Council for International Organizations of Medical Sciences

4th meeting of the CIOMS Working Group on Clinical Research in Resource-Limited Settings (CRRLS)

27–28 February 2019, Geneva, Switzerland

Minutes

As at 26 March 2019

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Meeting objectives

- To review the current draft sections of the CIOMS guidance on clinical research in resource-limited settings and provide comments;
- to continue working on the drafts; and
- to agree on next steps.

Opening and introduction

Dr Lembit Rägo opened the meeting and informed the participants of current events at CIOMS. An Open Meeting of the Working Group (WG) on Patient Involvement in the Development and Safe Use of Medicines will be held on 30 April 2019 to obtain wider input to the group's current thinking. The meeting will also mark the 70th Anniversary of CIOMS. A new CIOMS WG on MedDRA Labelling Groupings has been established and will hold its 1st Meeting at the beginning of April *(Post-meeting note: The concept paper and a more concise one-pager on MLGs are available on the CIOMS website.)* Potential new WGs on severe cutaneous adverse reactions (SCARs) and benefit/risk assessment (update of the CIOMS IV WG report) are at the planning stage.

Lembit welcomed the new group members (see participant list in Annex 1). All participants briefly introduced themselves.

Dr Bert Leufkens took the chair.

Approval of 3rd meeting minutes

The minutes of the 3nd Working Group meeting were approved.
Post-meeting note: Christoph Conrad from Paul-Ehrlich-Institute, Germany has noted that he should be listed under "Regulators" (not "Academia/Research") in the List of participants. The meeting minutes have been corrected accordingly.

The proposed structure of the WG report, as shown in Annex 2 of the 3rd Meeting minutes, is carried forward to **Annex 2** of the present minutes, with modifications to document progress and decisions made at the 4th Meeting.

"Tour de table"

Each participant briefly presented her/his news or recent experiences in the field of clinical trials in resource-limited settings. The contributions are shown in **Annex 3**.

The following points from the "Tour de table" were noted for inclusion in the CIOMS guidance:

1. Include a paragraph in the main text on the challenge of **stratifying age groups in paediatric studies**
2. Call for efforts to **sustain site capacity**; emphasize the social value of research for community health care services
3. Include a section on how to create a **legal basis** for trials in countries where this is absent (possibly proposing some basic definitions, and/or referencing provisions of the Declaration of Helsinki for actions in case of serious incidents).
4. Advocate for **adapted trial designs** with state-of-the-art statistical methods. Trial designs can be pioneered in post-registration trials, and the lessons learned adopted in registration trials.

Professor Leufkens suggested that the experiences presented in the "Tour de Table" should be recorded in a living document uploaded to the shared member area on the web.

Reports from the drafting sub-teams

The sub-team leads presented their current drafts on screen for comment by the WG. The comments made on each section are summarized below.

Main text

Chapter 1, Background and problem statement – comments from the WG:

- Link to the Sustainable Development Goal 3, "Ensure healthy lives and promote well-being for all at all ages";
- flag issues of internal brain drain;
- flag the need for raising awareness about the value of research among civil and health authorities;
- mention new research partners that are emerging in the global environment (e.g. CEPI for vaccines, CARB-X to combat antimicrobial resistance);
- add a paragraph on the widespread use of traditional medicines, which may cause adverse events and interactions; and
- introduce the need for a single, flexible, implementable standard: *"The ultimate goal is … not necessarily perfect data, but absence of errors that matter"*[1].

[1] (from: Academy of Medical Sciences, Bill & Melinda Gates Foundation, Wellcome Trust. Exploring Good Clinical Practice guidance in clinical trials – meeting summary)

Chapter 2, Principles of clinical research – comments from the WG:

- Advocate for regional centres/observatories, with independent data committees;
- highlight the relevance of data-sharing and clinical trial registries. Efficiency and access to trials are particularly important in CRRLS, where limited funds require difficult trade-offs between research and health care;
- add a section on adapting current ICH standards for implementation of research in RLS (see Exploring Good Clinical Practice guidance in clinical trials);
- add a paragraph about data ownership / data custodianship; and
- state that funding is central for access to research and should be considered upfront (more details on funding are given in Chapter 3).

