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ETHICS CHARTER OF THE NIDIAG CONSORTIUM

What follows are guiding principles for research that will be conducted within the NIDIAG consortium, an EU-funded project aimed at improving the quality of the diagnostic work-up of a set of clinical syndromes in contexts affected by neglected infectious diseases. The NIDIAG partners commit themselves to the highest ethical conduct in their research as set out in this Charter.

NIDIAG investigators will conduct their studies in adherence to the fundamental ethical principles applicable when conducting the studies:

- The principle of respect for **human dignity**, including the principles of non-exploitation, non-discrimination, and non-instrumentalisation;
- The principle of **individual autonomy** (entailing the giving of free and informed consent, and respect for privacy and confidentiality);
- The principle of **justice** (the equitable distribution of the burdens and benefits of research);
- The principle of **beneficence** (and non-maleficence) with regard to the improvement and protection of health;
- The principle of **proportionality**, including that research is necessary to the aims pursued and that no alternative more acceptable methods or interventions are available);

This document describes how these principles will be applied in practice and is structured in 11 sections, as follows:

1. Ethics framework
2. Legal and regulatory framework
3. Informed consent procedures
4. Protection of the individual
5. Ethics review
6. Use of biological samples
7. Patient care and management
8. Data protection
9. Social relevance
10. Collaborative partnership
11. Bioethics Advisory Board

Appendix: Sample Information sheet and informed consent form

1. ETHICS FRAMEWORK

Research in countries participating in NIDIAG is regulated by both national and international legal and ethics rules. All scientists involved in NIDIAG will take into consideration the following international guidance in ethics:

- Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 59th WMA General Assembly in October 2008;
- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002);
- CIOMS International guidelines for ethical review of epidemiological studies (1991);
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (1996) Guideline for good clinical practice E6 (R1);
- World Health Organization (1995) Technical Report Series No. 850, Annex 3, Guidelines for GCP for trials on pharmaceutical products. WHO, Geneva;
- Nuffield Council on Bioethics (2002). The ethics of research related to healthcare in developing countries;
- Universal Declaration of Human Rights (1948);
- UN Convention on the Rights of Child (1989);
- The convention for the protection of human rights and dignity of human being with regard to the application of biology and medicine called the "Convention on Human Rights and Biomedicine" (Council of Europe, 1997);

2. LEGAL AND REGULATORY FRAMEWORK

The phase-I and phase-II laboratory-based studies will take place in two European member states (UK and Belgium), in two sub-Saharan African countries (Democratic Republic of Congo and Sudan), and in two Asian countries (India and Indonesia). Cross-sectional surveys and phase-III field studies will take place in the Democratic Republic of Congo, Côte d'Ivoire, Mali, Sudan, Nepal, Cambodia and Indonesia.

The framework that will be established for the NIDIAG activities will use the internationally agreed, appropriate standards in Good Laboratory Practice, Good Clinical Practice, Good Epidemiological Practices, and Best Practices in Ethics, having reference to WHO guidance and EU regulation. NIDIAG partners will comply with the following relevant EU documents and guidelines:

- The Charter of Fundamental Rights of the EU;
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data;

- Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC,75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation or administrative action relating to proprietary medicinal products;
- Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions;
- Human tissue banking, when necessary, will follow the opinions given to the European Commission by the "European Group on Ethics in Science and New Technologies" on "ethical aspects of human tissue banking" (N° 11, 21 July, 1998);
- Directive 2005/28/ECC of the European Parliament and of the Council of 8th April, laying down principles and detailed guidelines for good practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products;
- EU Clinical Trial Directive (2001/20/EC) when applicable (for clinical trials conducted in Europe).

All procedures involving living animals will conform to:

- Amsterdam Protocol on animal protection and welfare;
- Council Directive 86/609/EEC of 24 November 1986 on the Protection of Animals Used for Experimental and Other Scientific Purposes, updated in the Council of Europe's Appendix A (http://conventions.coe.int/Treaty/EN/Treaties/PDF/123-Arev.pdf);
- Commission Recommendation of 18 June 2007 on guidelines for the accommodation and care of animals used for experimental and other scientific purposes (2007/526/EC).

