Council for International Organizations of Medical Sciences

7th meeting of the CIOMS Working Group (WG) on Clinical Research in Resource-limited Settings (CRRLS)

22 June 2020, virtual meeting

Minutes

Version: 18 August 2020

Overview:

Summary and action points

The CIOMS CRRLS WG held its 7th meeting by video call on 22 June 2020. A proposed meeting agenda and the revised draft WG report were circulated on 17 June. Further revisions to the draft were subsequently received, and an updated draft was circulated on 22 June. (also available on the WG's private web area).

The Working Group discussed progress and next steps. Lead authors will provide a last round of updates and additions before the next WG meeting (to be held on 20-21 August 2020). An editorial team will then take forward the finalization of the report. A more mature draft will be posted for external comment during 2020; the report is expected to be published in the first half of 2021.

The following action points were agreed:

Action points	Responsible person	Timeline
(Pending action points from the 6th WG meeting:) Provide revised sections as agreed	Christoph, Adrian, Nathalie	ASAP
From the 7th WG meeting:		
1. Circulate draft meeting minutes for comment by participants	Monika	*Done*
2. Draft a section on COVID-19 and clinical research in RLS	Nick, Ames; Nathalie (TBC)	Send to Monika by 7 August
3. Provide revised chapters as discussed	Pol, Nick	
4. Update appendices with COVID-19-specific sections and/or cross-references, and other edits as discussed	Roli, Luc, Lembit, Kalle, Jerry, Adrian	
5. Draft language and recommendations regarding vulnerable populations, for inclusion in the main text	Kalle	
6. Circulate revised draft report for discussion at the 8th WG meeting (to be held on 20-21 August 2020 on a virtual platform)	Monika	By 14 August

Minutes of discussion

1. Opening and welcome

Lembit Rägo welcomed the group to its 7th Meeting (for a list of participants see **Annex 1)**. Bert Leufkens then took the chair.

2. Introduction by WG Chair

General remarks on the draft WG report

The WG Chair invited several speakers to express their views on the current draft. The following main points were made:

- The WG report should strike a better balance between general principles (some have been described elsewhere as well) and practical aspects of research in resource-limited settings (RLS).
- The chapter length is not balanced: Chapter 2 (Principles of clinical research), while important, is disproportionately long.
- The appendices still need to be made more uniform, and some of them may be grouped and/or moved to the main text.

Several participants suggested that the next step should be for WG members to read the report in full before attempting to address these issues.

Previous meeting minutes

The minutes of the 6th WG meeting (held on 22 April 2020 by video call) had been circulated to the WG on 28 April for comment by 4 May. No comments have been received, nor were any comments raised at the 7th meeting. The minutes of the 6th WG meeting as posted on the CIOMS website are thus considered accepted. The chair highlighted the fact that the action points in WG minutes reflect the commitments

ACTION POINT 1. CIOMS will circulate draft minutes of the 7th WG Meeting for comment by participants.

3. COVID-19 and clinical research in RLS

Nick briefly summarized the challenges described in a recent Lancet paper[1]: research has been rushed and poorly coordinated; the bureaucratic obstacles are as daunting as ever, and regulatory and ethics review processes are slow. On the other hand there is a genuine commitment for working together, and tools and information are being shared.

The COVID-19 pandemic has amplified the challenges of conducting clinical research in resource-limited settings. The participants raised the following specific points:

- Challenges and lessons learned on data-sharing
- Good and bad examples of COVID-19 research
- Hardships faced by migrant workers, and consequences for transmission
- Unavailability of testing

[1] COVID-19 Clinical Research Coalition. Electronic address: nick.white@covid19crc.org. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. Lancet. 2020;395(10233):1322-1325. doi:10.1016/S0140-6736(20)30798-4. (Journal full text, PMC full text)

- Value of research not understood by governments, *e.g.* in Latin America
- Absence of nationally enforceable ethical guidance, *e.g.* on standards of care including availability of personal protective equipment, or on informed consent.
  Post-meeting note: Ames Dhai shared a paper from South Africa.

The participants agreed that COVID-19 must be reflected at least in an Appendix or separate section, and possibly throughout the report. A section will be drafted, and will be positioned in the report as appropriate during the editorial process.

ACTION POINT 2. Nick, with support from Ames (and Nathalie?), will draft a section on COVID-19 and clinical research in RLS.

4. Lead authors' feedback on past and anticipated future progress

Chapter 1, Introduction and problem statement (Aita)

Comments on the structure of Chapter 1 and any missing elements had been invited at the 6th WG meeting. No comments have been received.

