La pianificazione di uno studio clinico: gli elementi essenziali di un protocollo

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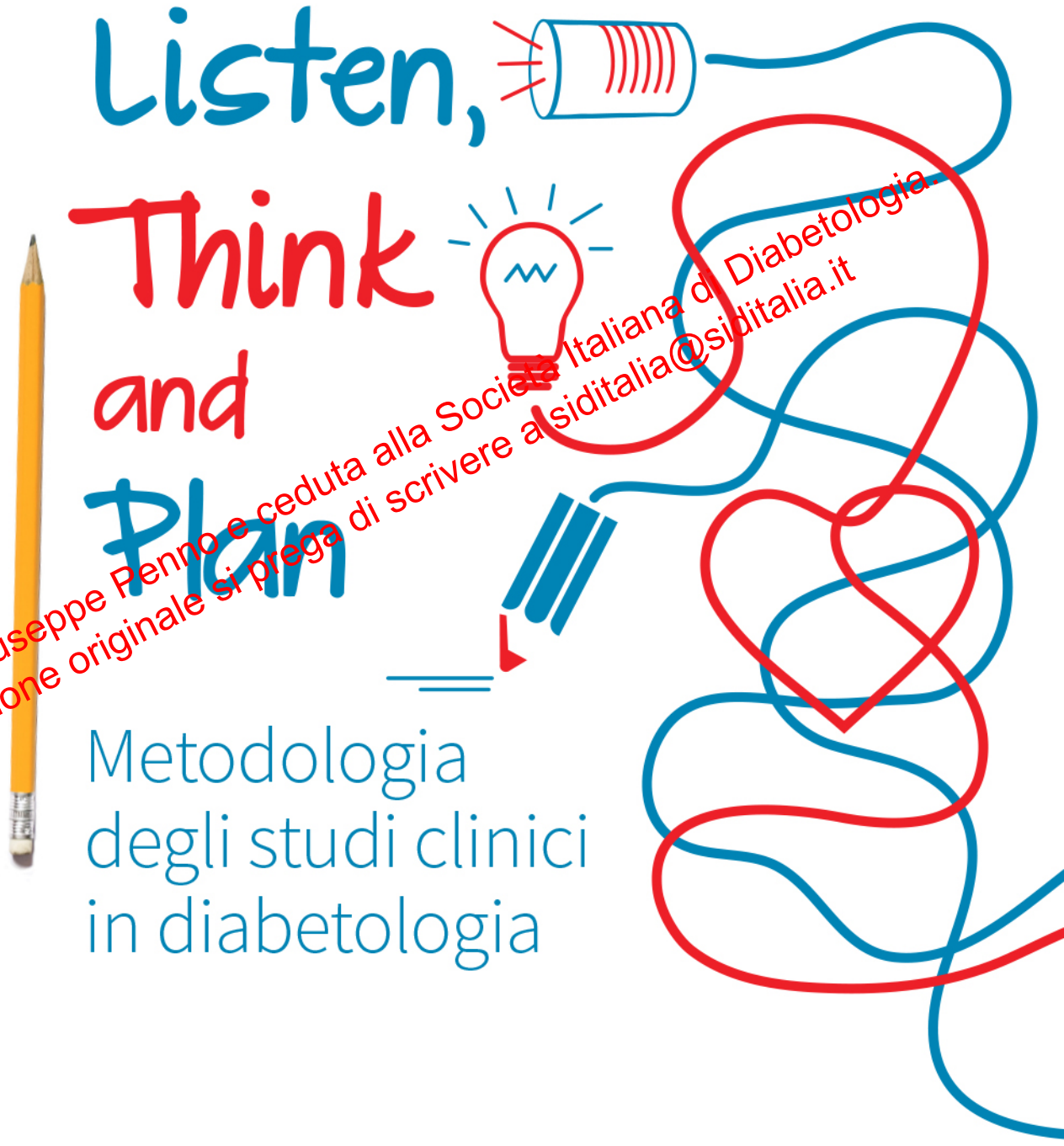

Metodologia degli studi clinici in diabetologia

Embarking on a Research Project

WHAT IS A PROTOCOL ?

- A research proposal (protocol) is a **detailed description** of a study designed to investigate a problem.
- A (clinical *vs.* non-clinical) research is conducted according to a protocol, i.e., an **action plan**.
- The **primer** of a study protocol is an **idea** that address a (clinical vs. non-clinical) need.
- The protocol (the **DNA of the project**) serves as a guide for conducting the study.
- The plan illustrates what will be made in the study and how it will be carried out. It should be **complete**, **robust**, **credible** and **doable**.
- Format may vary, but the **basic principles and key components remain the same**.

A BRIGHT IDEA: essential but not sufficient

KEY POINTS OF A RESEARCH PROPOSAL

- To raise **the research question** and to clarify its relevance (justify for the need of the project, clarify why the study is important).
- **To collect existing knowledge** and discuss the effort of other researchers who worked on the topic (literature search).
- To clearly **formulate the hypothesis and the objectives**.
- To state **where** and **when** the study will take place (the setting, the sites).
- To address **ethical** considerations.
- To describe **the design** of the study and **the methodology** required for solving the question and achieving the objectives.
- To discuss the **limitations** in achieving the objectives.
- Propose **time table** and budget.

Embarking on a Research Project

Components of a Research Protocol

WRITING THE PROTOCOL - Components

- **Title of the study**
- Administrative details (contact details, signatures, …)
- **Project summary**
- **The format:**
  - **Introduction, background, literature review** (references)
  - **Study goals and objectives**
  - **Methodology: study design, study population, follow-up …**
  - **Work plan** (project management), **timeline, milestones, data management and statistical analysis**
- Strenght and limitations of the study
- **Issues for ethical review and approvals** (safety considerations)
- **Significance** of the study (expected outcomes)
- **Dissemination** of results and publication policy
- **Budget proposal**
- **Appendixes**

Title of the Study

- Concise, accurate, descriptive, **informative**, relevant, and **attractive**
- **Acronym**
- The title should … :
  - … highlight the main objective in a plain manner
  - … convey the idea and the research area
  - … convey the main purpose
  - … state, eventually, functional relationships
  - … mention the target population
  - … carry the **maximum information in a few words** (12-15)

Title of the Study - Acronym

Renal Insufficiency And Cardiovascular Events (RIACE)

This study is ongoing

Sponsor:
Diabetic Nephropathy Study Group

Collaborator:
Italian Society of Diabetology

Information provided by (Responsible Party):
Giuseppe Pugliese, Diabetic Nephropathy Study Group

ClinicalTrials.gov Identifier:
NCT00715481

First received: July 10, 2008
Last updated: February 9, 2015
Last verified: February 2015
History of Changes

ClinicalTrials.gov

Title of the Study - Acronym

Efficacy and Safety of Pioglitazone in Treating Subjects With Vascular Complications Associated With Type 2 Diabetes Mellitus. (SPLENDOR)

This study has been completed.

