PROTOCOL NAME
Comparative efficacy of Vedolizumab (VDZ) and Ustekinumab (UST) in a real-life cohort of moderate-to-severe CD patients**.**

PROTOCOL IDENTIFYING NUMBER

PROTOCOL VERSION DATE Ver 1.0 14/11/2019

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CENTRE SIGNATURE – PRINCIPAL INVESTIGATOR

I have read this Protocol Amendment relevant to the study entitled "Comparative efficacy of Vedolizumab (VDZ) and Ustekinumab (UST) in a real-life cohort of moderate-to-severe CD patients " and I agree to conduct the study as detailed herein and in compliance with guidelines for Good Clinical Practice and applicable regulatory requirements. I will provide all study personnel under my supervision with all information provided by the Sponsor and I will inform them about their responsibilities and obligations.

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Printed name

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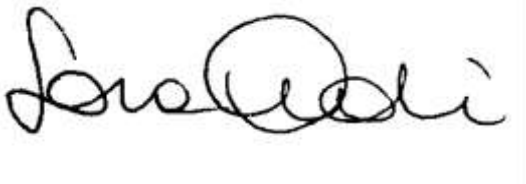


Signature

05/11/2019
Date

Glossary of abbreviations

IEC	Indipendent ethics committee
ICH/ GCP	International Conference on Harmonisation (ICH) /Good Clinical Practice standard
MoH	Ministry of Health
UST	Ustekinumab
VDZ	Vedolizumab
IFX	Infliximab
TNF	Turmor Necrosis Factor

INDEX

1 Summary

(limit to 1-2 pages)

Title	**Comparative efficacy of Vedolizumab (VDZ) and Ustekinumab (UST) in a real-life cohort of moderate-to-severe CD patients.**
Study coordinator **Protocol identifying number** **Protocol version date**	Dott.ssa Sara Onali
Background and rationale	Positioning of new biologics with different mode of action in CD patients who failed Infliximab is unclear. In this setting, data comparing the efficacy of drugs with different mechanisms of action such as the anti integrin. anti α4-β7, Vedolizumab (VDZ) and the anti p40 (anti IL-12-23) Ustekinumab (UST), are currently missing.
Population and patient selection criteria	CD patients, previously failure to one or more anti-TNFs, (including primary, secondary and intolerant), with clinical indication to receive a second-line therapy with UST or VDZ, for moderate-to-severely active luminal disease
Study design and study duration	Multicenter retrospective, real–life study
Objectives	Primary end-point will be the clinical response rates at 6 months in VDZ vs. UST-treated patients. Secondary endpoint will be clinical remission at 6 (week 26) and 12 months (week 52) in VDZ- vs UST-treated patients. Clinical response at 12 months, objective remission and response at 12 months in VDZ- vs UST-treated patients. If available, VDZ vs UST FC and CRP variations at 6 and 12 months as compared to baseline. Comparative evaluation of clinical response in VDZ vs UST-treated patients stratified by reason of anti-TNF-alpha discontinuation (i.e. primary/secondary failure and intolerance). Evaluation of the cost-efficacy ratio and need for optimization of the drugs. Safety.
Statistical methods, data analysis	The continuous variables will be described including the number of observations, mean, standard deviation (SD), median, ranges (minimum and maximum) and number of missing values. The categorical variables will be described including the frequency and percentage of subjects in each category. Comparisons between treatment groups will be performed by Mann-Whitney and Wilcoxon's tests. Based on data from two real-life retrospective studies considering the same endpoints and a relatively unselected population of CD patients (1-2), we estimate that to catch a significant difference ($p<0.05$) assuming a 6 months response rate of 76% among patients treated with VDZ and 60% among patients treated with UST a sample size of 270 patients (135 VDZ vs 135 UST) will be necessary to obtain a study power of 80%.

Ethical considerations No specific ethical issues have been identified.

Study time table Data collection and analysis should be completed in 18 months.

2 BACKGROUND AND INTRODUCTION

Crohn's disease (CD), one of the major form of inflammatory bowel disease (IBD), is believed to result from an excessive activation of the mucosal immune system leading to chronic inflammation and inflammation-related tissue damage (e.g. abscess, fistulas and stenosis). In the last decade the clinical management of CD has changed, and the use of biological therapies, aimed at reducing the intestinal damage, has considerably increased.