NIDIAG participants will also take into account the opinions of the European Group of Advisers on the Ethical Implications of Biotechnology (1991 – 1997), the opinions of the European Group on Ethics in Science and New technologies (as from 1998), the OECD Principles on Good Laboratory Practice (as revised in 1997), and the opinion of Paris Organisation for Economic Co-operation and Development, Environment Directorate, Chemical Group and Management Committee 1998 (ENV/MC/CHEM(98)17).

In addition to the above listed international regulations, clinical studies will abide to specific regulations in these countries. Below are listed important national and EU regulations that the contractual NIDIAG research partners will systematically abide by in their respective countries.

- Belgium
  - Loi du 8 décembre 1992 relative à la protection de la vie privée à l'égard des traitements de données à caractère personnel (loi vie privée).
  - Arrêté royal du 13 février 2001 portant exécution de la Loi du 8 décembre 1992 relative à la protection de la vie privée à l'égard des traitements de données à caractère personnel.
  - Service Publique Fédéral Santé Publique, Sécurité de la chaine alimentaire et environnement. Loi relative aux expérimentations sur la personne humaine du 7 mai 2004
- UK

- Medical Research Council Operational and Ethical Research Guidelines "Human tissue and biological samples for use in research" April 2001;
- Animals (scientific procedures) Act 1986;
- Code of Practice for the housing and care of animals (21/03/2005);
- Code of practice part 2 - the housing of animals in designated breeding and supplying establishments (21/03/2006);
- Code of Practice for the Humane Killing of Animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986;

- Switzerland
  - Loi fédérale sur la protection des données (LPD) du 19 Juin 1992;
  - Ordonnance relative à la loi fédérale sur la protection des données (OLPD) du 14 Juin 1993.
- Nepal
  - National Guidelines on Clinical Trials with the Use of Pharmaceutical Products, National Health Research Council, Kathmandu, 2005;
  - National Ethical Guidelines for Health Research in Nepal, National Health Research Council, Kathmandu, 2001;
  - Drug Act 2035 (1978).
- India
  - The Drugs and Cosmetics Act, 1940;
  - Licensing of new RDT will require an evaluation by the National Institute of Biologicals (NIB).
- Indonesia
  - 1995 Government Regulation No.39/1995 on Health Research and Development
  - 2001 Guidelines for Good Clinical Practice" issued by Indonesian FDA
  - 2002 Decree no. 1333/2002 on informed consent in health research
  - 2003 National Guidelines on ethics on Health Research
- Cambodia
  - Cambodian Ministry of Health. Ethical guidelines for health research involving human subjects. Phnom Penh, Cambodia: Cambodian Government, 2002.
- Mali
  - Projet de loi du 14 octobre 2009 régissant la recherche biomédicale sur l'être humain
- Côte d'Ivoire
  - Ethics review capacity in Côte d'Ivoire is currently being strengthened. The NIDIAG Consortium will comply with the most recent guidelines published by the Ministère de la Santé et de l'Hygiène Publique.
- Democratic Republic of Congo
  - There is no national legislation yet regarding clinical research in DRC.

- Sudan
  - National Guidelines for Ethical Conduct of Research Involving Human Subjects; National Health Research Ethics Committee, Health Research Council, Federal Ministry of Health, The Republic of Sudan 2007.

3. INFORMED CONSENT PROCEDURES

For both the cross-sectional survey and the phase-III field study, an informed consent procedure will be developed and implemented. This procedure will involve the delivery of both written and oral information to patients and healthy volunteers participating in these studies. Informed consent documents will be developed by the WP6 team in close collaboration with the local investigators and after consultation with community representatives. A sample Informed Consent form is provided in the Appendix. These documents will be developed taking into consideration the local language, traditions, religion and other aspects of the social and cultural context.

Informed, freely given consent will be sought from the participant or his/her legally authorized representative (parents/guardians). The informed consent document will provide a brief overview of the study and describe possible harm and benefit that participation in the study might cause. It will describe the study goal, procedures, timelines and expected results. The document will also give a short account of how samples will be collected, stored, processed and analysed. Patients will be asked for informed consent for storage of their samples for future research related to neglected infectious diseases. The document will further explain to the participant that his/her decision to participate in the study will not affect his/her right to obtain the standard health care that he/she is entitled to, and that he/she may withdraw at any time from NIDIAG studies. Participants and/or their legally authorized representative will have the opportunity to ask questions to the study physician and sufficient time will be allowed to them to make a decision. Contact details of the local investigator will be provided to all subjects.