Sponsor:
Takeda

Information provided by:
Takeda

ClinicalTrials.gov Identifier:
NCT00770835

First received: October 8, 2008
Last updated: July 11, 2011
Last verified: July 2011
History of Changes

ClinicalTrials.gov

Project Summary/Protocol Synopsis

- Concise, descriptive, informative, relevant, and **attractive**.
- The summary should … :
    - … sum up all **the essentials** of the protocol
    - … include …
        - … the main research question
        - … the **rationale** of the study
        - … the **hypothesis** and the **objectives**
        - … the **methods** (shortly the design, the procedures)
    - … **stand on its own**, and not refer the reader to points in the full project description.
- Remember … :
    - … the abstract and summary are **prepared the last**, **read the first**

- ***Embarking on a Research Project***
- ***Components of a Research Protocol***
- ***The format of the protocol: introduction, hypothesis, objectives, variables, …***

The traditional format: Introduction

- The introduction should … :
    - … provide the **background** information
    - … **update published research** in the field
    - … establish a **framework for the research** (the context)
- The introduction is necessary for the investigators … :
    - … to familiarize with the existing knowledge
    - … to find out **whether or not others** have explored the same problem
    - … ensures that the study is not “re-investing the wheel”
    - … **describe link to other projects**
- The literature selected should be pertinent and relevant
- **Against this background, it will be presented the rationale** of new the study and why it is worth doing (**why the study**)

The traditional format: Hypothesis

- The hypothesis is a statement **based on sound scientific theory** that recognizes the predicted correlation between two or more variables.
- A research hypothesis poses a relationship between two or more variables but phrases this relationship as a question.
- A hypothesis represents a declarative statement of the relationship between two or more variables.
- A hypothesis can be defined as a tentative prediction or explanation of the relationship between two or more variables.

The traditional format: Objectives

- These are the **goals to be achieved** by conducting the research
- The objectives should be … :
  - … explicitly stated
  - … consistent with the study questions/hypothesis
  - … logical and coherent, feasible and realistic
  - … relevant and time based
- The objective (goals) are to be distinguished in … :
  - … **primary objective**
  - … secondary objective(s)
  - … safety objective(s)
  - … exploratory objective(s)
- They should be stated in action verbs, i.e. *"to determine, to compare, to verify, to assess, to describe"*
- **For each objective, an outcome measure** should be defined
- It is advisable to resist the temptation to put too many objectives (**2 to 5 best**) or over-ambitious objectives that cannot be reasonably achieved
- Too many objectives often lead to inaccurate and poorly defined results

The traditional format: Objectives

1

Primary Objective:	Outcome Measure:
To compare the mean change from baseline in HbA1c between and placebo, after 24 weeks of oral administratic double-blind treatment in patients with type diabetes and CKD stage 3A.	Change from baseline in HbA1c at Week 24

3

Secondary Objective:	Outcome Measure :
To compare the percent change from baseline in total body weight betwe mg and placebo, after weeks of oral administration of double-blind treatment.	Percent change from baseline in total body weight at Week 24
To compare the change from baseline in fasting between 24 weeks of oral le-blind treatment.	Change from baseline in FPG at Week 24
e from baseline in seated (SBP) between d placebo, after 24 weeks atment.	Change from baseline in seated SBP at Week 24

3

Safety Objective:	Outcome Measure :
To examine eGFR changes during the study and 3-weeks post-treatment for mg and placebo.	Change in eGFR from baseline to end of treatment and 3-weeks post-treatment
To assess the proportion of patients disco from study medication because of worse renal insufficiency (defined as patients confirmed eGFR levels <30 m /1.73 between mg and placebo	from study
To evaluate th ty and tole bility of	

20

Exploratory Objective:	Outcome Measure
To compare the from the initiation of insulin therapy between dapagliflozin 10 mg and placebo in patients not receiving insulin therapy at baseline after 24 weeks of oral administration of double-blind treatment.	Proportion of patien after study start
To assess differences in the percent change from baseline in urinary albumin to creatinine ratio (UACR) at the end of oral administration of double-blind treatment in patients with baseline UACR ≥30 mg/g (and m albuminaria) between dapagliflozin 10 ebo.	Percent change fron of treatment

Exploratory Objective:	Outcome Measure :
To assess differences in percent change from baseline in UACR at the end of oral administration of double-blind treatment in patients with baseline UACR ≥15 mg/g and <30 mg/g (high normal albuminuria) between dapagliflozin 10 mg and placebo.	Percent change from baseline in UACR to end of treatment
To compare the change from baseline in eGFR between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in eG
To assess differences in change from baseline in HbA1c after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Change from baseline in Hb subgroup defined by baseli
To assess differences in percent change from baseline in total body weight after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Percent change from baseli weight at Week 24 by subg baseline HbA1c
To assess differences in change from baseline in seated SBP after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Change from baseline in sea by subgroup defined by bas
To compare the proportion of patients achieving a therapeutic glycemic response defined as HbA1c < 7% achieved between dapagliflozin 10 mg and placebo after 24 weeks of oral administration of double-blind treatment (or prior to rescue).	Proportion of patients achie Week 24 (or prior to rescue
To assess differences in the percent changes from baseline in total body weight after 24 weeks of oral administration of double-blind treatment in patients with a baseline BMI <25 kg/m², ≥25 kg/m², ≥27 kg/m², and ≥30 kg/m² between dapagliflozin 10 mg and placebo.	Percent change from baseli weight at Week 24 by subg baseline BMI

Exploratory Objective:	Outcome Measure :
To assess differences in percent change from baseline in UACR at the end of oral administration of double-blind treatment in patients with baseline UACR ≥15 mg/g and <30 mg/g (high normal albuminuria) between dapagliflozin 10 mg and placebo.	Percent change from baseline in UACR to end of treatment
To compare the change from baseline in eGFR between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in eGFR at Week
To assess differences in change from baseline in HbA1c after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Change from baseline in HbA1c at Wee subgroup defined by baseline HbA1c
To assess differences in percent change from baseline in total body weight after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Percent change from baseline in total b weight at Week 24 by subgroup defined baseline HbA1c
To assess differences in change from baseline in seated SBP after 24 weeks of oral administration of double-blind treatment in patients with baseline HbA1c ≥ 8.5%, baseline HbA1c ≥ 7.5% and < 8.5%, baseline HbA1c < 7.5% between dapagliflozin 10 mg and placebo.	Change from baseline in seated SBP at by subgroup defined by baseline HbA1
To compare the proportion of patients achieving a therapeutic glycemic response defined as HbA1c < 7% achieved between dapagliflozin 10 mg and placebo after 24 weeks of oral administration of double-blind treatment (or prior to rescue).	Proportion of patients achieving HbA1c Week 24 (or prior to rescue)
To assess differences in the percent change from baseline in total body weight after 24 weeks of oral administration of double-blind treatment in patients with a baseline BMI <25 kg/m², ≥25 kg/m², ≥27 kg/m², and ≥30 kg/m² between dapagliflozin 10 mg and placebo.	Percent change from baseline in total b weight at Week 24 by subgroup defined baseline BMI

