol (mmol/L, mean[SD])
- LDL cholesterol (mmol/L, mean[SD])
- HDL cholesterol (mmol/L, mean[SD)
- Triglycerides (mmol/L, median, IQR)
- Hemoglobin A1c (%, median, IQR)
- Creatinine (mM, mean [SD])
- Homocysteine (mM, median[IQR])
- Dyslipidemia (%)
- Microalbuminuria (%)
- Macroalbuminuria (%)

4.2.2 Visit 2

During visits 2 to 4 the following data should be collected:

- HbA1c level (%) or mmol/mol;
- Fasting Plasma Glucose (FPG);
- Fasting insulin levels and
- Body weight. [10]

[10] Associations between the use of metformin, sulphonylureas, or diet alone and cardiovascular outcomes in 6005 people with type 2 diabetes in the FIELD study, David Sullivan a,*, Peta Forder b,1, John Simes b, Malcolm Whiting c, Leonard Kritharides d, Alistair

Also, the compliance rate with the treatment should be calculated: This rate will be calculated by dividing the actual number of administrations by the planned number and results will be defined as:

- Excellent (100%);
- Very good (90-99%);
- Good (80-89%) and
- Poor (<80%).

Furthermore, all Adverse Events (AE) should be recorded in each visit.

4.3 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, or due to AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the Case Report Form (CRF).

4.3.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for this last visit as the early termination visit.

An "Early Termination Visit" questionnaire should be completed. An indicative questionnaire is the following:

1. _____ Confirm the participant's identity.
2. _____ Review/update locator information.
3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s).
4. _____ Review elements of informed consent as needed. Explain the content and sequence of procedures for today's visit. Determine visit code for this visit (regular or interim) based on participant's completed visits and visit window calendar.
5. _____ Complete AE Log form(s), based on interval medical history, clinical exams/assessments, and lab tests available.
6. _____ Complete the Termination CRF and End of Study Inventory CRF.

Also, the following logs should be completed:

- Adverse Experience Log;
- Concomitant Medication Log;
- Missed Visit.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The variables that should be abstracted from the medical chart are the following:

- Date of birth;
- Gender;
- Race (*for the purpose of this study should be Caucasian-Greek*);
- Diabetes duration;
- Weight;
- Prior cardiovascular disease;
- Stroke;
- Angina;
- Peripheral vascular disease;
- Coronary revascularization;
- Hypertension;
- Microvascular disease;
- Current;
- Ex-smoker;
- Blood pressure;
- Total cholesterol;
- LDL cholesterol;
- HDL cholesterol;
- Triglycerides;
- Hemoglobin A1c;
- Creatinine;
- Homocysteine;
- Dyslipidemia;
- Microalbuminuria;
- Macroalbuminuria.

5.1.2 Physical Examination

- General Appearance;
- HEENT (i.e. Head, Eyes, Ears, Nose and Throat);
- Neck;
- Chest and Lungs;
- Cardiovascular;
- Abdomen;
- Musculoskeletal;
- Lymph Nodes;
- Extremities/Skin;
- Neurological.

5.1.3 Vital Signs

- Temperature (measured with a certified thermometer);
- Pulse (resting pulse);
- Blood pressure (measured with a certified automated device or with an aneroid sphygmomanometer);
- O2 saturation 100% on room air (measured with a certified finger pulse oximeter).

5.1.4 Laboratory Evaluations

5.1.4.1 Table: Clinical Laboratory Tests

Category	Tests
Hematology	**RBC, hemoglobin, hematocrit, platelet count, White Blood Cell Count (WBC) with differential** (*The differential totals the number of each type and determines if the cells are present in normal proportion to one another, if one cell type is increased or decreased, or if immature cells are present. This information is useful in helping to diagnose the specific cause of an illness, such as: Inflammation, Infections caused by bacteria, viruses, fungi or parasites, Allergies, asthma.)*
Liver function tests	**SGOT/AST** (*i.e. Serum glutamic oxaloacetic transaminase /aspartate aminotransferase→enzymes that are normally present in liver and heart cells*), **SGPT/ALT** (i.e. serum glutamic-pyruvic transaminase and alanine transaminase→*reasonably sensitive indicators (enzymes) of liver damage or injury from different types of diseases or conditions*)
Renal function tests	Blood Urea Nitrogen (BUN), creatinine