Two original information and consent forms will be completed, co-signed and dated personally by the patient or his/her legal representative and by the person responsible for collecting the informed consent. The patient will be given one signed original information and consent form; the second original will be kept by the investigator. Any study related procedure will only be conducted once the appropriate and adequate informed consent process has taken place and the informed consent has been signed off by the participant or his/her legally authorized representative. In case the participant or legal representative is illiterate, an impartial witness should be present during the entire informed consent discussion. The participant will be asked to give consent orally and to thumbprint the form; and the impartial witness will be asked to complete, sign and date the form together with the person responsible for collecting the informed consent.

Regarding the cross-sectional surveys, national and local endorsements must be collected. Where appropriate, community consent will be obtained through meetings with local leaders within the area where information on the relevant study will be provided and questions answered. Verbal consent will be sought from heads of all the households before seeking individual written consent from individuals, parents or guardians. During individual interviews, information about the studies will be given to individuals, legally authorized representatives of children and it will be made clear that participation in the study is voluntary and they are free to withdraw from the study without any consequences.

4. PROTECTION OF THE INDIVIDUAL

Research subjects will be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research (healthy volunteers) will also receive a fair sum of money for inconvenience due to their participation in the research.

An insurance will be made available for all participants enrolled in NIDIAG studies to cover all pecuniary consequences of damages which may result from research. Subjects who suffer injury as a result of their participation in NIDIAG studies will be entitled to free medical treatment for such injury and to such financial assistance as would compensate them equitably for any resultant impairment, disability or handicap.

5. ETHICS REVIEW

For each study the full protocol, the informed consent forms and all key study documents and data collection tools e.g. CRF (including any additional educational or recruitment materials) will be submitted to the ethics committee and to the competent national authorities. In the spirit of international partnership, the NIDIAG protocols will undergo a double ethical review, and be submitted to a least one ethics committee in the EU and one in the host country. This requirement responds to the need of complementarity of opinions (from an ethics committee close to the sponsor and one close to the study population), of avoiding any North-South double standards, building common practices in international collaborative research, so it should not be seen as a "compensatory mechanism" in case of weakness of the ethical review in the host country.

In case of diverging opinions between ethics committees, NIDIAG will try to facilitate the dialogue between the committees, but the opinion of the ethical committee of the host country should take precedence. Studies will only start once the approvals have been obtained. Each time, the co-ordinator will provide to the Commission copies of the necessary authorisations obtained from the relevant bodies. Any substantial amendments will be submitted for approval to the same ethics committees and competent authorities.

6. USE OF BIOLOGICAL SAMPLES

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products; appropriate blood and body fluid precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens in this project.

In all settings in which specimens are collected and prepared for testing, laboratory and health care personnel will follow current recommended sterile techniques, including precautions regarding the use of needles and other sterile equipment as well as guidelines for the responsible disposal of all biological material and contaminated specimen collection supplies. If needed, the project can provide the burners required for adequate waste disposal.

Access to stored samples will be limited using a locked room. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

As one of the objectives of NIDIAG is to establish biobanks of reference samples, the samples may be stored for an indefinite period of time. Nevertheless, the collected blood and tissue samples will only be used for the specific purpose covered by the informed consent given, i.e. research on neglected infectious diseases. Any potential use of the samples must be identified in the informed consent process.

In the future, other investigators may wish to study the stored samples and/or data. In that case, ethics committee approval must be sought prior to any sharing of samples. Any clinical information shared about the sample would similarly require prior ethics committee approval. A new application must be submitted to the ethics committees, including copies of the ethical clearance of the approved protocol along with project documents.

7. PATIENT CARE AND MANAGEMENT

The NIDIAG investigators will seek to ensure that enrolled participants receive medical care that is at least as good as the existing local norms. Therefore, they will make sure that any clinically relevant information that emerges from the diagnostic work-up performed in the clinical study will be communicated in a timely manner to the treating physician. Once a diagnosis is established, local investigators will facilitate referral to medical care of the best available local standard.

If subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the enrolment criteria, investigators will advise them to obtain, or refer them for, medical care at the appropriate health institutions. In this situation, identified medical care institutions and referral system must be organized, keeping in mind that the work is directly related to infectious diseases and may be multi infectious with different severity levels.