Exploratory Objective:	Outcome Measure :
To compare the proportion of patients meeting all criteria of a 3-item endpoint of clinical benefit after 24 weeks of treatment (or prior to rescue) between dapagliflozin 10 mg and placebo, defined as: • an absolute drop of 0.3% or more from baseline HbA1c, and • a relative drop of 3% or more from baseline for total body weight, and • an absolute drop of 3 mmHg or more from baseline in seated SBP	Proportion of patients meeting the specified criteria in HbA1c (drop of ≥0.3%), body weight (drop of ≥3%), and seated SBP (drop of ≥3mmHg) to end of treatment (or prior to rescue)
To compare the change from baseline in 24 hour urinary glucose excretion after 24 weeks of oral administration of double-blind treatment (or prior to administration of anti-diabetic rescue medication) between dapagliflozin 10 mg and placebo.	Change from baseline in 24h urinary glucose excretion at the end of treatment (or prior to rescue)
To assess the differences in proportion of patients with baseline elevated blood pressure (baseline SBP ≥130 mmHg and baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated SBP of <130 mmHg and a seated DBP of <80 mmHg after 24 weeks of oral administration of double-blind treatment between dapagliflozin 10 mg and placebo.	Proportion of patients with baseline elevated blood pressure (baseline SBP ≥130 mmHg and baseline DBP ≥80 mmHg) who achieve a seated SBP of <130 mmHg and a seated DBP of <80 mmHg at end of treatment
To assess the relationship between changes from baseline in HbA1c over baseline eGFR values for dapagliflozin 10mg treatment and for placebo after 24 weeks of oral administration of double-blind treatment (or prior to rescue)	Predicted change from baseline in HbA1c at end of treatment (or prior to rescue) at baseline eGFR=45 mL/min/1.73m², baseline eGFR=50 mL/min/1.73m², and baseline eGFR=55 mL/min/1.73m²

The traditional format: Variables

- Identify the **key variables** of the study (and the methods of measurement)
- Four types of variables:
  - **Dependent variables** (outcome, endpoint)
  - **Independent variables** (cause, predisposing factor, risk factor, determinant, antecedent) = variables that are manipulated or treated (one or more) in order to see the effects on the dependent variables (one or more)
  - **Confounding or intervening variables** = variables that may exert a confounding role in the relationship between the independent variables and the dependent outcome
  - **Background variables** = mandatory variables such as sex, age, ethnic origin, but also education, social status, ….

- ***Embarking on a Research Project***
- ***Components of a Research Protocol***
- ***The format of the protocol: introduction, hypothesis, objectives, variables, …***
- ***The format of the protocol: methodology, study design, sample size, …***

The traditional format: methodology

- This is the plan to tackle the research problems.
- It should contain sufficient information to determine whether the methodology is sound.
- It explains the study design and procedures and techniques used to achieve the proposed objectives.
- Possibly, a good proposal should contain sufficient details for another qualified researcher to implement the study.
- In details: “where”, “who”, “how”

The traditional format: study design

- The **selection of the research strategy** is the core of research design and is probably the most important decision the investigator has to take.
- The choice of the strategy is in relation to the study objectives.
- Pilot data or trial runs may be appropriate.

Purpose	Study Design
To determine frequency and burden of a disease	• Cross-sectional survey (prevalence) • Cohort study, longitudinal (incidence)
To identify the risk factors	• Cohort study • Case-control study
To determine prognosis of a disease	• Cohort study
To determine efficacy, effectiveness, safety of a (new) treatment	• Randomized Controlled Trials (RCT) • Non-Randomized Controlled Trials (Observational Designs) • Community intervention
To evaluate community programs	• Evaluation

The traditional format: study population/subjects

- Why this **population**, why these **individuals**.
- The choice is in relation to the study objectives.

Point	*Note*
Sampling procedure	• *To ensure representativeness and reliability*
Criteria for eligibility: inclusion or selection	
Criteria for no eligibility: exclusion	
Criteria for discontinuation	
Allocation of subjects to study arms	• *Randomization, ….*
Control group	• *Essential in epidemiological studies, in drug trials, in research on effects of intervention programmes, ….*
Sample size	• *A smaller than needed sample size might preclude sound scientific improvement*

EURODIAB IDDM Complications Study

1. To define the geographical catchment area

- To stratify all eligible individuals into the 14 sex-age-duration of diabetes groups:

Age-Duration Structure of the Sample							
Sex		Males			Females		
Age at examination (years)		15-	30-	45-	15-	30-	45-
Duration of diabetes (years)	1-7	n	n	--	n	n	--
	8-14	n	n	--	n	n	--
	≥15	n	n	n	n	n	n

- Use random number tables to select 12 patients for each group with the aim of including 10 patients for each cell (2 acting as reserves)

EURODIAB IDDM Complications Study

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Age-Duration Structure of the Sample							
Sex		Males			Females		
Age at examination (years)		15-	30-	45-	15-	30-	45-
Duration of diabetes (years)	1-7	12 ← 10	12 ← 10	--	12 ← 10	12 ← 10	--
	8-14	12 ← 10	12 ← 10	--	12 ← 10	12 ← 10	--
	≥15	12 ← 10	12 ← 10	12 ← 10	12 ← 10	12 ← 10	12 ← 10

- Use random number tables to select 12 patients for each group with the aim of including 10 patients for each cell (2 acting as reserves)

Inclusion & Exclusion criteria

3.1 Inclusion criteria

Patients should meet all inclusion criteria at the time of randomization. If at the time of enrolment (Visit 1) or start of lead-in (Visit 2) it is known that the patient will not meet criteria after a successful lead-in period, they should not be entered into single-blind placebo lead-in.

For inclusion in the study, patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.
2. Female or male aged ≥18 years and <75 years.
3. History of T2DM for more than 12 months.
4. Inadequate glycemic control, defined as HbA1c ≥7.0% and ≤11% measured at Screening. Note that HbA1c will be rechecked at Visit 4, and must then be ≥7.0 and ≤10.5% (value from blood sample obtained at Visit 3) for patient to be randomized.
5. Stable anti-diabetic treatment regimen, defined as stable diet and exercise therapy alone or in combination with any or both of the two following alternatives:
   - A regimen of any approved oral anti-diabetic medication (except SGLT2 inhibitors) where no dose-changes have occurred during 12 weeks before randomization
   - Long acting or intermediate acting insulin and mixed insulin permitted, as long as the dose is stable during last 12 weeks before randomization. Changes ± 10% are allowed (in relation to number of units at randomization). For example, if the patient is taking 50 units/day of insulin at randomization, the total daily doses in the past 12 weeks should not have exceeded 55 units, or been less than 45 units. However, occasional exceptions (≤ one day/week) during this time period are permitted.
6. Renal impairment: CKD 3A
   - eGFR* 40 – 65 mL/minute/1.73 m^2 at Visit 2 (value from blood sample obtained at Visit 1) to enter the lead-in period.
   - eGFR* 45 – 59 mL/minute/1.73 m^2 at Visit 4 (average value calculated from the eGFR values at Visit 2 and Visit 3) for randomization.

   *according to the re-expressed abbreviated (four-variable) MDRD Study equation, using central laboratory measurements of serum creatinine(sCr). [eGFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL]
7. Body mass index (BMI) between 18 and 40 kg/m^2, inclusive.

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3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Sex and Reproductive Status

1. Women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable m
2. Women who
3. Women with administrati

Central Laboratory T

4. Aspartate Am
5. Alanine Am
6. Total Bilirul
7. Serum Potassium (K) >5.5 meq/L (5.5 mmol/L).
8. Serum Calcium (Ca) <8 mg/dL or > ULN
9. Positive for hepatitis B surface
10. Positive for anti-hepatitis C virus antibody.
11. Hemoglob (90 g/L).

Target Di e Exclusions

12. History of diabetes
13. Symptoms
14. History of diabetic ket
15. History of ≥2 major hy defined as symptomati impairment in consciou <54 mg/dL (plasma gl after glucose or glucag

Medical History and Concurre

CV/Vascular diseases:

16. Severe uncontrolled hy mmHg at any visit up

Any of the following CV/Vascu consent at visit 1:

17. Myocardial infarction.
18. Cardiac surgery or rev
19. Unstable angina.
20. Unstable heart failure
21. HF New York Heart A
22. Transient ischemic att
23. Unstable or previously undiagnosed arrhythmia.