Chapter 3, Obstaclers and enablers – comments from the WG:

- Call for efforts to sustain trial site capacity–including not only staffing and equipment, but also documentation–, for example by:
  - Encouraging sponsors to ensure sustainable aftercare (note: anything beyond laboratory upgrades and clinical aftercare can be criticized as "unfair inducement");
  - Re-using sites for other studies, beyond infectious diseases e.g. cancer studies (possibly with the help of specialists who market the site);
  - Avoiding the use of over-sophisticated equipment, and recycling equipment through online platforms (e.g. as offered by The Global Health Network); and
  - Better coordination of investments, e.g. through standing clinical trial networks or collaborations (such as the HERO Research Agenda).
- Highlight the challenge of bureaucracy, which impedes purchases, shipment of samples etc.
- Consider rewording the title (e.g.: "Challenges and opportunities").

Appendices

It was agreed that no appendices are needed on Innovative trial designs (as they are not specific to RLS) and Informed Consent (this is covered in Appendix 1). The status of the remaining appendices and comments made at the meeting are summarized below.

It was noted that the appendices should include full references for further reading, so that they can serve as stand-alone guidance on specific topics.

Appendix 1: Vulnerable populations

A draft was shared with the full WG before the meeting. It was suggested to:

- Add an explicit statement that medical problems are concentrated in vulnerable populations (i.e. migrants, children, dispossessed etc.), and that research therefore must be conducted in these groups;
- address the issue of displaced populations; and
- edit the appendix to make the style more uniform.

Appendix 2: Digital health

A draft will be shared with the WG within the next few weeks. This appendix will describe the innovations that can be used at each step of clinical trials, including e.g.: software to develop protocols, e-consent, wearables, telemedicine for follow-up consultations, use of mobile phones for reminders and as diagnostic tools (e.g. scanning), etc.

It was suggested to reword the title, e.g. "Digital technologies in clinical research in RLS".

Appendix 3: Electronic health records

An early draft will be reviewed by a sub-team by the end of March, a revised draft will be shared with the full WG.

Appendix 4: Paediatrics
The WG has reviewed the first draft and has provided comments, which will be addressed after the meeting.

Appendix 5 – Outbreaks
A draft is in development. Comments will be sought from WHO members of the WG. It was suggested to frame this topic in a positive way: IF preparations have been made before an outbreak, it is possible to obtain data that are compliant with GCP (if not with registration requirements).

Appendix 6 – Women of childbearing age
A draft will be developed. It was suggested that this appendix should include guidance on:

- How women can be included in research despite limited access to contraception; and
- the need for, and value of, research in pregnant and breastfeeding women

Appendix 7 – Pharmacogenetics, personalized medicine
An outline has been shared within the sub-team. WG members made the following suggestions:

- Highlight the situations where local trials are justified (e.g. to investigate drug clearance through the P450 pathway, or potential adverse effects in specific populations);
- refer to a global mapping for G6PD deficiency and recommend that new drugs should be tested for this; and
- mention the challenges posed by migration and medical tourism.

Breakout sessions and report-back

Two breakout sessions were held from 16:00 to 18:30 on Day 1, and from 09:00h to 10:30 h on Day 2. The drafting teams discussed and addressed the comments received during the meeting, and developed their drafts further. A brief report-back was provided by each group on Day 2.

Conclusions

The recommendations of the proposed CIOMS guidance were discussed. It was agreed that the sub-teams should include recommendations at the end of their draft chapters. These will serve as the basis for a "Recommendations" section to be compiled at a later stage. WG members suggested that the Recommendations should be:

- Concrete and aspirational ("have teeth");
- short and punchy, as they may be the only section of the report that people will read;
- targeted to a specific group where applicable (e.g. governments, sponsors); and
- reflecting consensus by the WG, so as to ensure maximum impact.

In another "Tour de table" WG members were asked to propose some messages to convey in the guidance. The participants suggested that the report should:

- Discuss the **shifting disease burden** and the implications for research in RLS
- Call for **coordination among funders** (as done for example by the Global Alliance for Chronic Diseases). The WG decided against recommending to establish a "Global fund for research", as creating yet another funding mechanism would increase complexity with little added value.
- Highlight the importance of defining **relevant research questions** that will translate into better health care in communities.
- Encourage the use of **innovative study designs** in RLS.

- Encourage adequate inclusion of **children and pregnant women** in clinical trials. A possible approach is to include children in adult trials or vice-versa, especially in emergencies.
- Call for including research methodology and statistics in **medical school curricula** in RLS
- Encourage more post-registration research.
- Recommend more **advocacy for research among civil and health authorities** in RLS (reference Guideline 1:Scientific and Social Value and Respect for Rights of the 2016 CIOMS ethical guidelines, and mention return on investments.