The NIDIAG project does not include clinical trials testing an investigational therapeutic product. Nevertheless, for each specific study, the relevance and need of systematic recording and reporting of adverse events will be evaluated.

8. DATA PROTECTION

Researchers will take every reasonable step to protect the confidentiality of subjects' health and personal information and to prevent misuse of this information. Upon inclusion in one of the NIDIAG studies, each subject will be assigned a unique identification code that will be used for the data collection on the clinical record form, data transfer, data entry and data analysis. Subjects' medical records, the key to the unique identifier codes, Informed Consent documents, and all documents displaying subject personal identifiers will be kept in a locked cabinet in the local investigator's office. These documents will be accessible only to the local investigator and his/her team. Monitors, auditors and inspectors can be granted access for the sole scope of their activity and under confidentiality agreement, as described below.

Researchers will also make sure biological samples are handled with care at the storage facility(ies) and that subjects' privacy is protected during collection, shipment, storage, analysis and publication. The collected biological samples will be anonymized and labelled with the subject's unique identification code before being sent to the laboratory(ies) for analysis.

Data management procedures will protect the confidentiality of all individual data, in compliance with national and European regulations: names will not be listed nor any set of data, which could allow specific identification of study patients. Study data will be stored in password-locked files with the necessary physical and technical safeguards.

Disclosure of personal information from the study to third parties may only occur for purposes of study monitoring, audits and inspections. Study subject confidentiality and welfare will always be maintained as the highest priority. Study participants will be permitted to request removal of the coded data from the study for any reason at any time before the database lock, without penalty or loss of benefits to which they are otherwise entitled and this will be mentioned in the consent form.

9. SOCIAL RELEVANCE

Clinical research in vulnerable populations is only justified if the research is socially relevant to that population and if the study population will have access to any beneficial intervention resulting from it. As explained in Article 17 of the Helsinki Declaration, "medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research".

Social relevance has to be considered at individual as well as at population level. There is an individual benefit for patients participating in NIDIAG studies as they will have access to state-of-the art diagnostic methods that may exceed those available to them under routine care conditions. Each patient will be followed-up until a definite diagnosis can be established. This intensive diagnostic work-up should result in improved clinical management for both NID and severe diseases that would otherwise not be detected.

At population level, post-trial access for new products developed under the NIDIAG scheme should be considered. NIDIAG aims to improve quality of clinical care by adopting state of the art diagnostic technology into diagnostic algorithms for common syndromes. To maximize the benefits of research for communities involved in NIDIAG studies, a comprehensive translation to policy strategy will be put in place (see WP7). This strategy will aim to facilitate access to new diagnostic products after research is terminated. Also, knowledge gained through NIDIAG studies will be widely disseminated among patient groups and participating communities. Even if the NIDIAG researchers cannot be expected to solve the problem of access to diagnostics in resource-poor countries, a realistic plan for future access should always be proposed, based on the model developed by Product Development Partnerships such as DNDi: prior dialogue with national and international health authorities, "access" plan (e.g. preferential prices, IPR-measures).

10. COLLABORATIVE PARTNERSHIP

NIDIAG research is carried out as a true collaborative partnership between research institutions from north and south. Any scientific (or other) rewards of the research will be fairly shared amongst them. The NIDIAG consortium will work in close collaboration with local researchers, health staff of primary care centres, policymakers and community representatives, as the ultimate objective of the project is integration of research outputs into

national health programmes. All partners involved in this project will respect the community's values, culture, traditions, and social practices.

11. BIOETHICS ADVISORY BOARD

The NIDIAG bioethics advisory board contributes to ensuring that the highest ethical standards are in use in the NIDIAG programme. The board has added to the development of this document, the NIDIAG ethics charter. During the project, the board will oversee the compliance of the consortium with ethics regulations, e.g. regarding patients' safety and data protection. The members of the bioethics advisory board will receive a copy of the correspondence with ethical committees. In case of complex ethical issues or divergent views, they will be asked for advice on an *ad hoc* basis. The chair of the advisory board will be asked to file a periodic report that will be attached to the consortium report.

The board consists of two bioethics advisors, Professor Francis Crawley and Dr Faiza Osman. They have proven substantial expertise in dealing with ethical issues posed by clinical research in the developing world and will take into account the multidisciplinary nature of ethical issues.