5.2 Efficacy Evaluations

5.2.1 Diagnostic Tests, Measures and Scales.

During this study, patients will be required to visit the study center at weeks 0, 4, 8, 12, 16, 20 and 24 or at the time of discontinuation. At each visit, efficacy and safety will be evaluated by the investigator. The levels of daily HbA1c (in % or mmol/mol) will be collected for each patient and mean score and Standard Deviation (SD) will be calculated.

Diagnostic Test: The efficacy of the drug is determined by the difference in HbA1c before and after drug administration in the clinic.

Measures: HbA1c will be assessed by high-performance liquid chromatography using the Bio-Rad Diamat ionexchange method. Secondary efficacy variables will be measured at each visit using the hexokinase method.[11]

Scales: If the HbA1c level is ≥6.5% or 48mmol/mol or over then the subject is considered to have type 2 diabetes (According to World Health Organization (WHO)). If HbA1c is below 42 mmol/mol (i.e. 6.0%): the subject is considered non-diabetic, whereas if HbA1c is between 42 and 47 mmol/mol (i.e. 6.0–6.4%) the subject is considered to be prediabetic.[12]

5.3 Safety Evaluation

Adverse events (AEs) and vital signs will be evaluated at each visit. Body weight and clinical laboratory test results will be evaluated every 4 weeks or at the time of discontinuation. AEs will be summarized by the preferred term using the Medical Dictionary for Regulatory Activities version 18.0

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is to assess the efficacy of metformin hydrochloride therapy for adults with type 2 diabetes mellitus. The efficacy of the drug is determined by the difference in HbA1c before (week 0) and after (week 24) drug administration in the clinic.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

Change before and after drug administration in the clinic, in:

- Fasting Plasma Glucose (FPG);
- Fasting insulin;
- Fasting glucagon;
- Body weight;
- Safety and tolerability of metformin based on Adverse Events.

Degree of compliance with the treatment: will be calculated by dividing the actual number of od administrations by the planned number and results will be defined as:

- Excellent (100%);
- Very good (90-99%);
- Good (80-89%) and

[11] DIABETES CARE, VOLUME 23, NUMBER 11, NOVEMBER 2000.Nateglinide Alone and in Combination With Metformin Improves Glycemic Control by Reducing Mealtime Glucose Levels in Type 2 Diabetes, EDWARD S. HORTON, MD CYNTHIA CLINKINGBEARD, MD MARJORIE GATLIN, MD JAMES FOLEY, PHD SUSAN MALLOWS, BA SHARON SHEN, MS.
[12] Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus, WHO/NMH/CHP/CPM/11.1

- Poor (<80%).

6.3 Control of Bias

Selection Bias: The study population is not a random selection from the target population for which a statement is to be made. Individuals are then recruited in such a way that they are not representative of the target population. Even if the study is well planned, it may happen that not all selected persons take part in the study, because the voluntary character of the study must always be guaranteed.[13]

Therefore, in order to avoid selection bias a stratified sampling will be performed in which all recorded patients of the hospital with diabetes type II, will be divided into strata based on their age. In more detail, the groups will be the following:

- 1st group: 20-25 years of age;
- 2nd group: 25-30 years of age;
- 3rd group: 30-35 years of age;
- 4th group: 35-40 years of age;
- 5th group: 40-45 years of age;
- 6th group: 45-50 years of age;
- 7th group: 50-55 years of age;
- 8th group: 55-60 years of age;
- 9th group: 60-65 years of age;
- 10th group: 65-70 years of age;
- 11th group: 70-75 years of age.

For each group, a simple random sampling will be performed (i.e. 10 subjects per group→total 110 subjects).

The above selected subjects will be approached by their doctors either in person or via email or telephone contact and it should be clearly stated that it is on the free will of the patient to participate.