Renal Diseases:

24. History of any biopsy or imaging verifying intercurrent kidney disease (such as glomerular nephritis or sign of renal artery stenosis) other than diabetic nephropathy or diabetic nephropathy with nephrosclerosis.
25. History of renal transplant.
26. Hemodialysis, ultrafiltration therapy, or peritoneal dialy signing the consent at visit 1.

Hepatic Diseases:

27. Significant hepatic disease, including, but not limited t and/or severe hepatic insufficiency.
28. Documented history of hepatotoxicity with any medica
29. Documented history of severe hepatobiliary disease.

Hematological and Oncological Diseases/Conditions:

30. History of hemoglobinopathy, or chronic or recurrent h
31. Donation of blood or blood products to a blood bank; bi participation in a clinical study requiring withdrawal of the 6 weeks prior to signing the consent at visit 1.
32. Malignancy within 5 years of the enrolment visit (with basal cell or treated squamous cell carcinoma).
33. Known immunocompromised status, including but not have undergone organ transplantation or who are positi immunodeficiency virus (HIV).
34. History of unexplained microscopic or gross hematuria. visit 2.

Allergies and Adverse Drug Reactions:

35. Known allergies or contraindication to the contents of tablets. The tablets contain lactose and may cause disco

Prohibited Treatments and/or Therapies:

36. Long term treatment with glucocorticoids (two temporary periods of no longer than 10 days each are allowed during the study); topical or inhaled corticosteroids are allowed.
37. A metformin dose which is outside the specified dose range for moderate renal impairment (eGFR 30– 59 mL/minute/1.73m^2, MDRD formula) according to local guidelines and investigator's judgement.
38. Ongoing treatment with any SGLT2-inhibitor at screening.
39. History of bariatric surgery or lap-band procedure.
40. Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, Victoza (liraglutide) indicated for anti-obesity treatment, and/or phendimetrazine, within 30 days prior to signing the consent at visit 1.

Other Exclusion Criteria:

41. Any unstable endocrine, psychiatric, or rheumatic disorders as judged by the Investigator.
42. Patient is, in the judgment of the Investigator, unlikely to comply with the protocol or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.
43. Patient who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion due to co-existing conditions.
44. Patient with any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient.
45. Patient is currently abusing alcohol or other drugs or has done so within the last 6 months prior to signing the consent at visit 1.
46. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
47. Previous enrolment in the present study.
48. Participation in another clinical study with an IP during the last 30 days prior to signing the consent at visit 1.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and to ensure that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

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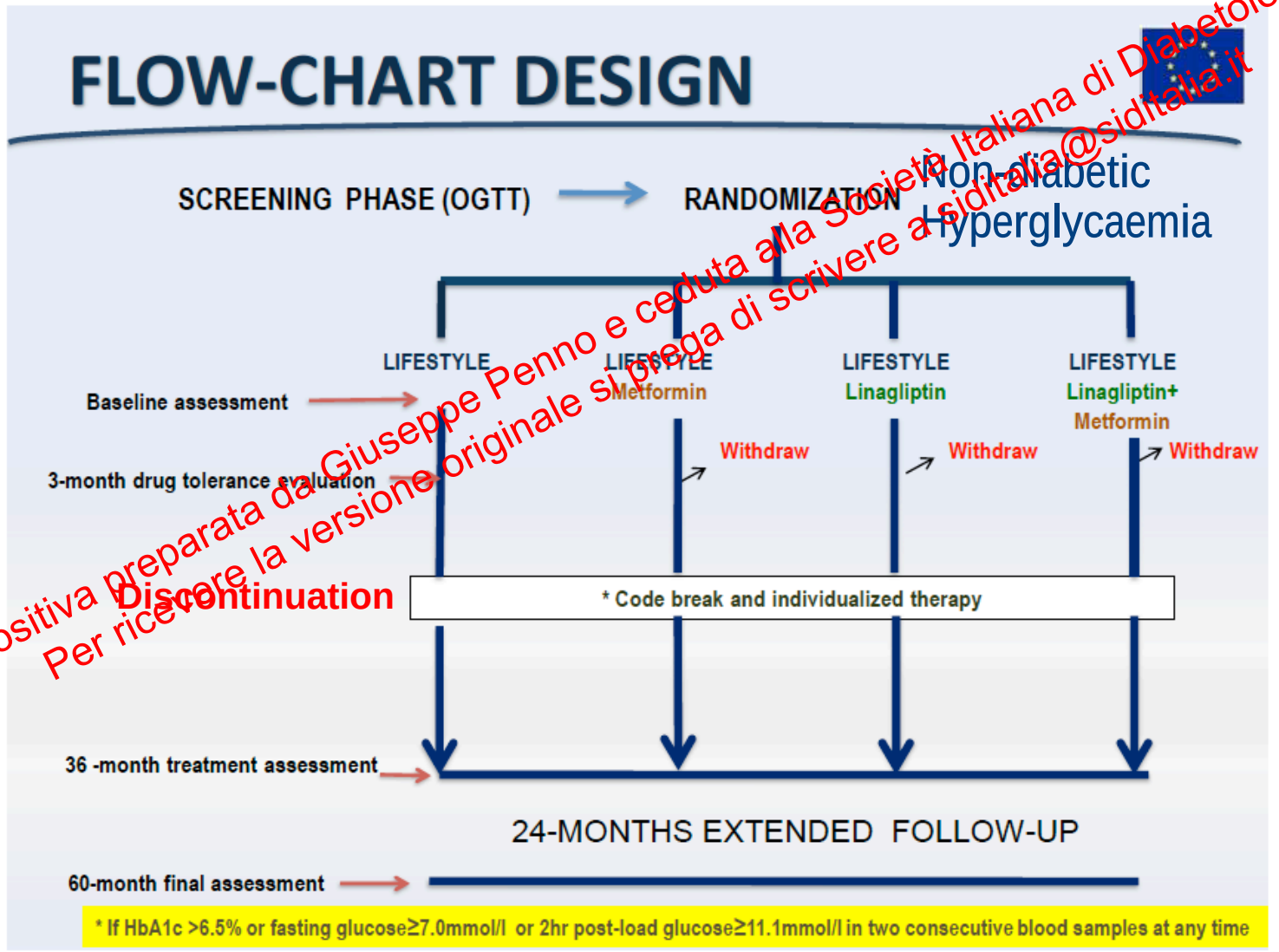
Early Prevention of Diabetes Complications in people with Hyperglycaemia in Europe: Study e-PREDICE



The traditional format: intervention(s)

- Full **description of proposed intervention** should be given.
- All activities and actions should be recorded in their order of occurrence.

Intervention/activities	*Note*
Drug/treatment	• *Scientific and brand name* • *Manufacturing company, city, country* • *Drug route, dosage, frequency of administration, duration of treatment* • *Approval of the drug regulatory agency*
Apparatus or device	• *Name and characteristics* • *Manufacturing company, city, country*
Involved personnel	• *Who is responsible* • *What activities each personnel will perform*

The traditional format: data collection/management

- Several details should be provided.