Next steps

Who	Action	By when
CIOMS Secretariat	Contact members that did not attend the meeting and link them up with sub-team leads	Mid- March
Sub-teams	Finalize the draft sections (please insert placeholders for any missing parts) and send them to CIOMS	Mid-April
CIOMS Secretariat	Combine the sections and circulate the combined draft for comment to the full group	End of May
All WG members	Send comments to the leads the respective drafting sub-teams	End of June
Sub-team Leads	Address the comments and send revised section to CIOMS	End of August
CIOMS Secretariat	Transfer the revisions to the combined draft. Circulate the revised combined draft (Version 2), for discussion at the 5th WG meeting.	End of September

Date of next meeting

The next face-to-face meeting will be held in Extremadura, Spain, in October 2019. The date will be confirmed by Doodle Poll.

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Annex 1: List of participants

* = new member

Regulators	Christoph **Conrad**	Paul-Ehrlich-Institut, Germany
	Jerry **Pierson**	National Institutes of Health, U.S.
Academia/ Research	Kalle **Hoppu**	Children's Hospital, Helsinki University Hospital, and University of Helsinki, Finland. Pediatric Clinical Pharmacology Section, IUPHAR
	Samia **Hurst** *(Day 1 only)*	University of Geneva, Switzerland
	Walter **Jaoko**	University of Nairobi, Department of Medical Microbiology, Nairobi, Kenya
	*Gustavo **Kesselring**	International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) – *new CIOMS member organization*
	H. (Bert) G.M. **Leufkens**	Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, the Netherlands
	Adrian **LLerena**	Universidad of Extremadura, Extremadura University Hospital and Medical School, Badajoz, Spain
	Irja **Lutsar**	University of Tartu, Estonia
	*Aita **Signorell**	Swiss Tropical & Public Health Institute
	Nick **White**	Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand & Wellcome Trust, London, United Kingdom
Product R&D	Puneet **Arora**	Roche
	Ruxandra **Draghia**	MSD, U.S.
	Elly **Kourany-Lefoll** *(Day 1 only)*	Merck KGaA, Global Health Institute, Coinsins, Switzerland
	Satu **Kujala**	Medfiles, Finland
	Luc **Kuykens**	Sanofi
	Florent **Mbo Kuikumbi**	Drugs for Neglected Diseases initiative (DNDi), Regional HAT Platform, Kinshasa, Democratic Rep. of the Congo
	Nathalie **Strub Wourgaft**	DNDi, Geneva, Switzerland
	Pol **Vandenbroucke**	Pfizer Inc. Chief Medical Office, New York, U.S.
	*Julian **Woelcke**	Novartis
CIOMS	Lembit **Rägo**	Secretary-General
	Monika **Zweygarth**	Technical writer

Apologies

WHO	Samvel **Azatyan**	WHO Regulatory Systems Strengthening (RSS) Team
	Vaseeharan **Sathiyamoorthy**	WHO Research, Ethics and Knowledge Uptake (REK) unit
Academia/ Research	Ames **Dhai**	University of the Witwatersrand, Steve Biko Centre for Bioethics, Faculty of Health Sciences, Johannesburg, South Africa
	Roli **Mathur**	Indian Council of Medical Research, National Centre for Disease Informatics and Research, Bangalore, India
Regulators	Alambo **Mssusa**	Tanzania Food and Drugs Authority (TFDA), Dar es Salaam, Tanzania
Product R&D	Pierre **Dôme**	Merck KGaA, Global Health Institute
	Aude **Le Roux**	Sanofi – company represented by Luc Kuykens
	Jutta **Reinhard-Rupp**	Merck Germany – company represented by Elly Kourany-Lefoll
	Rosanne **Rotondo**	Novartis – company represented by Julian Woelcke
	Estelle **Vester-Blokland**	Roche – company represented by Puneet Arora
	*Raj **Long**	Bill & Melinda Gates Foundation
CIOMS	Janis **Lazdins**	Adviser
	Hervé **Le Louët**	CIOMS President

Annex 2: Draft table of content (as at 28 February 2019)

Draft Chapter or Appendix
Subsections as at 27/02/2019

1 – Background
Problem statement

2 – Principles of clinical research
- General aspects
- Registries of clinical trials
- Responsible sharing of clinical data
- Combating "ethics dumping"
- Need for capacity-building among ethics committees and regulators
- Importance of good study design
- Justification for deviations from ICH guidelines, including in emergencies

3 – Obstacles and Enablers
- Introduction
- The environment
- The infrastructure
- Financing
- Design and conduct of trials

4 – Recommendations

5 – References

Appendix 1 – Vulnerable individuals and groups
- Health inequity
- Informed consent
- Payments vs inducements
- Additional safeguards / protection
- Dealing with special population groups
- Post-study benefits
- Absence of national ethical guidelines or regulatory framework
- Priority setting for research in low resource countries
- identifying barriers and suggested way forward

