

THE PROCESS OF HEALTH RESEARCH PROTOCOLS' REVIEW

*“PROCÉDURE D'ÉVALUATION DES
PROTOCOLES DE RECHERCHE EN SANTE”*

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Qualifications of contributors

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Name	Institution	Experience in review procedure
Dr Marceline Djuidje Ngounoue	University of Yaoundé I	8 years
Dr Jérôme Ateudjieu	DROS/MINSANTE & University of Dschang	8 years
Dr Charles Fokunang	University of Bamenda	7 years
Mr Chi Primus Che	Centre for the Study of Civil War (CSCW), Peace Research Institute Oslo (PRIO), Norway	5 years
Prof. Lazare Kaptue	CNERSH & Université des Montagnes	30 years

Objectives of the process

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- To contribute to the development of the quality and consistence of ethics in health research and any other research involving human beings (e.g. Social science research);
- To promote high standard scientific research;
- To safeguard the dignity, the rights, the safety and wellbeing of actual and potential participants to research projects;
- To meet the highest ethical standards in order to merit the international trust and confidence of the communities.

Outline of the presentation

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- I. Prerequisites
- II. Requirements for submitting an application for ethical clearance
 1. Administrative requirements
 2. Protocol requirements
- III. Review criteria
- IV. Review procedures
- V. Scientific and ethical aspects of the review
- VI. Decision-making procedure
- VII. Engagement of Independent Consultants
- VIII. Communicating results to Investigators
- IX. Challenges
- X. References

Prerequisites

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- Each and every Research Ethics Committee (REC) shall operate under up-to-date and publicly accessible Standards Operating Procedures (SOPs)
- RECs' Members and independent consultants must be trained on review procedures
- An independent review shall address conflicts of interests

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Confidentiality agreement

- Members of the Research Ethics Committee (REC) shall agree to hold all information, including proprietary trade secrets, completely confidential and in trust, agreeing to use that information only for assignment purposes.
- Information cannot be used for any other purpose, nor disclosed to any third party.
- REC members and independent consultants shall sign privacy and confidentiality agreements prior to their enrolment in the review process.

Conflict of interests

- It is a long-standing traditional policy that no member of the REC may participate in the review or approval of proposals in which he/she has a conflict of interest, except to provide information as requested by the Committee.
- Members pledge to disclose to the Executive Committee any actual or potential conflicts of interest in relation to any particular proposal submitted for review, and abstain from any participation in discussions and/or deliberations.

Requirements for submitting an application for Ethical Clearance

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□ Administrative requirements

1. Signed cover Letter from the Principal Investigator (PI) or co-PI, to the President of the REC: **application for ethical clearance**
2. Hard copies of the full research Protocol (either in French or in English), and the electronic version. **The protocol should be dated and signed by the PI; Version number is required**
3. Information sheet and consent form, in both French and English
4. Data collection Tools (questionnaires, interviews/discussion guides, checklists, CRFs, ...)
5. Detailed budget of the research project

Requirements for submitting an application for Ethical Clearance

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□ **Administrative requirements (continued)**

6. Up-to-date CVs of the PI and co-investigators (CVs should be dated and signed)
7. Agreement of the health institution where the study will be implemented
8. Funding sources, name and contacts of the sponsors
9. Application fees since June 2008 at the Cameroon National Ethics Committee

Requirements for submitting an application for Ethical Clearance

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□ Administrative requirements (finished)

Additional documents for clinical trials

11. Investigator's Brochure
12. Insurance coverage
13. Agreement for the access to treatment with the trial outcome

Additional documents for proposals involving materials transfer, external/international collaboration or with promoter out of Cameroon

14. Material Transfer Agreement (MTA)
15. Data Sharing Agreement (DSA)
16. Ethical approval from the competent REC in the foreign country

Requirements for submitting an application for Ethical Clearance

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□ **Protocol requirements: contents of full protocol**

Protocol contents should include but not limited to :

- Executive Summary
- Background
- Rationale
- Objectives (broad and specific)
- Methodology
- Timeframe of the project
- Expected results
- Ethical considerations and community sensitization
- Dissemination plan
- Detailed budget
- Funding sources
- Primary references

Protocol requirements: methodology section

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- **The Methodology section** is the most important part of the protocol. It should be well detailed as it is the guide on how the study will be done as well as the data analysed.
 - Study site (s)
 - Study Design
 - Type of the study
 - Study/target Population
 - Study/Selection criteria & Recruitment strategy
 - Sample Size and Justification
 - Data collection procedure
 - Laboratory investigations to be done
 - Plans for data Management and Statistical Analysis
 - Study Period

