Contents

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CREDO Overview

CREDO training consists of ten course modules. The training will be delivered in a blended format comprising face-to-face workshops and self-directed web-based learning.

The training will begin with a two day face-to-face workshop during which participants will be given an introduction to evidence-based medicine for epidemic infections and fundamental concepts of generating clinical evidence. After the initial workshop the participants will progress through the web-based modules. The CREDO training will conclude with a second two day face-to-face workshop during which the online training will be reinforced and built upon feedback on the final assignment will be provided. The entire CREDO course is expected to be completed within 3-4 months and will involve approximately 30 hours of face-to-face instruction, 40 hours of online learning and completion of a written, group assignment.

Our target is multidisciplinary research teams in LMICs that are susceptible to outbreaks. In order to qualify for the training, applicants must demonstrate some prior experience in clinical research and must work in a setting where clinical research is being or will be conducted.

The first CREDO pilot workshop was held at the Uganda Virus Research Institute in Entebbe, 9-10th March 2017. There were four multi-disciplinary teams from Côte d'Ivoire, Ethiopia, Ghana and Uganda in attendance. The initial workshop is being used to refine the content and delivery of the curriculum through participant feedback, and will be followed by the participants completing the on-line modules and a second and final workshop in Addis Ababa from 12-13 July, 2017.

The lectures and materials from the first CREDO workshop are available for review here.

CREDO Overall Intended Learning Outcomes

- Describe the steps in the planning and implementation of a clinical research study

- Explain how an outbreak setting might influence the approach to these steps
- Rapidly develop a research plan for an observational study or a clinical trial for a disease of epidemic potential

CREDO Course Content

1. Good Clinical Practice

Online module - this is a prerequisite for CREDO.

a. Intended Learning Objectives

- How GCP should be adopted in the conduct of clinical research
- The basic principles of GCP
- The responsibilities of the investigator
- What being 'GCP' qualified means and why conducting a study according to GCP is important
- What Good Clinical Practice (GCP) is

b. Module Outline

1. **ICH Good Clinical Practice**
2. **Course Objectives and Contents**
3. **What is Good Clinical Practice**
4. **Who is Involved with GCP?**
5. **Recognition of GCP**
6. **Being GCP Qualified**
7. **Investigators' GCP Responsibilities**
   - 7.1. Gaining informed consent from study participants
8. **Randomisation procedures and unblinding**
9. **Medical care of participants**
10. **IEC/IRB communication and approvals**
11. **Investigational product(s) management**
12. **Study protocol compliance**
13. **Investigator qualifications and agreements**
14. **Records and reports management**
15. **Safety reporting**
16. **Ensuring adequate resources**
17. **Management of premature termination or suspension of a trial**
18. **Practical application of GCP**
19. **Key Points to Remember**
20. **References and Resources**
21. **Quiz**

2. Evidence-based medicine for epidemic infections

Face-to-face lecture delivered at Workshop 1. Lecture recording is available here.

a. Intended Learning Objectives

- Critique the clinical research response to emerging infections
- Define emerging and epidemic infections and discuss their importance
- Define evidence-based medicine

3. Rapid 'Evidence Needs' Appraisal Module

Online module - available here.
Author: Mike Clarke - Professor, Queen's University Belfast and Research Director of EvidenceAid

a. Intended Learning Objectives

- Understand the key elements in a rapid systematic review
- Critically appraise literature.
- Identify gaps in literature.
- Prioritize a research area.
- Formulate a relevant research question.