Bert suggested to spell out the reasons why there is a need for research in RLS.

The WG agreed to leave this Chapter unchanged for the time being, and to come back to it when the rest of the report is more mature.

Chapter 2, Principles of clinical research (Pol)

The subgroup has met by teleconference several times since the 6th WG meeting and has addressed previous. References to, and/or brief summaries of, relevant principles from the CIOMS 2016 ethical guidelines have been included, and some examples on LMIC-specific issues added. Some sections from Appendix 1 have been transferred to this chapter by Roli and fit well into the flow of the chapter.

The subgroup will read the full text and seek to make Chapter 2 more concise, highlighting the importance of following research principles, along with some lessons learned in the COVID-19 pandemic. Ames suggested considering an Appendix on "planning for future pandemics".

Other possible additions:

- Case study on how rapid review has been addressed informally by South African research ethics committees (Ames, for inclusion in an Appendix)
- Examples of good and bad trial designs in COVID-19

Chapter 3, Obstacles and enablers (Nick)

The chapter is largely unchanged since the 6th WG meeting. Useful language on informed consent and indemnities has been added by Roli from Appendix 1. More examples of good practices (e.g. on laboratory infrastructure, monitoring) are yet to be included. The section on funding will be updated in light of experiences with COVID-19, where funding has not always been equitable to benefit the local populations.

The subgroup will add COVID-19-specific points and aim for good balance and minimal redundancies with other sections.

ACTION POINT 3. Pol and Nick will provide revised draft Chapters 2 and 3 for review at the August meeting.

Synthesis and recommendations (Bert, Lembit)

This is a pivotal section as it summarizes the messages and recommendations of the report. Bert invited feedback from the Working Group. None was provided at the meeting. The section will be further developed when the overall report is more mature.

Appendices

The lead authors of the appendices reported back on progress. Apart from the restructuring related to Appendix 1 (see below), the appendices are unchanged since the 6th WG meeting. This is mainly because it has not yet been determined how some of the material will be redistributed across the main text and the appendices. This re-structuring will need to be guided by an editorial team (see Point 5 below).

In the discussions following each report-back, summarized below, some COVID-19-specific issues were suggested for inclusion in the appendices. Overlap with the separate section to be drafted on COVID-19 (see Point 3 above) should be minimized. Some redundancies may be inevitable at this stage and can be addressed in the editorial process.

- **Appendix 1: Vulnerable populations (Roli):** As agreed at the 6th WG meeting parts of this appendix have been moved to the main text. Roli suggested to add challenges faced during the COVID-19 pandemic by specific vulnerable groups: migrant workers who lose their livelihoods and travel back to their homelands, people submitted to stigma and discrimination (e.g. students being asked to vacate their hostels), and people with disabilities, whose special needs are not met. The role of the media and handling misinformation is also a major issue, but is beyond the scope of the WG report. Roli asked for guidance on what to add, and how to further reduce the size of this Appendix.

  Luc noted that there should not be a general appendix on vulnerable groups alongside separate appendices on women of childbearing age and paediatrics. Possible solutions include renaming Appendix 1 along the lines of "Taking good care of study subjects", or moving it to the main text.

- **Appendix 2: Digital technologies in clinical research in RLS (Luc):** Comments received previously for this appendix have been addressed. It has not been merged with Appendix 3 because there was also a suggestion to move the latter the main text as a stand-alone section. Bert suggested adding a COVID-19-related example. *(See also next paragraph)*

- **Appendix 3: Electronic health records (Lembit):** This appendix may be moved to the main text, but could still be grouped with Appendix 2, which would then introduce the section and can speak to the mixed experiences with use of digital platforms in COVID-19. This would be followed by the more specific topic of electronic health records, with a call for ensuring that the systems emerging in RLS are designed in such a way to yield useful data for research.

- **Appendix 4: Paediatrics (Kalle):** Some comments from the WG have been received but not yet been addressed. Janis suggested to highlight successful examples of clinical trials conducted in children, e.g. with antimalarials or antimicrobials; Kalle will cover these aspects.

  Kalle supported the idea of moving the general sections on vulnerable populations to the main text, and including specific recommendations on (1) the need to include vulnerable groups in research so that they gain access to evidence-based treatments, and (2) the importance of catering for their needs as they can impact outcomes for the population at large (e.g. transmission rates of influenza, Ebola and COVID-19).

- **Appendix 5: Outbreaks (Jerry):** Useful references have been received from Nick; Bert will provide a reference on SARS. This appendix is intended to focus on outbreaks emanating from RLS. Jerry will add a brief reference to the separate section to be drafted on COVID-19.