Training of members of Research Ethics Committees

Additional requirements for submitting a clinical trial

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Investigator's brochure: If the proposed study is a clinical trial, the investigator's brochure must be submitted and should provide:

- adequate summary of all safety, pharmacological, pharmaceutical and toxicological data available on the study product, together with
- a summary of clinical experience of the study product to date (e.g. recent investigator's brochure, published data, summary of the product's characteristics etc)

Review criteria

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1. **Social value**
2. **Scientific validity**
3. **Risk-benefit** ratio
4. **Selection** of research participants
5. Provision for **confidentiality**
6. **Informed consent** process
7. Collaborative **partnership**
8. **Ethical clearance** from a competent ethics committee
9. **Administrative authorization** when applicable

Type of review:

- Initial and normal review (4-6 weeks)
- Expedited review (1-2 weeks)
- Protocol amendments (1-2 weeks)
- Continuing review (1-2 weeks)

Initial and normal review procedure

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- Full proposals as per the administrative requirements are submitted to the permanent secretary
- The executive committee decides on the type of review and assigns protocols to reviewers taking into account their expertise
 - The REC's administrator keeps the list of members with their up-to-date CVs
- Reviewers have 1 to 2 weeks to prepare their comments
- Written comments are subsequently sent to the REC's administrator prior to the meeting
- Review comments are discussed thoroughly in meetings

Initial and normal review procedure (continued)

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- For protocols with critical ethical issues, investigators might be invited to defend and address these issues during meetings. They can answer to members' questions/concerns but can not participate to the deliberation.
- Only members having prepared review comments in advance shall qualified for meetings. However, other members shall always be informed on the review outcome.
- A reasonable number of protocols should constitute the business of the day (e.g. a maximum of 4 complexes protocols, up to 10 student protocols).

Expedited review: eligibility criteria

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- A research protocol shall qualified for expedited review when:
 - It is not a clinical trial or any project with invasive procedures;
 - It does not involve sensitive social issues (e.g. homosexuality, commercial sex work, drug abuse, child abuse, gender violence, female genital mutilation, etc);
 - It does not involve vulnerable persons (e.g. pregnant women, prisoners, mental disables, orphans, children);
 - It does not involve international collaboration/transfer of materials abroad;
 - It is not a multicentre protocol;
 - It has no risk (?), or it has minimal potential risks;
 - It is a protocol amendment with minimal potential risk to participants and community;
 - It is a request for renewal of ethical clearance for research projects with minimal potential risk to participants and community.

Expedited review procedure

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- The REC administrator in consultation with the President makes the initial assessment to determine if it qualifies for expedited review.
- 1 to 2 members whose area of expertise and experience is in the same field as the proposed research project are assigned to review the proposal.
 - ▣ If the review involves a project amendment or renewal of ethical clearance, the selected members to review the protocol are preferably members who reviewed the previous version of the protocol.
- A summary of the protocols reviewed through the expedited process is submitted to other members before the (full) meeting.
- Expedited review shall not be longer than 2 weeks.

Review of protocol amendments

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- Any intended modifications/changes or revisions from the approved **protocol** and/or **consent forms** should be submitted to the REC as protocol amendments for review before they can be implemented.
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- Investigators must submit the amended proposal with track changes and a cover letter with brief explanation and justification of the changes

Review of protocol amendments

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- ▣ Protocol amendments are reviewed by the full committee, unless it is qualifies to undergo expedited review
- ▣ The committee assesses if the intended protocol amendments are scientifically and ethically justifiable and if they do not compromise the safety and welfare of the potential participants and communities
 - Change of investigators in the course of protocol implementation is an amendment
 - Change of the title of the protocol is an amendment
 - Other amendments include modifications of the objectives, methodology and inform consent documents
 - Implications of any proposed amendment on the timeframe and budget of the research project should also be scrutinized

Continuing review

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- This type of review is for approved research protocols that are due for renewal of ethical clearance
- After initial ethical approval, projects are to be **reviewed preferentially annually** as per the SOPs.

Continuing review

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- Continuing review :
 - ▣ Is based on progress reports submitted by the PIs to the committee
 - ▣ Meant to provide a mechanism of **passive monitoring** of the research projects so as to pick up any ethical issues that may need to be addressed to protect the wellbeing of participants and the integrity of the data generated.