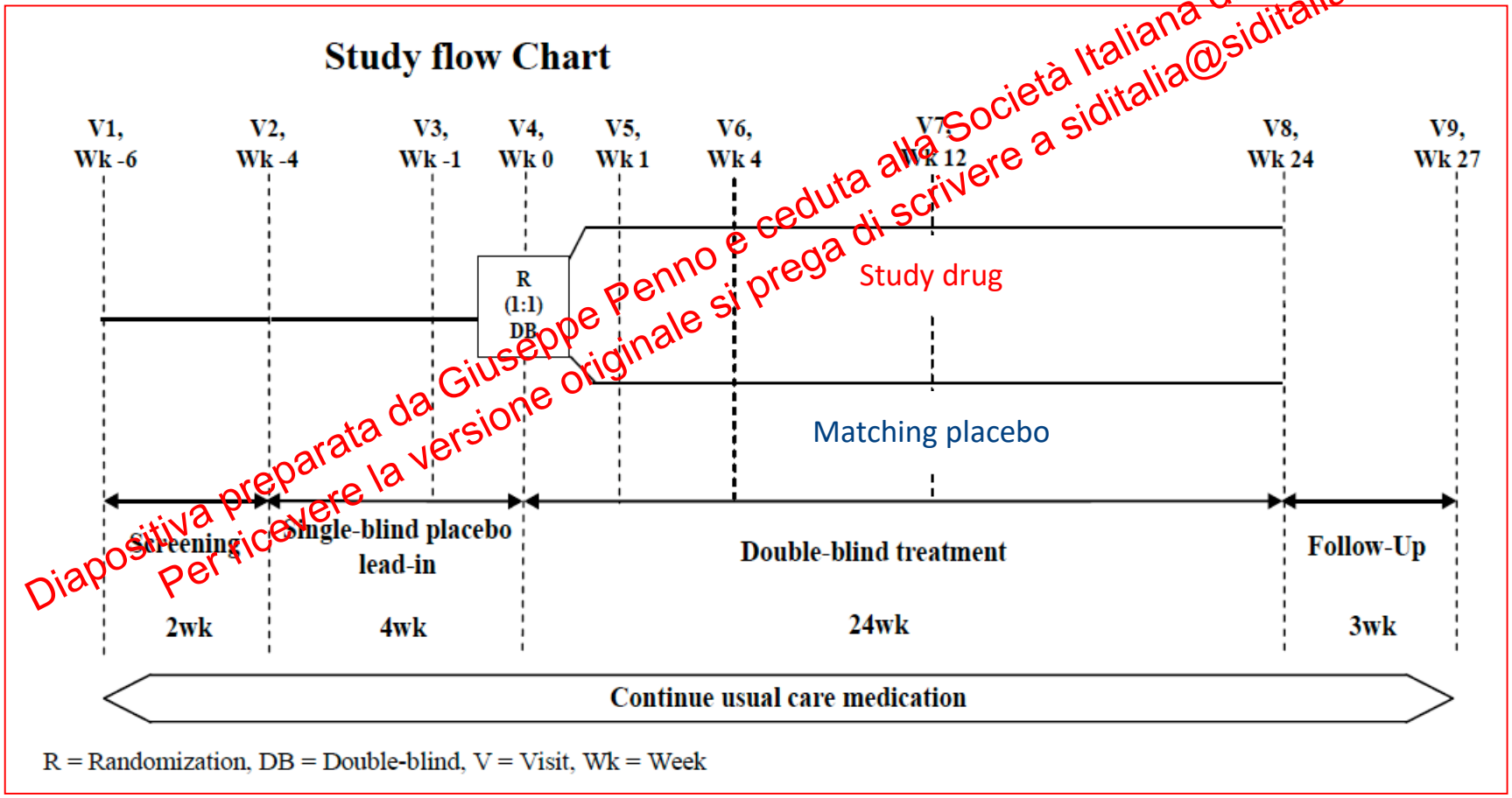
Tools/instruments	*Note*
Retrospecive data	• *Medical reports* • *Laboratory reports*
Validated questionnaires/Interview schedules	• *Structured* • *Semi-structured*
Specifically designed questionnaires	• *Details about preparing, precoding and pretesting* • *Appended to the proposal*
Laboratory test	• *Established tests (literature)* • *Not established tests (description)*
Clinical examinations, screening procedures, techniques	• *Established (literature)* • *Not established (description)*
Description of instruments	• *Tools used for data collection/extraction* • *Validity of the procedures employed*

The traditional format: data collection/management

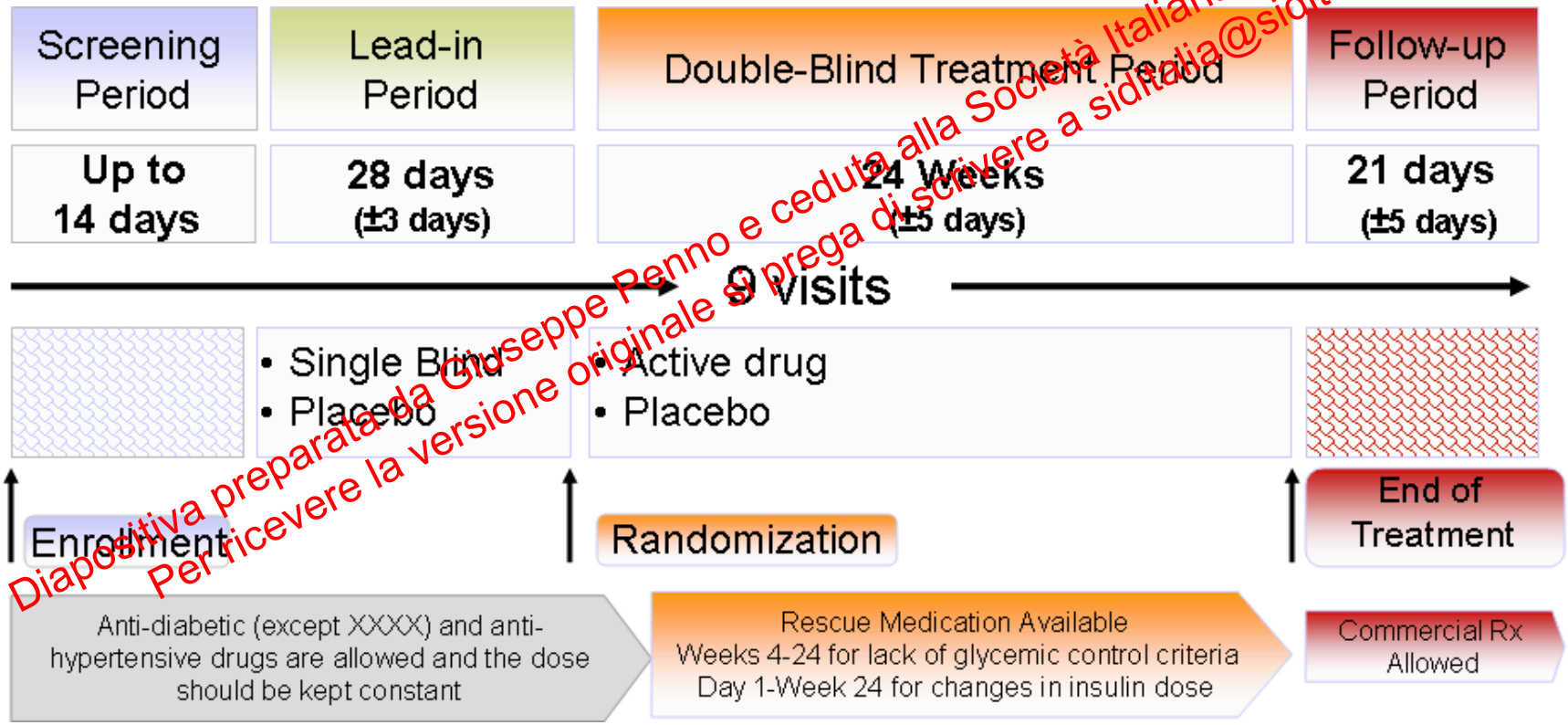
- Several details should be provided.