- **Appendix 6: Women of childbearing age (Nathalie):** This appendix is still to be drafted. Monika will follow up with Nathalie.

- **Appendix 7: Pharmacogenetics and personalized medicine (Adrian):** The draft remains to be shortened to about 2-3 pages.

ACTION POINT 4. The lead authors will update their appendices with COVID-19-specific sections and/or cross-references, and other edits as described above.

ACTION POINT 5. Kalle will draft language and recommendations regarding vulnerable populations, for inclusion in the main text.

5. Way of working / editorial team

CIOMS reports are usually finalized by an editorial team composed of 5-6 WG members. Lembit outlined the possible timelines for the CRRLS WG report. An editorial team would take over after the August meeting. A near-final draft would be brought back to the full WG at a possible final meeting at the end of 2020. The report would then be published in the first half of 2021.

The following WG members agreed to serve on the editorial team: Bert, Nick, Ames, Roli, Pol, Luc, Jerry and Marie. The team will be supported by Monika.

Lembit informed participants about the newly published CIOMS WG report on Drug-induced liver injury[2]. The free PDF has some elements to improve readability that could also be useful for the CRRLS WG report, i.e.: hyperlinks to further information, certain appendices offered in electronic format only, breakdown into topical chapters instead of the three original subgroup chapters, and consistent, meaningful formatting (e.g. boxes for examples and case studies, as also suggested by Roli during the discussion).

Once published, the CRRLS WG report will be made available as a free PDF as well as in hard copy, with a print run of 500 copies or less.

6. Any other business

Janis asked whether, given the ambitious target timelines for publication of the report, external comments on the draft WG report will still be sought, as discussed at previous WG meetings. Lembit considered that a consultation will be possible within the envisaged timelines. A more mature draft for comment by external reviewers may be available in August, or else later in 2020. That mature draft would then be posted on the CIOMS website for comments within one month, and CIOMS would reach out to specific networks to ensure sufficiently wide input.[3]

7. Next steps / next meeting

The dates for the final full WG meeting (20-21 August 2020) will be maintained. Participants based outside Europe do not expect to be able to travel to Geneva due to COVID-19, and the situation in Europe remains volatile. The meeting is therefore likely to be held on a virtual platform for most or all non-Geneva-based participants.

ACTION POINT 6. CIOMS will circulate a revised draft WG report for discussion at the August meeting.

[2] cioms.ch/publications/product/drug-induced-liver-injury

[3] *Post-meeting note: Ames sent CIOMS the contact details of Barbara Sina, who runs an International Research Ethics list serve, and recommended to also disseminate to RECs in LMICs.*

8. Annex 1: List of participants

Academia/ research	Ames **Dhai** (Steve Biko Institute/ University of Witwatersrand) Kalle **Hoppu** (Pediatric Clinical Pharmacology Section, IUPHAR) Walter **Jaoko** (DNDI/ University Nairobi) Gustavo **Kesselring** (International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine, IFAPP) Bert **Leufkens** (Utrecht University) **- WG Chair** Irja **Lutsar** (University of Tartu) Roli **Mathur** (Indian Council of Medical Research) Aita **Signorell** (Swiss Tropical & Public Health Institute) Nick **White** (Wellcome Trust)
Regulators	Jerry **Pierson** (formerly: NIAID Division of Clinical Research)
Product R & D	Satu **Kujala** (Oy Medfiles) Luc **Kuykens** (Sanofi) Aude **Le Roux** (Sanofi) Florent **Mbo** (DNDI Regional HAT Platform) *–intermittently, connection difficulties* Pol **Vandenbroucke** (Pfizer)
WHO Regulatory systems strengthening	Samvel **Azatyan** Marie **Valentin**
CIOMS	Lembit **Rägo** Janis **Lazdins-Helds** Monika **Zweygarth**

Apologies:

Academia	*Samia **Hurst** (University Geneva)* *Adrian **LLerena** (Universidad of Extremadura) – connection difficulties* *Honorio **Silva** (IFAPP – alternate for Gustavo Kesselring)*
Regulators	*Christoph **Conrad** (Paul-Ehrlich-Institut, Germany)* *Alambo **Mssusa** (Tanzania FDA)*
Product R & D	*Ruxandra **Draghia** (Janssen)* *Elly **Kourany-Lefoll** (Merck Germany)* *Isobel **Lakatos** (Roche/Genentech)* *Rosanne **Rotondo** (Novartis) – until 16:30* *Nathalie **Strub Wourgaft** (DNDI)*