Council for International Organizations of Medical Sciences

8th meeting of the CIOMS Working Group (WG) on Clinical Research in Resource-limited Settings (CRRLS)

20 August 2020, virtual meeting

Minutes

Version 28 August 2020

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Summary and action points

The CIOMS CRRLS WG held its 8th meeting by video call on 20 August 2020. A proposed meeting agenda and the revised draft WG report were circulated on 17 August (also available on the WG's private webpage).

The meeting participants reviewed the updated draft report and the remaining comments from WG members, and agreed on a number of revisions. They also discussed some overarching issues and made suggestions for further restructuring of the text during the editorial phase.

The Working Group concluded its discussions on the first of two scheduled meeting days. The second day marked the start of the editorial phase, which will be driven by the Working Group members identified at the 7th WG meeting. The timelines for the next phases (editorial process, external consultation, report finalization) as envisaged at the 7th WG meeting were maintained.

The following action points were agreed:

Action point	Responsible person	Timeline
1. In consultation with subgroups/WG members, revise draft chapters and appendices as discussed at the meeting (see minutes hereafter) and send to Monika	Lead authors (see minutes hereafter)	*14 September 2020**
2. Circulate draft meeting minutes to WG for comment	Monika	*Done, 25 August*
3. Integrate lead authors' revisions in the master draft WG report and periodically upload updated working versions of the report to the WG's private webpage	Monika	Ongoing
4. Support the editorial group and liaise with the full WG as appropriate	Monika	Ongoing

**Timeline proposed by Monika after the 8th WG meeting.*

Minutes of discussion

1. Opening and welcome

Bert Leufkens and Lembit Rägo welcomed the group to its 8th Meeting (for a list of participants see **Annex 1)**. Bert Leufkens then took the chair.

While awaiting the establishment of everyone's audio connections Aude flagged two issues reflected below under *General remarks* in Point 4.

2. Meeting management

Agenda and previous meeting minutes

The meeting agenda was adopted. The minutes of the 7th WG meeting (held on 22 June 2020 by video call) had been circulated to the WG on 26 June for comment by 10 July. Comments were received from Bert and Lembit and were addressed. No further comments were raised at the 8th meeting. The minutes of the 7th WG meeting have been posted on the CIOMS website.

3. Walk through the proposed revised report outline

An alternative report outline had been proposed by Bert after the 7th WG meeting to achieve a better balance of chapter lengths and a more logical flow of chapters. The outline was uploaded to the WG's private webpage on 23 June 2020 for the record (available here). Before the 8th WG meeting Monika re-organized the draft WG report in line with this proposed outline and made some editorial changes (e.g. subheadings, reference lists) to improve readability.

The group endorsed the re-structuring as it makes the report clearer and more coherent. The structure may change further as the report evolves.

4. Walk through restructured report

The group reviewed the chapters and appendices of the current draft (version 17 August 2020) as summarized below. Each part was introduced by the respective lead author, followed by group discussion and proposals for further revisions to be addressed by the lead authors. The Chair invited WG members to send any further comments to the lead authors with cc. to Monika.

> ▶ **Action Point 1:** Lead authors, in consultation with subgroups/WG members, will revise their draft chapters and appendices as discussed at the meeting (see minutes hereafter) and send them to Monika. (*Post-meeting note - proposed timeline: 14 September 2020*)

General remarks

Aude flagged two recurring language issues in the draft report that need to be addressed: (1) Women, and pregnant women, should not be regarded as vulnerable groups per se. Wherever they are referred to as such, the specific context making them vulnerable (cultural, environmental…) should be specified. (2) As defined in Chapter 1, resource-limited settings (RLS) exist in low- and in high-income countries. The report should refer to low- and middle-income countries (LMIC) only where this is justified (e.g. when referring to national statistics).

These two issues will be addressed throughout the report as part of the editorial process.