Tools	*Note*
Data analysis plan	*Statistical advice from a statistician*
Statistical tests	• *Which (name of statistical tests)* • *Steps*
Variables	• *Dependent, independent, confounders, etc*
Software/version	

The traditional format: study plain and timing of procedures



The traditional format: study plain and timing of procedures



The traditional format: study plain and timing of procedures

Study Period	Screening period	Lead-in period		Treatment period					Follow-up period	For details see Protocol Section
Visit	Enrolment	Start of lead-in	Lead-in	Random-ization	Treat-ment	Treat-ment	Treat-ment	End of Treatment/ Discontinuat-ion/Rescue	Follow-up	
Visit Number (Fasting/Non-fasting)	1[a] Non-fasting	2[b] Fasting	3[c] Fasting	4[c,d] Fasting	5[c,d,e] Non-fasting	6[c,d,e] Fasting	7[c,d,e] Fasting	8[c,d,e] Fasting	9 Fasting	
Week	-6	-4	-1	0	1	4	12	24	27	
Day	-42 to -29	-28	-7	0	7	28	84	168	189	
Visit Window		± 0	± 1	± 1						
Signed and Dated Informed consent[f]	X									
Inclusion/Exclusion Criteria	X	X								
Allocation of E-code via IVRS/IWRS	X									
Randomization to study treatment via IVRS/IWRS				X						
Demographics	X									
Medical and Surgical History	X									
Brief Physical Examination	X			X						
Complete Physical Examination		X								
Height	X									
Weight	X	X	X	X						

The traditional format: study plain and timing of procedures

Procedure	Name	Description	Visit 9 m 36
CRFs	Medical Interview	Patient's personal data and update background information	M
	Physical examination	Height, weight, waist circumference, blood pressure (BP)	M
	Drug Accountability Log		M
	Adherence Questionnaire	Includes Pills count	M
	Lifestyle	Nutrition questionnaire	M
		physical activity (RPAQ), 3x24h, PA diary	M
		7 X 24 pedometer	O
		workshop records and individual intervention forms	M
	Neuropsychological assessment	Quality of life (5D)	M
		Cognition (MOCA, TMT AB, Digit Span – Forward and Backward)	M
		Extended test series	O
		Anxiety and depression (Hamilton and MINI)	M
		Sleep disorders	M
		Neuropathic symptoms (MNSI_ Scoring Version)	M

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The traditional format: study plain and timing of procedures

.....

Local Laboratory Test	Hemogram		M
	Complete OGTT	0, 30, 60, 90 and 120 min glucose	M
	HbA1c		M
	Hepatic profile	AST, ALT, ALP, gamma-GT	M
	Pancreatic profile	Amylase, Lipase	M
	Renal profile	Creatinine, uric acid, MDRD-4, CKD-EPI	M
	Lipid profile	Total-Cholesterol, HDL-Cholesterol, Triglycerides, LDL-Cholesterol	M
	Morning urine spot	albuminuria, creatinine, alb/creat ratio,	M
FJD SPAIN	Insulin and C-peptide	0, 30, 60, 90 and 120 min	M
	Biomarkers		M
	Morning urine	albuminuria, creatinine, alb/creat ratio	M
Diagnostic Procedure	EKG		O
	Endo-PAT	Microvascular endothelial index	O
	CCA-IMT (CHS)	Common carotid intima-media thickness	O
	Retinography	Retinal vasculature	M
	SUDOSCAN	Sudomotor index	M
	Sleep and Cardiorespiratory recording	Nocturnal respiratory, blood pressure variation indices	O
M: Mandatory, O: Optional			CA.

- ***Embarking on a Research Project***
- ***Components of a Research Protocol***
- ***The format of the protocol: introduction, hypothesis, objectives, variables, …***
- ***The format of the protocol: methodology, study design, sample size, …***
- ***Ethical issues***

Issues for Ethical Review and Approvals

- Ethical considerations apply to all types of health research.
- Documents to be appended to the proposal (where appropriate) before submission to the Ethics Committee:
  - **Statement about Conflict of Interest**
  - **The Informed Consent form:**
    - Subjects' mother tongue
    - Simple language, lay summary
    - To describe, in sequence, what will happen in the course of the study
    - To describe possible benefits and risks
    - To state freedom to withdraw from the study at any time
  - **Ethics checklist:**
    - Accordance with the Declaration of Helsinki
    - Agreement with the Good Clinical Practices (GCP)
    - Answers to the following questions:
      - Is the study adequate to the research question?
      - Is the selection of research subjects justified?
      - Are the intervention justified in terms of risk/benefit?
      - Is confidentiality ensured? (data safety)

- ***Embarking on a Research Project***
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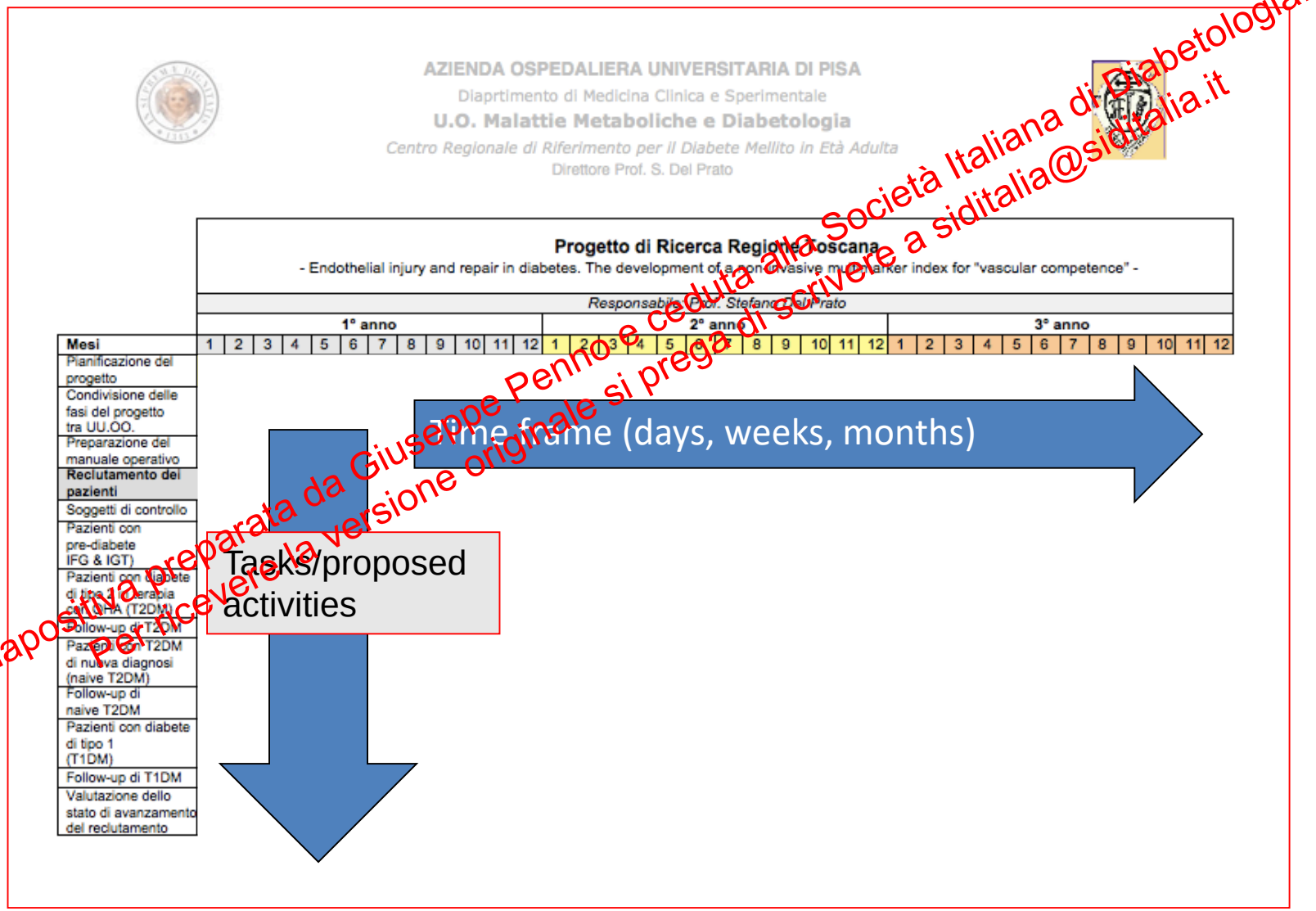
- ***Ethical issues***
- ***Gantt chart***