If the subjects are not sufficient to achieve the study goals then the remaining number will be covered by subjects recruited by paid website advertisements (*note: all recruitment materials that subjects will see and/or hear must be reviewed and approved by the IRB before they are used to recruit subjects*).

Information bias: results from wrong or inexact recording of individual factors, either risk factors or the disease being studied. With continuous variables (*such as blood pressure*), this is referred to as measurement error; with categorical variables (*such as tumor stage*), this is known as misclassification. Measurement error or misclassification may result from lack of care by the investigator or from poor quality of measuring or survey instruments.[14]

[13] [14] Medicine, Review Article, Avoiding Bias in Observational Studies, Part 8 in a Series of Articles on Evaluation of Scientific Publications, Gaël P Hammer, Jean-Baptist du Prel, Maria Blettner.

Therefore, to avoid information bias/measurement error, all blood samples will be taken in the morning (*7 h fasting (overnight) before each scheduled visit*) and will be analyzed at the same time in the certified laboratory of the hospital (*see chapter: 4.4.4.1 Clinical Laboratory Tests*).

6.4 Statistical Methods

6.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (*see chapter 4.2.1. → e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender*).

6.4.2 Analysis of Primary Outcome of Interest

The primary endpoint will be the change in the difference in HbA1c before (i.e. week 0) and after drug administration (i.e. week 24) in the clinic.

The difference in change will be analyzed with a paired t-test (*standard error (s.e.) and 2-sided confidence intervals (CIs) will be calculated*) or with a Wilcoxon rank-sum test if the distribution of the data is found to be not normal.

6.4.3 Analysis of Secondary Outcomes of Interest

The secondary objectives are to determine changes before (i.e. week 0) and after drug administration (i.e. week 24) in the clinic, in:

- Fasting Plasma Glucose (FPG);
- Fasting insulin;
- Fasting glucagon;
- Body weight

For the above-mentioned variables, the difference in change will be analyzed with a paired t-test (*standard error (S.E) and 2-sided confidence intervals (CIs) will be calculated*) or with a Wilcoxon rank-sum test if the distribution of the data is found to be not normal.

- Safety and tolerability of metformin based on Adverse Events.

The safety will be calculated with the overall frequency (%) of adverse events and tolerability will be calculated by the rate (%) of "dropouts" due to adverse events.

Degree of compliance with the treatment will be calculated by dividing the actual number of administrations by the planned number and results will be defined as:

- Excellent (100%);
- Very good (90-99%);
- Good (80-89%) and
- Poor (<80%).

Furthermore, investigators could use One-Way ANOVA to analyze the primary of secondary objectives (*apart from safety and tolerability*) by age groups or gender.

Another approach would be to use a multivariate analysis such as the Hoteling T2 test (*as a generalization of the typical t-test*) in order to examine the individual secondary variables (*i.e. FPG, Fasting insulin and Fasting glucagon*) as accumulated evidence of the overall test.

6.5 Sample Size and Power

An average difference in HbA1c of Δ=1,4% will be considered as clinically significant.[15]

For the purpose of the study, it will be considered that the standard deviation from last visit to baseline is around s=4%.

Therefore, in order to detect a significant difference at p-value=0,05 with a power of 90% (*which is considered sufficient for our study*) the subjects needed to be recruited are ≥ 86 based on the below formula:

$$n \geq 2\left(\frac{s}{\Delta}\right)^2 (1.96+1.28)^2$$

The goal of the study is to recruit approximately 110 subjects that will take part in the study.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Adverse events (AEs) and vital signs will be evaluated at each visit. Body weight and clinical laboratory test results will be evaluated every 4 weeks or at the time of discontinuation. AEs will be summarized by the preferred term using the Medical Dictionary for Regulatory Activities version 18.0.

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk*, Serious Adverse Events (SAEs) are not expected.