Summary and recommendations (Lead authors: Bert, Lembit)

These sections were originally intended to be placed at the end of the report, to synthesizing the content of the preceding chapters and presenting the resultant recommendations. The two sections

were then moved together upfront. The synthesis may be developed further into an executive summary. The recommendations may be moved back to the end. The two sections will be finalized when the rest of the report is more mature.

The participants raised some cross-cutting issues and agreed that the report should:

a) Emphasize the need for clinical research in RLS not only for diseases specific to these settings but also those occurring globally, taking into account the local point-of-care context, laboratory infrastructure, co-morbidities, ethnicity, social context, and other factors.
b) Take a strong stance against exploitative research.
c) State when research on topics already studied elsewhere is justified in RLS, and when it is not.
d) Distinguish clearly between vulnerable populations (those who need additional safeguards to protect their rights; e.g. migrants, refugees, children, women in certain contexts) and special populations (those who need to be studied separately because of biological factors; e.g. children, pregnant women, the elderly)

Chapter 1: Background & problem statement (Subgroup 1, lead: Aita)

This chapter starts with a description of the global health divide as illustrated by figures from the Global Burden of Disease study. It then defines the term "resource-limited settings" (RLS), describes why clinical research is needed in these settings and how the global landscape has evolved, and ends with the problem statement.

The meeting participants discussed a comment from Janis to the effect that overly stringent standards can prevent research in RLS, resulting in missed opportunities. Participants agreed that in RLS international (ICH) standards cannot always be implemented literally, and that a central theme in this report is how to adapt procedures without compromising on the validity of the research. It was agreed that CIOMS should not recommend anything that may be perceived as double standards. All research, whether in RLS or elsewhere, should meet internationally accepted standards. The drafting team will consider any concrete proposals from Janis for revisions in this chapter.

Agreed revisions:

- Mention the high proportion of neonates and children in RLS, and high under-five mortality
- Highlight the need for research to be conducted in RLS on "global diseases" (see also Point a) under *Summary and recommendations* above)
- Limit the examples of new players in the evolving scientific landscape to those that have made a significant difference

Chapter 2: COVID-19 (Lead author: Nick)

This chapter describes the unfolding of the COVID-19 pandemic and the main challenges, including fragmented research, overwhelmed health care systems, a politicized research agenda (example: hydroxychloroquine), suboptimal testing, and the risk of inequitable access to interventions once they become available.

The participants discussed the chapter title and the significance and position of the chapter within the report. This chapter has the potential to increase the impact of the report, as COVID and related research are on everyone's mind. While the challenges described are not necessarily specific to RLS, many of them are amplified in these settings. The lack of COVID-related trials in RLS illustrates the need to build research capacity in these settings. There is also a lack of safety data. Ames suggested to mention some of the ethical issues arising in COVID research in RLS, such as rushed ethics applications and reviews, and problems with study recruitment and informed consent.

It was suggested to position this chapter towards the end of the report, giving more weight to the recommendations. Roli suggested (via Zoom chat) that it could be merged with the appendix on Outbreaks. These issues will be taken forward by the editorial team.

Agreed revisions:

- Improve the chapter title
- Mention specific ethical issues arising in COVID-related research in RLS.
- Highlight the lessons learned in RLS and possible solutions to improve preparedness: build research capacity, adapt legal structures
- Add information on R & D of vaccines (>100 products of variable quality are currently in development)
- Recommend proper regulatory evaluation of products, and their deployment in line with scientifically sound strategies.

Chapter 3: Value of research in RLS (Subgroup 1, lead: Aita)

This chapter describes the direct benefits of research in RLS (access to health interventions) as well as the indirect benefits (capacity-building), discusses the sharing of benefits and burdens of research between high- and low-resource settings, and states the need for a scientifically sound rationale for clinical studies.

Regarding sharing of burdens and benefits, Pol and Aude remarked that disadvantaged groups tend to be overrepresented in Phase I studies, while the reverse is the case in Phase III studies which offer more promise of benefits.