b. Module Outline

1. **Why is it important to design new research carefully**
   - 1.1. Accumulating evidence
   - 1.2. Minimising waste
   - 1.3. Getting funding
2. **Systematic reviews and Rapid Reviews**
   - 2.1. What is a systematic review
   - 2.2. How common are systematic reviews
   - 2.3. Rapid reviews
3. **Planning a rapid review**
   - 3.1. Developing the scoping question for the rapid review
   - 3.2. Finalising the scoping question for the rapid review
   - 3.3. Setting the eligibility criteria for the rapid review
   - 3.4. Registering the rapid review
4. **Using an existing systematic review**
   - 4.1. Searching for an existing systematic review
   - 4.2. Deciding if an existing systematic review is of adequate quality
   - 4.3. Deciding if an existing systematic review is up to date
5. **Searching for studies for your scoping review**
   - 5.1. Deciding on the sources to search
   - 5.2. Deciding on the terms to use in the search
   - 5.3. Limiting your search to increase the proportion of the retrieved records that will be relevant to your rapid review
   - 5.4. Screening the titles and abstracts
   - 5.5. Checking the full text articles
6. **Appraising the eligible studies and extracting information**
   - 6.1. Extracting data and other information
   - 6.2. Assessing study quality and risk of bias
7. **Reporting the rapid review**
8. **Prioritising topics for future research**
   - 8.1. Who should be involved in setting priorities
   - 8.2. How should the stakeholders set the priorities
9. **Formulating the research question for a prioritised study**
   - 9.1. Framework for the implications for research
   - 9.2. Choosing the outcomes to measure
10. **Summary**
11. **Quiz**

4. Study Design Module

Online module in development.
Author: Dr Nzelle Kayem, Research Associate, Centre for Tropical Medicine & Global Health, University of Oxford, UK. Reviewed by Prof Peter Horby and Dr Eric Ohuma, University of Oxford

a. Intended Learning Objectives

- Describe different types of trial designs
- Describe the characteristics of Emerging and epidemic prone infectious disease (EEID) that make them challenging for clinical trial design
- Describe the key statistical issues relevant to clinical trials in epidemic settings

- Identify issues to consider when designing a trial, including defining outcomes, carrying out sample size calculation, and analysing trial data
- Outline possible approaches to trial design that can be used to mitigate the challenges of conducting clinical research on EEIDs

b. Module Outline

1. Introduction
- 1.1. What is clinical research
- 1.2. Taxonomy of clinical research
- 1.3. Observational study designs
  - 1.3.1. Descriptive studies
    - 1.3.1.1. Ecological Studies
    - 1.3.1.2. Case reports and Case series
    - 1.3.1.3. Exploratory designs
  - 1.3.2. Analytical Studies
    - 1.3.2.1. Cross-sectional studies
    - 1.3.2.2. Case-Control Studies
    - 1.3.2.3. Cohort studies

2. Clinical trials
- 2.1. What are clinical trials?
- 2.2. Phases of clinical trials

3. Design of clinical trials
- 3.1. Non randomised controlled study
- 3.2. Randomised Controlled Trials
  - 3.2.1. Efficacy trials
  - 3.2.2. Effectiveness trials
  - 3.2.3. Superiority trials
  - 3.2.4. Equivalence trials
  - 3.2.5. Non-inferiority trials
  - 3.2.6. Cluster Randomised Controlled Trials
  - 3.2.7. Parallel Group Designs
  - 3.2.8. Cross-over trial designs
  - 3.2.9. Factorial designs
  - 3.2.10. Stepped Wedged Design
- 3.3. Adaptive designs

4. Characteristics of Emerging and epidemic prone infectious disease (EEID) that make them challenging for clinical trial design.

5. Possible approaches to trial design that can be used to mitigate the challenges of conducting clinical research on EEIDs

6. Key statistical issues relevant to clinical trials
- 6.1. Some Basic Principles
- 6.2. Risk of Bias, Randomisation and Treatment Allocation
- 6.3. Sample size Calculations
- 6.4. Possible outcomes and measures of effect size or disease occurrence
  - 6.4.1. Dichotomous (binary) outcome data
  - 6.4.2. Continuous outcome data
  - 6.4.3. Ordinal outcomes
  - 6.4.4. Time-to-event (survival) outcomes
  - 6.4.5. Counts and rates
- 6.5. Missing data and Intent to Treat
- 6.6. Interim analysis and Stopping Rules