Scientific & ethical aspects of the review

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- **Social value:** the committee assesses the social need and/or value of the proposed research as follows:
 - Review of study objectives;
 - Assessment of the presence of the health problem in the study community (ies);
 - Evaluation of morbidity and mortality related to the health problem targeted by the research;
 - Assessment of the feasibility of the implementation of the study in the target community (ies);
 - Assessment of the accessibility to products as study outcome.

Scientific & ethical aspects of the review

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- **Scientific validity**: the committee assesses the scientific merit, the validity of the proposed research, and the qualifications of investigators
 - Inclusion and exclusion criteria, recruitment strategy,
 - Sampling methodology
 - Sample size determination and statistical justification
 - Specificity and sensitivity of techniques, data analysis
 - Dissemination plan
 - CVs of investigators
- If a research proposal is scientifically unacceptable, it is **automatically unethical!**

Scientific & ethical aspects of the review

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□ Risk-benefit ratio analysis

- Potential risks already stated in the proposal and any other that may have been omitted but are deemed likely to occur are assessed in light of potential benefits
- All types of risk are scrutinized
 - Social risk
 - Psychological/emotional risk
 - Physical risk

Scientific & ethical aspects of the review

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- **Fair selection of research participants**
 - Eligibility criteria are assessed.
 - Criteria for withdrawal or discontinuation of participants are assessed to ensure fairness and safety of participants.
 - The recruitment process ought to be suitable for the targeted prospective participants and their communities in terms of cultural, traditional, religious or socioeconomic factors.

Scientific & ethical aspects of the review

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□ Informed consent process

- Adequate privacy and voluntariness of participants
- Satisfactory procedure to preserve the confidentiality
- The appropriateness of the informed consent process for the category of people to be enrolled in the study. These include:
 - provision for community consent, individual consent, proxy consent and assent;
 - duration of contact with potential participants to seek consent;
 - non-technicality of the consent form and its completeness;
 - the language in the informed consent documents must **be in lay terms**
 - provisions for the protection of vulnerable populations;
 - provision for consenting illiterate potential participants; process to eliminate undue inducement;
 - provision to continue providing study information to participants throughout the study period

Scientific & ethical aspects of the review

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- Basic elements of the **information sheet** and **informed consent form**:
 - Purposes of the research,
 - Procedure including the duration of the participation,
 - Foreseeable risks and potential benefits,
 - Confidentiality,
 - Voluntariness,
 - Local contact information (PI and REC contacts should be included),
 - compensation,
 - Brief questions to assess comprehension,
 - Signature options

Scientific & ethical aspects of the review

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□ Confidentiality

- Adequate privacy of participants
- Satisfactory procedure to preserve the confidentiality

□ Collaborative partnership

- The committee assesses if there is satisfactory collaboration between scientists (transfer of knowledge and technology...), and with the study communities.
 - for protocols with promoter out of Cameroon, the presence of a local PI who masters the protocol.

Scientific & ethical aspects of the review

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Particular important issues:

- Health research should be conducted on or with **vulnerable groups** such as orphaned children, pregnant women, children, prisoners and mentally ill people only if the research questions cannot be answered when non-vulnerable groups are used.
- Relevant mechanism(s) of **monitoring and auditing** the conduct of the research must be clearly spelt out in the protocol
- In the case of clinical trials,
 - **Data Safety and Monitoring Board** (DSMB) should be set up and should provide names and contacts of members, one of whom should be a national of at least one of the host countries.
 - If a **placebo** is to be used, there must be scientifically and ethically acceptable evidence-based justification that must be clearly explained in the protocol
 - There should be documentary evidence of **insurance** policy to cover trial participants

If the research project involves more than one institution (multicentre studies) and samples are to be transferred from one institution to another, signed Material Transfer Agreement (MTA) and Data Sharing Agreement (DSA) between institutions must be submitted for review to the committee

Decision-making procedure

General rule: Consensus

Alternative: Vote

Decision-making procedure

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- The committee can only make decisions if the quorum requirements as stipulated in the SOPs are satisfied.
- Any member with conflict of interest regarding a particular proposal does not take part in the review of the proposal and subsequent decision making process. Member with conflict of interest is expected to recuse himself/herself.
- Only members who participated in the review process and deliberations take part in the decision-making process.
- The committee decisions are either unanimous when all members are in agreement or by **consensus**. In case there is a tie, other members who were absent are consulted otherwise independent expert opinion is sought.

Decision-making procedure (continued)

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□ Decisions regarding applications are:

□ Ethical Clearance

- Approval,
- Conditional approval for proposal with minor changes required which can be verified by the executive secretariat without submitting to the committee.