Anti-tumour necrosis factor (TNF)-alpha has traditionally been the first-line biologic agent for the management of moderate-to-severe CD refractory to conventional therapy (1,2). Though, approximately one third of biologic-naıve patients with CD may not respond to the induction therapy, and among those who respond, up to 45% will progressively lose response over the time (3). Over the last 5 years, several new therapies including the anti-integrin alpha-4/beta-7 Vedolizumab (VDZ) and the anti-p40 IL12/IL23 Ustekinumab (UST) have been approved for the treatment of moderate-to-severe CD.

3 RATIONALE OF THE STUDY

The availability of different classes of biologics with different mechanisms of action, variable efficacy and safety profiles, poses the question about their positioning in the therapeutic algorithm of CD. In particular, the best choice between UST and VDZ in the case of failure to anti-TNF alpha remains an open issue. There are currently no published head-to-head studies comparing the efficacy of these drugs in this specific scenario, and the treatment of choice is primarily based on clinician experience, expert-opinion-based treatment algorithms, patient preference and economic issues. In the absence of prospective, randomized direct evidence, we plan to perform a retrospective, multicentre open-labelled real-life study in order to compare the effectiveness of UST and VDZ in active CD, failure to one or more anti-TNF alpha.

4 OBJECTIVES OF THE STUDY

4.1 General objectives

Objective of the present study is to assess, in an observational retrospective study, the effectiveness of VDZ and UST in CD patients who failed one or more anti-TNF alpha as first line of therapy.

End-points

4.1.1 Primary endpoint

To assess the clinical response rates at 26 weeks in VDZ- vs UST-treated patients.

4.1.2 Secondary endpoints

-Clinical steroid free remission at 26 and 52 weeks in VDZ- vs UST-treated patients.

-Clinical response at 52 weeks in VDZ- vs UST-treated patients.

-Objective remission and response at 52 weeks in VDZ- vs UST-treated patients, if data available (see definition of the variables).

-Variation of fecal calprotectin (FC) and/or C-reactive protein (CRP) levels at baseline week 26 and 52 in VDZ- vs UST-treated patients, if data available.

-Safety.

-evaluation of clinical response in anti-TNFs primary/secondary failures and intolerant patients.

-Evaluation of the cost-efficacy ratio and need for optimization of the drugs.

5 PATIENT SELECTION CRITERIA

All clinical records of CD patients in active follow up in each participating centers will be reviewed. Those CD patients who failed one or more anti TNF-alpha and match the following inclusion criteria, will be enrolled in the retrospective analysis.

5.1 Inclusion criteria

- CD diagnosis made according to current guidelines for at least 3 months.
- Able to understand informed consent.
- Clinical indication to receive UST or VDZ for intestinal disease within at least 6 months before the primary end point evaluation. It will be possible to include patients who started the second line treatment after Oct 2018 and who have not achieved the week 52 time point, but are scheduled for objective assessment.
- Moderately-to-severely active disease calculated by Harvey-Bradshaw Index (HBI>7) at baseline.
- Previous anti-TNF alpha therapy exposure (both primary and secondary failure and intolerant).
- Availability of "Objective activity "of the disease within 3 months before the start of biological therapy (VDZ or UST), assessed by ileocolonoscopy and/or MR enteroclysis and/or Ultrasound, and at 12 months of treatment (± 3 months), if available (see definition of the variables).
- All concomitant therapy will be permitted, in order to reflect real world experience.