7. Summary

8. Quiz

5. Ethics Module

The eLearning course has been adapted entirely from the WHO training manual 'Ethics in epidemics, emergencies and disasters: Research, surveillance and patient care'. Participants are encouraged to take the entire course but only modules 2, 4 and 6 are compulsory for CREDO

a. Intended Learning Objectives

- Describe "standard" procedures that should govern an ethics review of research activities, including public health research
- Describe possible variations to standard procedures of ethics review that are applicable to research in emergencies
- Identify potential harm and benefit to individuals and communities resulting from conducting research in emergencies
- Discuss moral theories, and identify frameworks applicable to research in emergencies
- Explain the current norms under which a waiver of consent could be deemed acceptable for research in critical care settings, and assess when they could be applicable to research in emergencies
- Explain the processes required to improve informed consent to research in emergencies, with particular consideration of traditional communities and low-resource settings
- Identify issues of equity of access to unproven treatments during research in the course of emergency response

b. Module Outline

Part 1 - Processes for ethics review in public health interventions, surveillance and research

1. **Learning objectives 2.1: Describe 'standard' procedures that should govern an ethics review of research activities , including public health research**
   - 1.1. Background
   - 1.2. Areas covered by standard ethics review
   - 1.3. Ethics review of public health research
   - 1.4. Challenges raised specifically by research in emergencies 1
   - 1.5. Challenges raised specifically by research in emergencies 2
   - 1.6. Case study 1
   - 1.7. Case study 1 Feedback
   - 1.8. Summary - Learning Objective 2.1
2. **Learning objective 2.2: Identify circumstances in which public health surveillance activities should possibly undergo formal ethics review**
   - 2.1. Ethical foundations for formal ethics oversight of public health surveillance
   - 2.2. Reasons for formal ethics review of surveillance
   - 2.3. Case study 2
   - 2.4. Case study 2 considerations
   - 2.5. Case study 2 feedback
   - 2.6. Summary - Learning Objective 2.2
3. **Learning objective 2.3: Describe possible variations to standard procedures of ethics review that are applicable to research in emergencies**
   - 3.1. Possible variations to standard procedures 1
   - 3.2. Possible variations to standard procedures 2
   - 3.3. Possible variations to standard procedures 3
   - 3.4. Frameworks for departure from normal review process
   - 3.5. Concern about departures from normal review process
   - 3.6. Case study 3
   - 3.7. Case study 4
   - 3.8. Summary - Learning Objective 2.3
4. **Quiz**

Part 2 - Conflict between the common good and individual autonomy in research and clinical trials

1. **Learning objective 4.1: Identify potential harm and benefit to individuals and communities resulting from conducting research in emergencies.**
    1.1. Potential benefits to individuals and communities of emergency research
    1.2. Potential harms to individuals and communities of emergency research
    1.3. Ethical concepts and principles for the conduct of research in emergencies
    1.4. Case study 1
    1.5. Case study 2
    1.6. Summary - Learning Objective 4.1
2. **Learning objective 4.2: Discuss moral theories, and identify frameworks applicable to research in emergencies.**
    2.1. Ethical principles
    2.2. Ethical principles 1
    2.3. Ethical principles 2
    2.4. Summary - Learning Objective 4.2
3. **Learning objective 4.3: Explain the current norms under which a waiver of consent could be deemed acceptable for research in critical care settings, and assess when they could be applicable to research in emergencies.**
    3.1. What types of research might require a waiver of consent?
    3.2. When is a waiver of consent requirements permissible?
    3.3. When are these criteria relevant to emergencies?
    3.4. Case study 3
    3.5. Case study 3 feedback
    3.6. Summary - Learning Objective 4.3
4. **Learning objective 4.4: Explain the processes required to improve informed consent to research in emergencies, with particular consideration of traditional communities and low-resource settings.**
    4.1. Background
    4.2. What processes are required for obtaining informed consent from traditional communities in an emergency?
    4.3. What processes are required for obtaining informed consent from traditional communities in an emergency? 1
    4.4. What processes are required for obtaining informed consent in low- resource settings in an emergency?
    4.5. Case study 4
    4.6. Case study 4 feedback
    4.7. Summary - Learning Objective 4.4
5. **Quiz**