Appendix 2 – Digital health
This appendix will provide a comprehensive description of innovations that can be used at each step of clinical trials

Appendix 3 – Electronic health records

Appendix 4 – Paediatrics
- Ethical issues including Informed consent
- Age appropriate scientific methods
- Lack of experience/experts in paediatric clinical trials
- Lack of regulatory capacity
- Infrastructure for paediatric clinical trials
- Access to study medicines after a trial

Appendix 5 – Outbreaks

Appendix 6 – Women of childbearing age

Appendix 7 – Pharmacogenetics, personalized medicine

Annex 3: "Tour de table"

Recent developments and experiences

Project	Experiences and lessons learned **(In bold: topics agreed to be added to the CIOMS WG report)**
Fexinidazole approved by stringent regulatory authority (EMA) and licensed in DRC (YouTube video)	• Certain studies can only be conducted in RLS • The logistic challenges are significant • Good science is possible in RLS • Health facilities in study areas –i.e. remote areas– must be upgraded: **essential to sustain site readiness**
Ebola vaccine trials	• 13 different protocols, making dossier preparation challenging • Group was not prepared for the worst-case scenario of outbreaks: complex logistics, lack of time, resistance by population (fear, rumours, armed conflict…) • Preparedness for future outbreaks is essential
Study in pregnant women	• Upfront buy-in from the community enabled the group to counter an anti-research campaign from the local church • Some advanced test methods were not feasible and had to be replaced by simpler ones: Testing must match available laboratory capacity • Team struggled to keep up with follow-up visits. Registration trials have huge documentation requirements – need to plan for adequate staff
Paediatric studies in remote areas	• Unexpectedly high prevalence of serious co-infections • Sanitary conditions are often very bad • Must educate the communities on health, hygiene etc.
Third Nordic conference on paediatric medicines, Helsinki, 8-9 October 2019	• Stratification of age groups in paediatric studies is a major challenge • Groupings are not currently based on physiological reasoning or population-specific characteristics • This issue is not sufficiently addressed in the ICH E11 revision •
Ebola vaccines and therapeutics in DRC	• Research design should be put in place before, not during outbreaks • "Toolboxes" / modules should be prepared with concurrent ethical input • Need to engage population – there is huge distrust and resistance, sometimes to a point resembling warfare
Trials for new antimalarials	• Challenge to find study sites and sufficient numbers of patients for Phase 3 trials: Not enough cases, investigators not ready… • It is essential to sustain site readiness in-between trials
HIV vaccine trial in Kenya	• Reference ranges from literature may not be applicable locally. Example: High bilirubin screened out more than half of potential study subjects in a Kenyan trial. A study was then conducted to establish a local reference range.
Perspective of contract research organization	• European ethics groups are not always equipped to review studies in RLS: Need for continuous training and processes • Large and small companies conducting registration studies should comply with GCP at a minimum, in any study setting
Global Health Protection Programme (GHPP) (German government)	• No legal framework at all was present in some West African countries participating in the GHPP. The African Model Law does not provide an adequate basis. • **A legal basis is essential** for regulators to handle any serious incidents. Without it, Phase 1 and first-in-human trials cannot be conducted in RLS
Follow-up trials for rhodesiense sleeping sickness	• **Adapted trial design:** As an RCT was not possible, a single-arm trial was conducted: This is not optimal but may be applicable in certain cases

Project	Experiences and lessons learned **(In bold: topics agreed to be added to the CIOMS WG report)**
Project on genomic sequencing	• Difficult to provide feedback to individuals: Data are anonymized, and the findings are not directly applicable to each subject. • Challenging to define the terms for informed consent
Personalized medicines projects in Latin America and India	• People feel that advances in biotechnology should be available to all • Test panels from one population may not be valid or useful for another • Challenging to engage with communities and get consent • **Traditional medicines** are widely used, and communities are concerned about interactions
Workshop on bioethics in a West African country	• Successful engagement was achieved by having both a visiting speaker and a local speaker for each topic • Work on the CIOMS ethical guideline linked up people with knowledge on protecting local communities with those who have the power to make recommendations. Personal contacts can make things happen
Exploring Good Clinical Practice guidance in clinical trials – meeting summary	• Need for a single, flexible, implementable standard for research • "ICH GCP inspectors often strictly adhere to the guidelines without paying attention to factors that matter" • "… the ultimate goal of a trial is to produce a result that is accurate, high-quality, safe and ethical. This quality then does not necessarily mean perfect data, but 'the *absence of errors that matter*'."

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