The traditional format: Gantt chart



AZIENDA OSPEDALIERA UNIVERSITARIA DI PISA
Diaprtimento di Medicina Clinica e Sperimentale
U.O. Malattie Metaboliche e Diabetologia
Centro Regionale di Riferimento per il Diabete Mellito in Età Adulta
Direttore Prof. S. Del Prato

Progetto di Ricerca Regione Toscana
- Endothelial injury and repair in diabetes. The development of a non invasive multimarker index for "vascular competence" -

Responsabile Prof. Stefano Del Prato

Mesi	1° anno												2° anno												3° anno											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Pianificazione del progetto																																				
Condivisione delle fasi del progetto tra UU.OO.																																				
Preparazione del manuale operativo																																				
Reclutamento dei pazienti																																				
Soggetti di controllo																																				
Pazienti con pre-diabete IFG & IGT)																																				
Pazienti con diabete di tipo 2 in terapia con OHA (T2DM)																																				
Follow-up di T2DM																																				
Pazienti con T2DM di nuova diagnosi (naive T2DM)																																				
Follow-up di naive T2DM																																				
Pazienti con diabete di tipo 1 (T1DM)																																				
Follow-up di T1DM																																				
Valutazione dello stato di avanzamento del reclutamento																																				

Time frame (days, weeks, months)

Tasks/proposed activities

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Test funzione endoteliale																																				
FMD/PWV																																				
ABPM/IMT																																				
EPCs																																				
CEC/EdMP																																				
Studi in vitro																																				
Isolamento, coltura, arricchimento ex.vivo																																				
Test di valutazione della funzione delle EPCs																																				
Espressione, attività, concentrazione di parametri di stress ossidativo																																				
Altre valutazioni																																				
Parametri biochimici																																				
Markers bioumorali di funzione endoteliale																																				
Screening genetico																																				
Altro																																				
Preparazione e manutenzione del database																																				
Analisi statistica ad interim																																				
Analisi statistica finale																																				
Preparazione manoscritti																																				

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Milestones																																				
Start-up																																				
Inizio/fine reclutamento																																				
Inizio/fine follow-up																																				
Inizio/fine test di "competenza vascolare"																																				
Inizio/fine studi in vitro																																				
Inizio screening genetico																																				
Inizio dosaggio markers bioumorali																																				

Entrate	40%	20%	20%	20%
Previsione di spesa		40%	40%	20%

The traditional format: Gantt chart

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- ***Gantt chart***
- ***Budget proposal***

The budget proposal

Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

Proposed total budget (Euro)

Costs	Budget Year 1	Budget Year 2	Budget Year 3	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the moh
1 Staff salary	138.645,00	138.645,00	138.645,00	415.935,00	415.935,00	
2 Researchers contracts	44.000,00	60.000,00	40.000,00	144.000,00	0,00	144.000,00
3a Equipment (leasing)	0,00	0,00	0,00	0,00	0,00	0,00
3b Supplies	80.000,00	130.000,00	81.505,00	291.505,00	29.085,00	262.420,00
3c Model costs	0,00	0,00	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00	0,00	0,00
5 Patient costs	1.250,00	2.500,00	1.250,00	5.000,00	0,00	5.000,00
6 IT services and data bases	0,00	0,00	0,00	0,00	0,00	0,00
7 Travels	0,00	0,00	0,00	0,00	0,00	0,00
8 Pubblication costs	0,00	0,00	0,00	0,00	0,00	0,00
9 Training and Dissemination	2.000,00	1.000,00	1.000,00	4.000,00	4.000,00	0,00
10 Overheads	12.533,00	12.533,00	12.534,00	37.600,00	0,00	37.600,00
11 Coordination costs	0,00	0,00	0,00	0,00	0,00	0,00
Total	278.428,00	344.678,00	274.934,00	898.040,00	449.020,00	449.020,00

The budget proposal

Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

Proposed budget distribution (Euro)

Costs	Unit 1 Total Budget	Unit 1 costs MOH funding	Unit 2 Total Budget	Unit 2 costs MOH funding	Unit 3 Total Budget	Unit 3 costs MOH funding
1 Staff salary	142.910,00		168.462,00		104.563,00	
2 Researchers contracts	96.000,00	96.000,00	24.000,00	24.000,00	24.000,00	24.000,00
3a Equipment (leasing)	0,00	0,00	0,00	0,00	0,00	0,00
3b Supplies	99.405,00	70.320,00	91.600,00	91.600,00	100.500,00	100.500,00
3c Model costs	0,00	0,00	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00	0,00	0,00
5 Patient costs	5.000,00	5.000,00	0,00	0,00	0,00	0,00
6 IT services and data bases	0,00	0,00	0,00	0,00	0,00	0,00
7 Travels	0,00	0,00	0,00	0,00	0,00	0,00
8 Pubblication costs	0,00	0,00	0,00	0,00	0,00	0,00
9 Training and Dissemination	4.000,00	0,00	0,00	0,00	0,00	0,00
10 Overheads	16.400,00	16.400,00	9.200,00	9.200,00	12.000,00	12.000,00
11 Coordination costs	0,00	0,00				
Total	363.715,00	187.720,00	293.262,00	124.800,00	241.063,00	136.500,00