Part 3 - Ethically relevant criteria for triage, resource allocation and standard of care

1. **Learning objective 6.1: Discuss ethical frameworks and criteria for triage and rationing in emergencies**
    1.1. Background
    1.2. Points to consider
    1.3. Levels of triage
    1.4. Triage criteria
    1.5. Alternatives to triage
    1.6. Ethical principles
    1.7. Ten substantive ethical values
    1.8. Five procedural values
    1.9. Case study 1
    1.10. Case study 2
    1.11. Summary - Learning Objective 6.1
2. **Learning objective 6.2: Understand how criteria for standards of care and treatment can be altered during emergencies.**
    2.1. Factors that may alter established standards of care in an emergency 1

2.2. Factors that may alter established standards of care in an emergency 2
2.3. Case study 3
2.4. Case study 4
2.5. Additional information for case study 4
2.6. Summary - Learning Objective 6.2

3. **Learning objective 6.3: Identify issues of benefit-sharing with communities under public health surveillance.**
   3.1. Background
   3.2. Definition
   3.3. Ethical justification
   3.4. Benefit- sharing and public health surveillance 1
   3.5. Benefit-sharing and public health surveillance 2
   3.6. Case study 5
   3.7. Summary - Learning Objective 6.3
4. **Learning objective 6.4: Identify issues of equity of access to unproven treatments during research in the course of emergency response**
   4.1. Background
   4.2. Avenues to increase accessibility 1
   4.3. Avenues to increase accessibility 2
   4.4. Considerations of equity
   4.5. Case study 6
   4.6. Case study 6 considerations
   4.7. Case study 6 feedback
   4.8. Summary - Learning Objective 6.4
5. **Quiz**

6. Ethics: Special Groups Module

This module is being coordinated by Dr Nathalie MacDermott, Wellcome Clinical Research Training Fellow, Imperial College London. Dr MacDermott has assembled two expert groups (see list below) to draft two consensus statements, one for children and one for pregnant women. The groups will then seek to get the consensus statements published, in order to have a reference point for the training module. The training module will be developed after the pilot phase of CREDO. For the pilot, Dr MacDermott will deliver a lecture at the second CREDO workshop to outline the main points of the consensus statement.

Obstetrics
Annick Antierens (MSF)
Armand Sprecher (MSF)
Francoise Bayliss (Professor of Ethics, Dalhousie University)
Anna Mastroianni (Professor of Law, Uni Washington)
Leslie Henry (Professor of Law, Uni Maryland)
Maggie Little (Professor of Obstetrics and Gynaecology Ethics, Georgetown)
Christine Grady (Chief of Bioethics, NIH)
Ann Lyerly (Professor of Social Medicine, UNC)
Annette Rid (Senior Lecturer Bioethics, KCL)
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Holly Taylor (Professor of Health Policy/Paediatrician, John Hopkins)
Robert Nelson (Ethicist Paediatric Medicinal Products, FDA)

Seema Shah (Professor of Law, Uni Washington)
Mike Sharland (Professor of Paeds ID, St Georges)
Jess Jarvis (Research fellow, St Georges)
Katharine Wright (Nuffield Bioethics)

a. Intended Learning Objectives

- Apply an ethically sound strategy for the inclusion of young people, children, infants and pregnant women in research in epidemic settings.
- Describe the complexities of incorporating young people, children, infants and pregnant women in research in epidemic settings.
- Evaluate the best manner in which to ensure fair and equal access to experimental therapies by young people, children, infants and pregnant women during research in epidemic settings.
- Identify the ethical principles of the incorporation of special groups such as unaccompanied minors, orphans, neonates and pregnant women, in research involving experimental therapies.