Chapter 4: Principles of CRRLS (Subgroup 2, lead: Pol)

This chapter describes the evolution of international standards and regulatory guidance for clinical research, speaks about study design, registries and databases, data collection and safety reporting, and ends with a detailed discussion of responsible data-sharing.

Agreed revisions:

- Clearly state that this report is intended to support the implementation of the 2016 CIOMS ethical guidelines. It is not intended to supersede any of the principles set out in those guidelines.
- Highlight the importance of sufficient sample size to detect even moderate but clinically important benefits. Collaborative research and harmonized endpoints will enable pooled analyses of study results.
- Expand on the reasons for sharing data, beyond strictly scientific reasons.

Chapter 5: Ethical principles (Subgroup 2, lead : Ames)

This chapter focuses on the ethical aspects of clinical research in RLS. It includes additional sections on vulnerable populations (moved to this chapter from Appendix 1).

Agreed revisions:

- Add systemic injustices as a reason for vulnerability of populations
- Qualify the statement on persisting colonial patterns to say that these are not generalized
- Mention migrant workers and refugees as vulnerable groups
- Explain when research in vulnerable groups is justified, and when it is not
- Clarify the distinction between “vulnerable populations” (discussed in Section 5.2) and “special” populations” (discussed in Appendix 1)

Bert expressed his appreciation of progress with this chapter.

Chapter 6: Obstacles & enablers of clinical research in RLS (Subgroup 3, lead: Nick)

Most comments have been addressed since the 7th WG meeting. A reference has been added on monitoring costs; some language could be added to point to these costs as a major obstacle.

The group discussed a comment inserted by Janis saying that this chapter comes across as more succinct than the rest of the report and should be made more prominent. Jerry felt that more

examples may be useful to illustrate the concepts for the uninitiated reader. The place of this chapter in the overall structure may also change. These issues will be addressed during the editorial process; more concrete suggestions will be sought from Janis.

References

The main text currently has about 150 references. The editorial group will ensure that only necessary and useful references are included.

Appendix 1: Special populations (lead authors : Kalle, Nathalie?)

This appendix focuses on two groups of individuals for whom separate research is needed for biological reasons. In the part on children, most comments from the WG have been addressed. The part on women of childbearing age still remains to be drafted. Monika will liaise with Nathalie on this during the editorial process.

Agreed revisions:

- Distinguish clearly between what is covered in this Appendix and in the section on vulnerable populations in Chapter 5 respectively.
- State, in the appropriate place(s), that neither the CIOMS 2016 guidelines nor this report aim to define an exhaustive list of vulnerable populations.
- Highlight issues affecting children in RLS disproportionately: loss of parents and family, institutionalization, lack of access to education, poverty
- Consider "Gender integration" as a title for the part on women of childbearing age

Appendix 2: Digital technologies/Electronic health records (lead authors: Luc/Lembit)

This appendix starts with a general introduction, reviews available digital technologies, and goes on to focus on electronic health records and the need to build them in such a way that they can be used for research. The report should make a strong call for this, using the present window of opportunity to prevent the repetition of mistakes made in other countries.

It was agreed that the main text of the report should point to this appendix in one or more prominent places. The appendix should be designed in such a way that it can easily be shared as a stand-alone document e.g. with donors intending to fund the development of electronic systems. Respective editing will be addressed as part of the editorial phase.

Appendix 3: Outbreaks (lead author: Jerry)

This appendix illustrates the issues encountered with clinical research in outbreaks. It does not discuss them in great depth as the relevant principles are described in other parts of the report.

The meeting participants appreciated this chapter and discussed the issue of priority-setting and funding of research in emergencies. The WHO roadmap is mentioned in the appendix, however it was noted that WHO does not have a decision-making mandate in this area.

Agreed revision:

- Flag the need to develop a set of principles for prioritization of research during emergencies.

Appendix 4: Pharmacogenetics (lead author: Adrian)

This appendix reflects the outcomes of the symposium held in conjunction with the 7th WG meeting. It has been shortened substantially as the RIBEF research network has meanwhile published the detailed outcomes of the symposium[1]. The group congratulated the network on this achievement.