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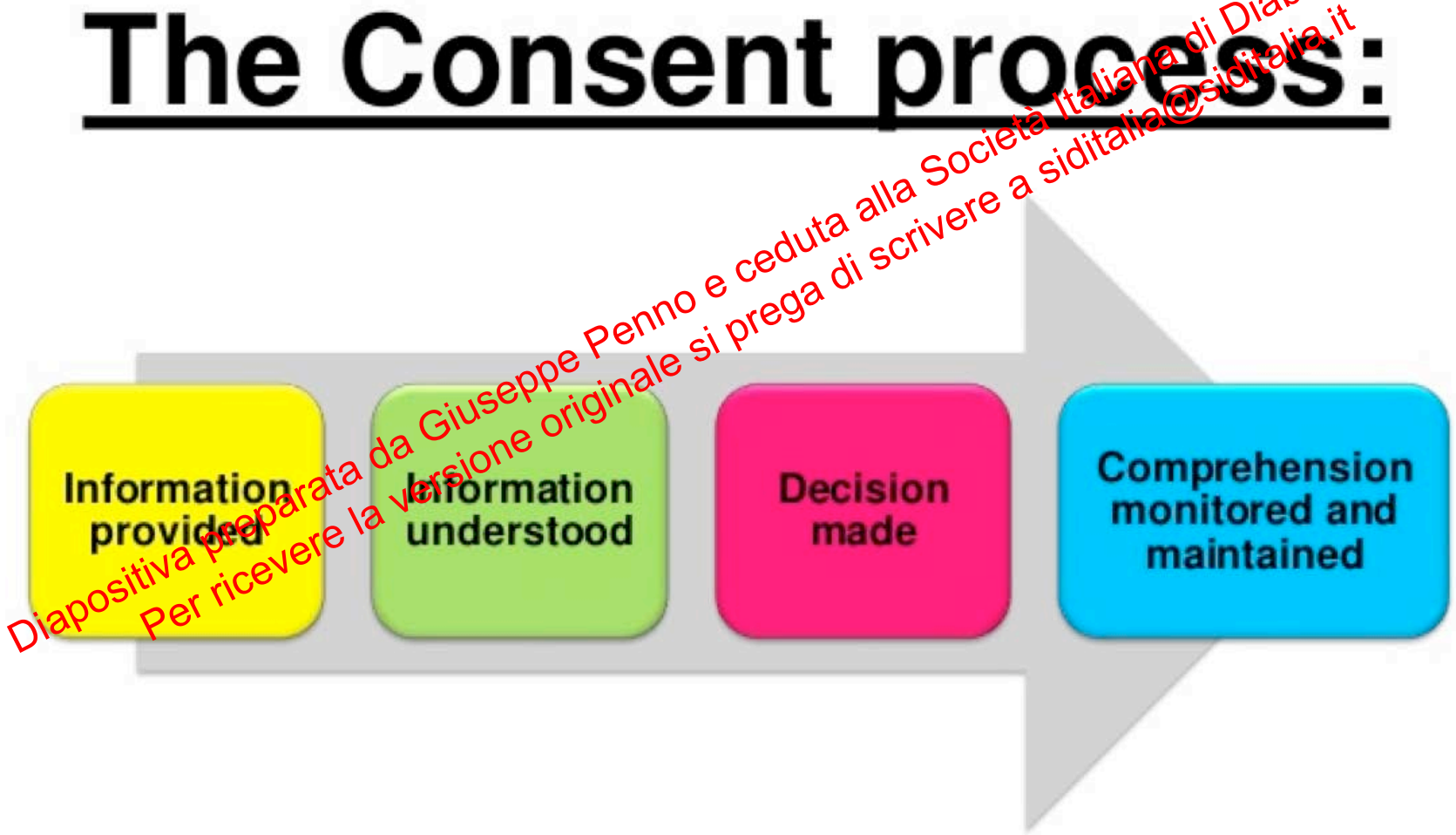
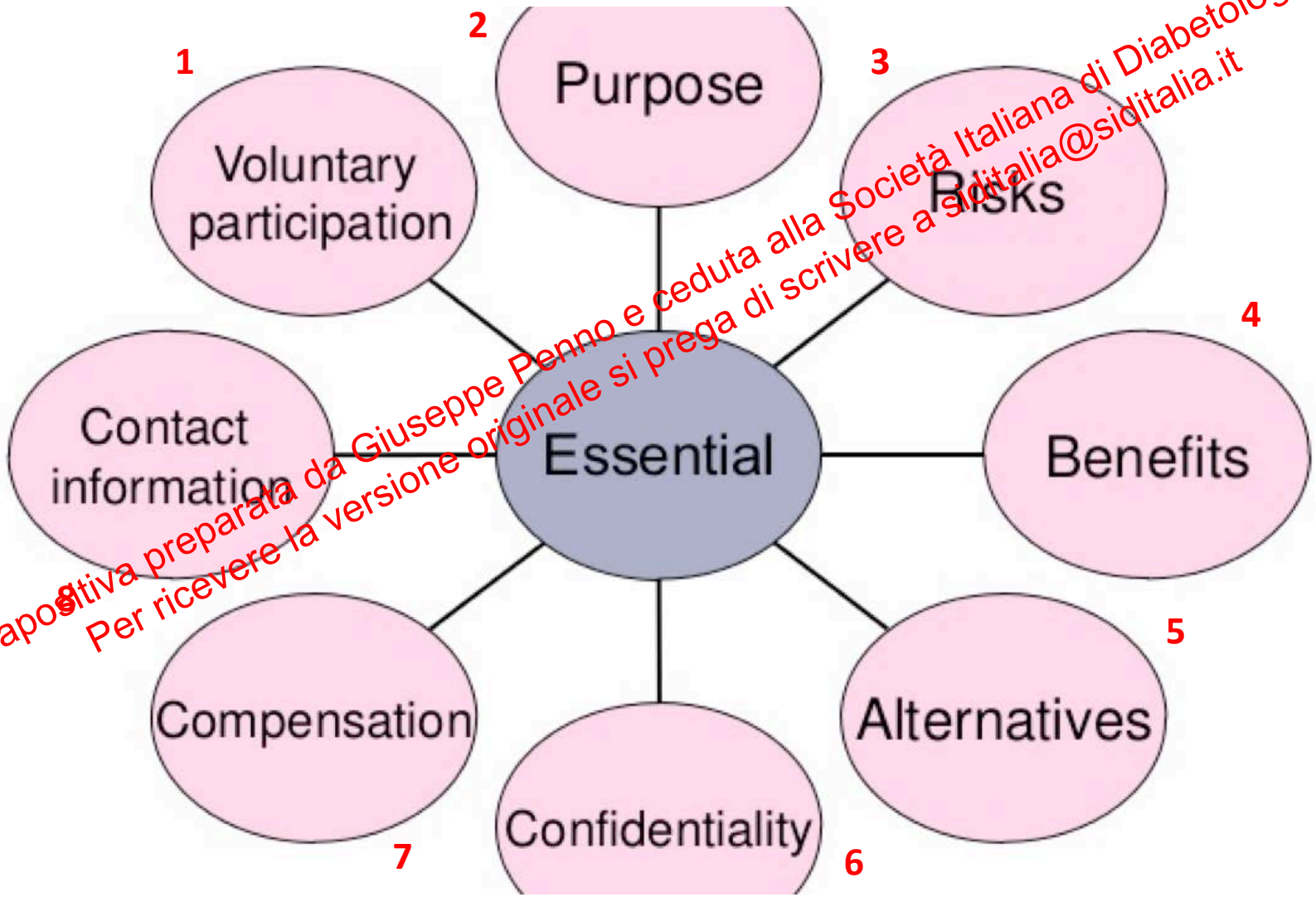
- ***Appendixes***

The central tenet of clinical research in humans is that participation is informed and voluntary

The informed consent



The informed consent



Appendixes

- To be attached at the end of the protocol:
  - Participant information sheets and informed consent forms
  - GP information letters
  - Letters from ethics committees
  - Study questionnaires
  - Case Record Forms (CRFs)
  - Budget details
  - Curriculum Vitae (CV) of the principal investigator and co-investigators and their role in the study

unite for diabetes