[*Accoridng to the "Institutional Review Board Guidebook- Chapter III, Basic IRB Review (Institutional Review Board):

Minimal Risk: *A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy §___.102(i)]. For example, the risk of*

[15] DIABETES CARE, VOLUME 23, NUMBER 11, NOVEMBER 2000.Nateglinide Alone and in Combination With Metformin Improves Glycemic Control by Reducing Mealtime Glucose Levels in Type 2 Diabetes, EDWARD S. HORTON, MD CYNTHIA CLINKINGBEARD, MD MARJORIE GATLIN, MD JAMES FOLEY, PHD SUSAN MALLOWS, BA SHARON SHEN, MS.

drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.)" **][16]**

If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (*including SAEs*) these will be reported to the IRB in narrative or other format and submitted to the IRB at the time of continuing review.

7.3 Definition of an Adverse Event

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (*including an abnormal laboratory finding*), symptom, or disease temporally associated with the use of a medicinal (*investigational*) product, whether or not related to the medicinal (*investigational*) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).[17]

Adverse events will be recorded throughout the study and will be rated by the investigator as to their severity and relationship to study medication. All AEs (*including serious AEs*) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (*mild, moderate, severe*), duration, causality, and outcome of the event.

7.4 Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR):

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
  or
- is a congenital anomaly/birth defect.[18]

7.5 IRB Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed in accordance with the timeline below. External SAEs that are both unexpected

[16] Institutional Review Board Guidebook

[17] Adverse Event Terminology, Norman M. Goldfarb, Journal of Clinical Research Best Practices, vol. 8, No. 7, July 2012.

[18] GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1), ICH HARMONISED TRIPARTITE GUIDELINE, Current Step 4 version dated 10 June 1996.

and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

7.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (*e.g., concomitant medication, medical history*) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

7.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting must be consistent with regulatory.

8 STUDY ADMINISTRATION

8.1 Data Confidentiality and Backing up system.

1. **Confidentiality:** A statement should be signed by the study personnel and investigator that all data and records generated during this study will be kept confidential in accordance with institutional policies on subject privacy and that the investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

   The confidentiality of the data will be ensured by keeping a master list containing protected health information (PHI) and case report forms password protected and located in a locked file cabinet.

2. **Recovering Security:** For recovering the master list and case reports, there should be a password protected copy on a separate removable disk of the investigator.

8.2 Regulatory and Ethical Considerations

8.2.1 Data and Safety Monitoring Plan

Since this is a minimal risk study, the principal investigator (PI) (or approved co-investigator) will monitor the study with prompt reporting of adverse events and other study related information to the IRB, National Institute of Mental Health (NIMH), and other agencies as appropriate. Non-serious adverse events and unrelated serious adverse events will be reported in the annual progress report to the NIMH. Serious adverse events that could be related to the study should be reported to the NIMH Program Officer within 7 days of becoming aware of the event. All study deaths must be reported to the NIMH Program Officer immediately. Team meetings by the PI and his/her staff will be conducted on a routine basis to discuss any new adverse events or changes in the protocol. A Data and Safety Monitoring Plan (DSMP) that addresses the potential risks of the study will be reviewed and approved by the NIMH Program Officer and the Office of Clinical Research (OCR). This plan will be revised and updated if the benefit-risk analysis changes.[19]

8.3 Recruitment Strategy

The subjects will be derived from the Hospitals' patients and will be approached by their doctor either in person or via email or telephone contact. During this process, it must be guaranteed that the subject is acting on his/her own free will in order to safeguard the voluntary character of the study. If the subjects are not sufficient to achieve the study goals then the remaining number will be covered by subjects recruited by paid website advertisements (*note: all recruitment materials that subjects will see and/or hear must be reviewed and approved by the IRB before they are used to recruit subjects*).

8.4 Informed Consent/Assent and HIPAA Authorization

An informed consent form will be obtained upon initiation of the screening period by the investigator. One week prior to visit 0, the consent form will be sent via email and an explanatory text will also be sent in order for the nature of the study to be comprehend. The telephone of the investigator will be provided for any further clarification that a subject might have.

[19] NIH Guidance NOT-OD-12-129

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