[1] Peñas-LLedó E, Terán E, Sosa-Macías M, Galaviz-Hernández C, Gil JP, Nair S, *et al*. Challenges and Opportunities for Clinical Pharmacogenetic Research Studies in Resource-Limited Settings: Conclusions From the Council for

5. Conclusion and next steps

The Chair thanked all participants for their contributions and good discussions. He highlighted the importance of clear language (e.g. on concepts of vulnerability and gender issues) in this report.

Lembit outlined the next steps. The work will be taken forward by the editorial group appointed at the 7th WG meeting[2]. Reaching out to WG members as needed, the editorial group will develop a more mature draft of the report by the end of 2020 or early 2021, to be posted on the CIOMS website during at least four weeks for public comment. CIOMS will approach a number of relevant groups inviting them to provide their comments. Thereafter the editorial group will address the comments received, liaising with the full WG and seeking its endorsement of the final report.

It was agreed that the editorial group would hold its 1st meeting on 21 August 2020 by video call to agree on a working process.

- **Action Point 2:** Circulate draft minutes of the 8th WG Meeting for comment by participants. (Monika – done)
- **Action Point 3:** Integrate lead authors' revisions in the master draft WG report and periodically upload updated working versions of the report to the WG's private webpage (Monika – ongoing)
- **Action Point 4:** Support the editorial group and liaise with the full WG as appropriate (Monika – ongoing)

In closing the 8th WG meeting Lembit thanked the group for their enormous support in these difficult times.

International Organizations of Medical Sciences-Ibero-American Network of Pharmacogenetics and Pharmacogenomics Meeting. Clin Ther. 2020;S0149-2918(20)30318-0. (PubMed)

[2] Ames, Bert, Luc, Nick, Jerry, Pol, Roli, and Marie, in collaboration with Lembit and supported by Monika

6. Annex 1: List of participants

*=Attended partially (joined late and/or left early)

Academia/ research	Ames **Dhai** (Steve Biko Institute/ University of Witwatersrand)
	Kalle **Hoppu** (Pediatric Clinical Pharmacology Section, IUPHAR)
	Samia **Hurst** (University of Geneva)
	*Walter **Jaoko** (DNDI/ University Nairobi)
	Gustavo **Kesselring** (International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine, IFAPP)
	Bert **Leufkens** (Utrecht University) **- WG Chair**
	*Adrian **LLerena** (Universidad of Extremadura)
	Raj **Long** (Bill & Melinda Gates Foundation) – new member
	Roli **Mathur** (Indian Council of Medical Research)
	Aita **Signorell** (Swiss Tropical & Public Health Institute)
	*Honorio **Silva** (IFAPP)
	Nick **White** (Wellcome Trust)
Regulators	Jerry **Pierson** (formerly: NIAID Division of Clinical Research)
	*Christoph **Conrad** (Paul-Ehrlich-Institut, Germany)
Product R & D	Satu **Kujala** (Oy Medfiles)
	Luc **Kuykens** (Sanofi)
	Aude **Le Roux** (Sanofi)
	*Florent **Mbo** (DNDI Regional HAT Platform
	*Nathalie **Strub Wourgaft** (DNDI)
	Pol **Vandenbroucke** (Pfizer)
WHO	*Samvel **Azatyan** (WHO Regulatory systems strengthening)
CIOMS	Lembit **Rägo**
	Monika **Zweygarth**

Apologies:

Academia/research	*Irja **Lutsar** (University of Tartu)*
Regulators	*Alambo **Mssusa** (Tanzania FDA)*
Product R & D	*Ruxandra **Draghia** (Janssen)*
	*Elly **Kourany-Lefoll** (Merck Germany)*
	*Isobel **Lakatos** (Roche/Genentech)*
	*Rosanne **Rotondo** (Novartis)*
WHO	*Marie **Valentin** (WHO Regulatory systems strengthening)*
CIOMS	*Janis **Lazdins-Helds***