5.2 Exclusion criteria

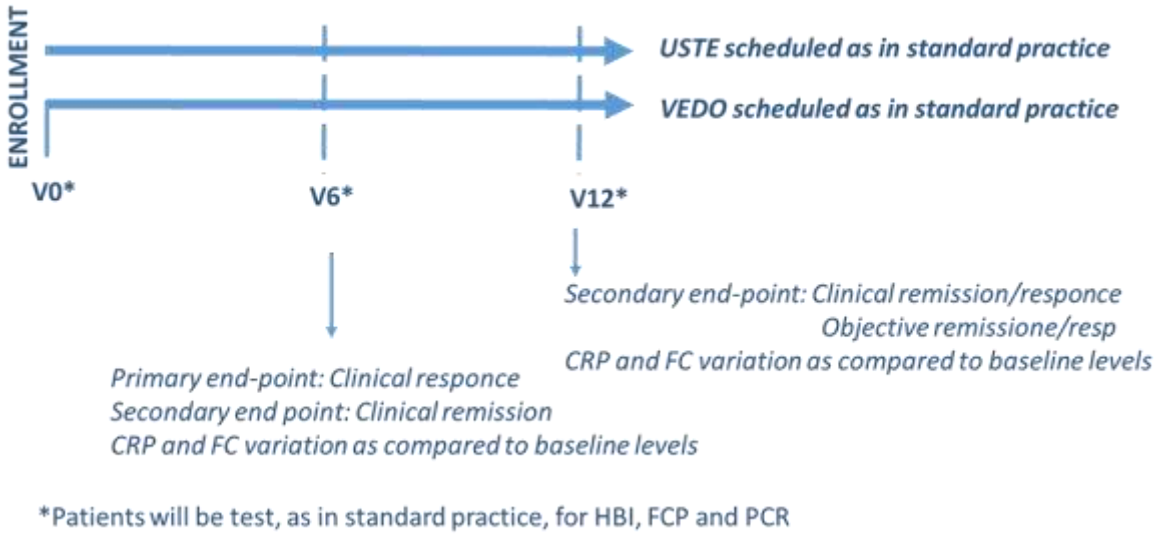
Not fully available data, regarding demographic, phenotypic and clinical activity of the disease.

6 STUDY DESIGN

In this retrospective, observational study, CD patients, previously failure to one or more anti-TNF, (including primary and secondary failures and intolerants) who received indication to receive a second-line therapy with UST or VDZ for moderate-to-severely active luminal disease as for clinical standard of care, and matching the inclusion/exclusion criteria will be included in the study.
Demographic and disease characteristic data of the included patients will be collected in a common database. Collected data will include gender, age, weight, smoking status, disease duration, disease extent and phenotype (by the Montreal Classification for CD), previous and concurrent CD treatments such as immunomodulators, anti-TNF alpha therapy (including data on primary/secondary failure and intolerance status) other biologics and previous surgery.
Data on disease activity by Harvey Bradshaw Index (HBI) at baseline, 26 weeks (V6) and 53 weeks (V12) will be also collected. Ileocolonoscopy and/or MR/CT enteroclysis and/or small bowel ultrasound performed within 3 months before the beginning of the treatment will be considered as baseline objective evaluation of disease activity and used to assess objective response/remission (see definition of variables) at 12 months (± 3months). The comparison between baseline and week 52 will be performed if data obtained from one or more technique will be available at both baseline

and week 52. For each patient, FC and CRP levels at baseline, 26 and 52 weeks will be collected and included in the database if available.
Side effects and all adverse events will be recorded and analysed.

Study Flow chart



Definition of the variables:

Clinical remission: Harvey Bradshaw Index (HBI) ≤ 4 in the absence of concomitant steroids.
Clinical response: Reduction of HBI ≥3 points from the baseline value.
Objective response/remission: Objective remission/response based on either MR/CT enteroclysis or small bowel ultrasound or endoscopy, as follows:

- Endoscopic response will be defined by an improvement of mucosal inflammation compared to baseline and the absence of deep ulcers.
- Endoscopic remission will be defined by achievement of complete mucosal healing, in the absence of any ulcer.
- Radiologic response will be defined by improvement in bowel wall thickness, inflammatory fat, mural blood flow and hyperenhancement compared to baseline imaging (2,4).
- Radiologic remission will be defined by complete normalization of inflammatory parameters on cross-sectional imaging (2,4).
- Ultrasound response improvement of bowel wall thickness defined as reduction of BWT (mm) as compared to baseline (5).
- Ultrasound remission bowel wall thickness will be considered normal if ≤3 mm (5).