7. Communications and Community Engagement Module

This module is currently in development. It has been adapted from:

1. The Engaging with Communities section of Research Ethics Online Training
2. ET Robinson, D Baron, LL Heise, J Moffett, SV Harlan. (2010). Communications Handbook for Clinical Trials: Strategies, Tips, and Tools to Manage Controversy, Convey Your Message, and Disseminate Results. Available at http://pdf.usaid.gov/pdf_docs/PA00J1QZ.pdf

a. Intended Learning Objectives

- Define “community” and identify research stakeholders
- Describe the special considerations for community engagement in disease outbreak situations
- Develop a Strategic Communications Plan with a specific focus on crisis communications
- Perform environmental scans and assemble a communications team

b. Module Outline

1. **Defining 'community'**
   1.1. Community: Two useful - and complementary – definitions
2. **What is community engagement?**
3. **The goals of community engagement**
4. **Mechanisms for community engagement**
5. **Stakeholders**
   5.1. Research: A partnership between interested stakeholders
   5.2. Identification of research stakeholders and their roles
6. **Why Communication is Important**
   6.1. WHO Outbreak Communication Guidelines
7. **Preparing for Communications**
   7.1. Complete a desk review
   7.2. Internal/External environmental scans
      7.2.1. Internal scan
      7.2.2. To conduct an external environmental scan, follow these steps
      7.2.3. Information gathering template
   7.3. Communications team
8. **Develop a Strategic Communications Plan**
   8.1. WHO Outbreak Communications planning steps.
   8.2. Outline team functions and chain of command

8.3. Develop an Activities Plan

9. **Crisis management**
   - 9.1. What is predictable in an epidemic?
   - 9.2. Overarching principles for crisis communications
   - 9.3. What is a crisis communications plan?
   - 9.4. Why is a crisis communications plan needed?
   - 9.5. Elements of a crisis communications plan
   - 9.6. Sample procedure for rapid response to crises
   - 9.7. Managing unexpected trial closures
10. **Develop a Dissemination Plan**
11. **Create materials that support the trial**
    - 11.1. External documents for distribution to stakeholders
    - 11.2. Stand-by and internal documents for staff use only
12. **Guidance specific to engaging with communities**
    - 12.1. UNAIDS/WHO. Ethical considerations in biomedical HIV prevention trials. Geneva: United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) (2007, updated 2012). Guidance Point 2
    - 12.2. UNAIDS/AVAC. Good participatory practice guidelines for biomedical HIV prevention trials 2011. Geneva, United Nations Joint Programme on HIV/AIDS and AVAC, Global Advocacy for HIV Prevention (2011).
    - 12.3. WHO. Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants. Geneva, World Health Organization, 2011.
    - 12.4. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Council for International Organizations of Medical Sciences (CIOMS), 2016.
    - 12.5. Declaration of Helsinki (World Medical Association)
13. **Summary – Engaging With Communities**
14. **Quiz**

8. Data management, sharing and harmonisation module

We will use two existing online modules and will reinforce the learning with interactive group exercises at the CREDO workshops.

1. Introduction to Data Management for Clinical Research Studies
2. Ethics and best practices in sharing individual-level research data

a. Intended Learning Objectives

- Describe the importance of data management in clinical research
- Explain the benefits of streamlined data collection
- Explain the important role of data sharing, harmonisation and collaboration in outbreak research

b. Module Outline

Part 1 - Ethics and best practices in sharing individual-level research data

1. **Introduction**
2. **The Data Management Plan**
3. **Case Report Form Design**
4. **Paper or Electronic Case Report Forms?**
5. **Case Report Form Completion**
6. **Choosing a Data Management System**
7. **Data Entry**
8. **Data Errors and Resolution**
9. **Quality Assurance, Data Cleaning and Locking**
10. **Data Analysis**
11. **Data Archiving**
12. **Staff**