□ Information letter

- Major changes necessitating resubmission of the application to the committee or to appointed members
- Disapproval

□ Deferment, pending a decision at a later date.

For any decision made by the REC, clear reasons and justifications are given and documented in the minutes and in the communication to the principal investigator

Engagement of independent consultants

- **If a proposal requires expertise that a REC does not have, it may engage independent experts to review and give their comments**

Engagement of consultants/experts

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- The Executive Secretariat keeps an up-dated list of independent experts with their CVs, and this is reviewed annually by the Committee.
- The independent experts also have to sign privacy and confidentiality forms as well as Conflict of Interest forms to ensure that the information in the proposal is protected and that the consultants do not have any conflict of interest regarding the proposal.
- The experts only give their views and respond to any specific questions that may have been asked, but they do not decide whether the proposal should be approved or not.
- The expert may be invited to the REC meeting to respond to questions and clarify issues but they do not participate in the decision-making process.

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Decisions regarding submitted protocols are officially communicated, in writing, to the principal investigator after the meeting that made the decisions.

Communicating decisions to investigators

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- ▣ **Communication of the REC decision must include the following:**
 1. A letter head of the REC with contacts and registration numbers (e.g. National, FWA number)
 2. The authorization references
 3. The date of the decision
 4. The title of the protocol
 5. The documents reviewed
 6. The name, title and address of at least the principal investigator
 7. The study site(s)
 8. A clear statement of the decision reached by the REC, with PI's responsibilities
 1. In case of a conditional decision, any requirements by REC, including suggestion for revisions are clearly explained in writing to the principal investigator
 2. In case of a positive decision, a statement of responsibilities of the principal investigator and any requirements as stipulated in the decision by the REC
 9. The validity period of the approval (**One year**)
 10. The official signature and stamp
- Training of members of Research Ethics Committees

Communicating decisions to investigators

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- In Cameroon, Ethical clearance and information letter must be written either in French or in English upon PI's request.
- The final letter (ethical clearance or information letter) is processed by the Administrator and signed by the Chairman or the Vice-Chair.
- Decisions must also be systematically communicated to the Division of Health Research Operations/Ministry of Public Health.

Challenges

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Challenges	Various ways to address
Lack of infrastructures and financial resources	<ul style="list-style-type: none">-Submission fee-Application for Grants-Functioning Budget
Review procedure: formal/written recommended, but only verbal comments given by some members	<ul style="list-style-type: none">-Written comments compulsory-Verbal comments accepted only in meetings

Challenges

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Challenges	Various ways to address
Nonattendance of members to meetings	-Letters to members -Annual review schemes/figures
Unavailability of the majority of members and extra work for regular members	Co-optation of experts/Independent consultants
Significant delay in the transmission of review comments by reviewers to the administrator	Reduction and selection of reviewers (1-2 for students protocols, at least 4 for complex protocols e.g. clinical trial)
High number of protocols to review (\approx 30-40/month)	Additional meetings
High Pressure from promoters and investigators	Information letters to investigators and invitation to defend protocols during meetings

References

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□ Core references

- Arrêté N°0977/A/MINSANTE/SESP/SG/DROS/ du 18 avril 2012 portant création, organisation et fonctionnement des comités d'éthique de la recherche pour la santé humaine au sein des structures relevant du Ministère en charge de la Santé Publique
- Déclaration d'Helsinki 1964 – 2008
- CIOMS Guidelines 2002
- ICH-GCP : 1996 – 2002
- EU DIRECTIVE 2001/20/EC on Clinical Trials
- US 45 CFR 46 Protection of Human Subjects - Common Rule
- Lignes Directrices Opérationnelles de l'OMS pour les Comités d'Ethique 2000
- Harmonized template SOPs for African Ethics Committees in Africa, AMANET 2010
- Harmonized template SOPs for RECs in Cameroon, CNEC-EDCTP 2012

□ Other reference

- Code Civil Camerounais; (Code Civil 2007 Minos Yaoundé-Cameroun)
- Ezekiel J. Emmanuel et al., 2004. What makes clinical research in developing countries ethical? The benchmarks of Ethical Research

Useful Basic Training in Research Protocol Review

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- Continuing training of RECs' members
- TRREE Programme (CNEC Partner)
 - Website: <http://elearning.trree.org/>
- Other free Online Course

THANK YOU FOR YOUR KIND ATTENTION

Merci de votre aimable attention