Route of Administration:
For UST as in standard practice, Intravenous (IV) for the induction, subcutaneously (SC) in the maintenance phase.

Dose: UST will be administered 6 mg/Kg IV in the induction followed by maintenance with UST 90 mg SC every 12 or 8 weeks according to standard clinical practice.
For VDZ as in standard practice, IV route for induction and maintenance phases.
Dose: VDZ will be administered 300mg IV at 0, 2 and 6 weeks for the induction. Additional 300mg VDZ infusion can be given at week 10 based on clinical judgment. VDZ 300mg IV every 8 weeks will be given as maintenance. Intensification dose every 4 weeks will be accepted, according to standard practice.

7 STATISTICAL CONSIDERATIONS

7.1 Sample size:

Sample size justification: considering the efficacy data from two real-life retrospective studies assessing clinical and objective remission response in a relatively unselected population of CD patients (1-2) we estimate that to catch a significant difference ($p<0.05$) assuming a 6 months response rate of 76% among patients treated with VDZ and 60% among patients treated with UST a sample size of 270 patients (135 VDZ vs 135 UST) will be necessary to obtain a study power of 80%.

7.2 Analysis

The continuous variables will be described including the number of observations, mean, standard deviation (SD), median, ranges (minimum and maximum) and number of missing values. The categorical variables will be described including the frequency and percentage of subjects in each category. Comparisons between treatment groups will be performed by Mann-Whitney and Wilcoxon's tests.
Cost-efficacy analysis (CEA) will be performed considering the obtained comparative efficacy data and the official price negotiated with the Italian drug agency (AIFA). Incremental Cost-Effectiveness Ratio (ICER) will be also calculated in order to assess the cost of one percent unit of efficacy gained using the most effective drugs as compared to the second best.

8 WITHDRAWAL OF SUBJECTS

Not applicable due to the retrospective design of the study.

9 FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING

Data from the clinical chart will be recorded anonymously in a common database.

10 ETHICAL CONSIDERATIONS

10.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

10.2 Subject identification – Personal Data protection

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. The study coordinator and all the investigators will be aware that a breach of such regulations may result in administrative or even criminal sanctions.

An information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data will accompany the informed consent administered to the patient (see paragraph 14.3 below). Such information must (i) identify the roles of the holder ("titolare") and processor ("responsabile", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patients's data will be collected in the study database and anonymized by attributing a unique ID number.

10.3 Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

A copy of Informed consent will be attached to this Protocol Template.

11 CONFLICT OF INTEREST

No conflict of interest

12 DATA OWNERSHIP

The proponent of the study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

13 PUBLICATION POLICY

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes. The timing of publications (in the event several Centers should be participating in the Study) will be set according to the MoH's Decree of May 12, 2006, since investigators cannot be precluded from or limited in publishing the results of their studies.

The Study Coordinator will be the Senior Author and the Corresponding Author of the relevant publications. The Authors' list will include all the investigators (up to the maximum required by the Journal to whom the article will be submitted) in a decreasing order of patients included into the final analysis for the primary outcome.

14 Study time table

Data collection and analysis should be completed in 18 months.

15 References

1. Kotze PG, Ma C, Almutairdi A, et al. Real-world clinical, endoscopic and radiographic efficacy of vedolizumab for the treatment of inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2018;48(6):626-637.
2. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. Alimentary pharmacology & therapeutics. 2017;45(9):1232-1243.
3. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Alimentary pharmacology & therapeutics. 2018;48(4):394-409.
4. Carucci LR, Levine MS. Radiographic imaging of inflammatory bowel disease. Gastroenterology clinics of North America. 2002;31(1):93-117, ix.
5. Castiglione F, Imperatore N, Testa A, et al. One-year clinical outcomes with biologics in Crohn's disease: transmural healing compared with mucosal or no healing. Alimentary pharmacology & therapeutics. 2019;49(8):1026-1039.

List of annexes to be included with the protocol

Annex 1: Declaration of Helsinki
Annex 2: List of partecipating centers
Annex 3: Database

Annex 1

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation
    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or

compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver

the information.
After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 2:

Participating centers: to be defined