13. **Summary**
14. **Key Points to Remember**
15. **References and Resources**
16. **Quiz**

Part 2 - Ethics and best practices in sharing individual-level research data

1. **Introduction**
    1.1. **Why share individual-level data?**
2. **Ethical issues raised by data sharing**
3. **A summary of reasons to share data and ethical issues raised by data sharing**
4. **Designing governance procedures for data sharing**
5. **Core considerations in ethical data sharing**
    5.1. **The value of data sharing**
    5.2. **Minimising harm**
    5.3. **Promoting fairness and reciprocity**
    5.4. **Trust**
6. **Ways forward**
    6.1. **Seeking consent to data sharing**
    6.2. **Governing data sharing**
    6.3. **Data sharing policy priorities**
    6.4. **Capacity building**
7. **Concluding thoughts**
8. **Quiz**

9. Research Study Planning and Governance Module

Online module in development.
Authors: Dr Nzelle Kayem, Research Associate and Emmanuelle Denis, Senior Clinical Trials Manager, Centre for Tropical Medicine & Global Health University of Oxford, UK. Reviewed by Dr Raffaella Ravinetto, Head of the Clinical Trials Unit, Institute of Tropical Medicine, Antwerp

a. Intended Learning Objectives

- Describe the basic elements of the different kinds of contracts used in clinical research
- Describe the difference between clinical study insurance and professional liability
- Identify a study Sponsor and describe the role and responsibilities of the Sponsor
- Identify potential sources of study funding and prepare grant applications

b. Module Outline

1. **Securing study funding**
    1.1. Identifying funders
    1.2. Budget development
    1.3. Investigator-initiated studies
    1.4. Peer Review Process
    1.5. Reasons for Lack of funding
    1.6. Conclusion
2. **Study Sponsorship**
    2.1. Identifying potential sponsors
    2.2. Roles and responsibilities of sponsor
3. **Trial insurance and professional liability**
    3.1. Introduction
    3.2. Selecting appropriate insurance cover
    3.3. Professional liability insurance

4. **Contracts**
    4.1. Clinical Study Agreements
    4.2. Legal Differences and Impact on Clinical Trial Agreements
    4.3. Confidentiality or Non-Disclosure Agreements (CDA or NDA)
    4.4. Material Transfer Agreements
    4.5. Data Sharing Agreements
    4.6. Memorandum of Understanding
    4.7. Terms of Reference
    4.8. Speeding up Contract and Agreement Review Processes
    4.9. Establishing a Time frame for Agreement and Contract Approval
    4.10. Conclusion
5. **Quiz**

10. Logistical and Operational Planning Module

Online module in development.
Authors: Emily Liddiard, Medical Student, University of Oxford, UK and Dr Amanda Rojek, PhD Candidate, Centre for Tropical Medicine & Global Health, University of Oxford, UK.
Reviewed by Prof Peter Horby, University of Oxford

a. Intended Learning Objectives

- Evaluate project plans that include operational elements
- Formulate mock project management timelines for a research project
- Identify logistical and operational barriers to implementing research during an outbreak

b. Module Outline

1. **Site assessment**
    1.1. Introduction
    1.2. Requirements of a research site for clinical research during a disease outbreak
    1.3. Further resources
2. **Staff health and safety**
    2.1. Introduction
    2.2. Relevance to disease outbreaks
    2.3. Infection risk
    2.4. Further optional reading and helpful resources
3. **Drug import and destruction**
    3.1. Cold chain and cold storage
4. **Field specific standard operating procedures**
    4.1. Introduction
5. **Laboratory partnerships**
    5.1. Introduction
    5.2. Setting up the laboratory for a research study
    5.3. Useful links
6. **References**
7. **Quiz**