Adopted by the governing council of NIDIAG by electronic vote on DATE

Appendix: Sample Information sheet and informed consent form

Institute responsible **XXXXX**

Study title **XXXXXXXXXXXXXXX**

Introduction

Visceral leishmaniasis (Kala azar) is caused by a parasite (*Leishmania*) that is transmitted by the bite of a small blood sucking insect – the sand fly.

If you get infected with the parasite you may become very sick and must have treatment with drugs.

The presence of the disease can be diagnosed by testing blood samples, urine samples or in some cases other samples.

However, the diagnostic tests are not very good and sometimes they may be harmful.

We want to develop better and more accurate diagnostic tests.

This will identify infected patients at an earlier stage of the disease, save lives and help to control the spread of the disease.

Information on the study

In this study we will look for factors in the blood or urine that are signs of the presence of *Leishmania* infection and that cannot be confused with other infections.

If you are being examined for presence of *Leishmania* infection you can help with the diagnosis by giving some blood or urine to be tested.

You can help with the development of better tests if you:

1. Allow us to keep some of the blood and urine for laboratory research on better diagnostic tests for *Leishmania* or other relevant conditions.
2. Sign the informed consent form.

If you are being examined for other infections that might be confused with *Leishmania* you can also help with the development of better tests if you:

1. Allow us to keep some of the blood and urine for laboratory research on better diagnosis for *Leishmania* or other relevant conditions.
2. Sign the informed consent form.

Conduct of the study

A small volume of blood 2-5 ml**,** which is about the volume of one small spoon, will be taken with a syringe from the arm. The medical personnel will do this. In addition, a urine sample (5 to 10ml) will also be collected. The usual routine diagnostic tests will be done on the blood

and urine, and sometimes also the new tests. The results of the routine diagnostic tests and the new tests will be studied by the investigators. The rest of the blood and urine samples will be stored for an indefinite period of time. These samples may be used to do more research on neglected infectious diseases but not for any other purposes. Whenever relevant for the patient welfare, the medical personnel taking care of the patient will be informed of any results.

Advantages and risks of the study

By participating to this study you will help with the development of new diagnostic tests for the disease. If these new tests work well, it will be easier to identify people who become infected and treat them to prevent the spread of the disease.

By participating in this study, you will not undergo any unnecessary invasive procedures beyond what is part of normal diagnostic methods.

Your participation in this study will not jeopardize your access to medical treatment.

Voluntary participation

Your participation is voluntary. If you refuse to participate in this study, you will receive the same care and treatment as people who accept to participate.

You are free to withdraw yourself from the study at any moment. This decision will not affect in any case the medical care you will receive.

Costs and compensations

It will not cost you anything to participate in this study. You will not be paid for your participation.

Confidentiality

The obtained information will remain confidential. Your medical data will only be noted by the medical personnel and will be stored in a confidential centralized electronic database. Your name will not be used to identify samples. Your name or any confidential information will not be used in written reports.

Questions

If you have questions on the study, you can ask information to the local medical personnel or to the principal investigator at any time.

Contact details for:

Your medical personnel: ……

The local principal investigator: ……

Number in the study: …….

Informed consent form

I, undersigned, ……, declare that:

- The study has been explained to me and I understand the objectives and conditions of the study.
- I had the possibility to ask questions. All my questions have been answered to my satisfaction.
- My participation in the study is voluntary. Obtained information on my person stays strictly confidential and will not appear in publications and any formal documents.
- I agree that my blood and urine may be taken to do tests for visceral leishmaniasis or for other conditions relevant for the improvement of diagnostic tests for leishmaniasis.
- I agree that anonymous data will be stored in an electronic research database.
- I agree with publication of the results of this project in anonymous form.
- I received a copy of this information and of the consent form.
- I understand that if I would still have questions concerning this study or if I do not want to participate anymore, I can contact the local medical personnel of the principal investigator.

☐ I declare that I agree to participate to this study.

☐ I agree that after this study, my blood will be stored and used for further research into better diagnostic tests.

Name and signature (or fingerprint) of the patient

or of the responsible accompanying person if the above person is not capable to sign or in case of a person less than 18 years old.

Name Signature / fingerprint

…… ……..

Name and signature of the medical personnel who explained the study

Name Signature

…… ……..

Place: ……

Date: ……