Council for International Organizations of Medical Sciences

6th meeting of the CIOMS Working Group (WG) on Clinical Research in Resource-limited Settings (CRRLS)

22 April 2020, virtual meeting

Minutes

Draft: 5 May 2020

Summary and action items

The CIOMS CRRLS WG met by Zoom video call on 22 April 2020, as its face-to-face meeting planned for 22-23 April had to be postponed due to the COVID-19 pandemic. A proposed agenda for the video call was circulated on 15 April.

Participants agreed to the call being recorded to support CIOMS in preparing the minutes. No link to the recording will be shared, as this was not the agreed purpose of the recording.

The draft CRRLS WG report of 22 April 2020 was shared on screen. The lead authors reported back on progress, this was followed by WG discussion.

▶ ***The following action items were agreed:***

	What		Who	Proposed timelines*
1.	Circulate draft minutes of the call		**CIOMS**	*Done*
2.	Circulate a Doodle for next video call (end of June)		**CIOMS**	*Done*
3.	Circulate draft CIOMS cumulative glossary to WG		**CIOMS**	*Done*
4.	Lead authors to revise drafts as discussed, and see general points below**			
	Chapter 2	Revise as discussed	**Lead authors**	By 15 May latest (send to CIOMS, for ongoing posting on the WG area)
	Chapter 3	Revise as discussed		
	Appendix 1	Shorten and identify parts for main text		
	Appendix 2	Revise as discussed		
	Appendix 4	Address comments received, link to main text		
	Appendix 5	Revise in line with WG comments received		
	Appendix 6	Provide draft		
	Appendix 7	Shorten		
5.	Circulate revised combined draft to WG		**CIOMS**	19 May
6.	Send comments on all sections to lead authors***		**WG members**	29 May
7.	Address comments and send revised draft to Monika		**Lead authors**	12 Jun
8.	Circulate revised draft for discussion end-of-June TC		**CIOMS**	14 Jun

*Timelines proposed by CIOMS, based on approximate timelines mentioned during the meeting.

****General principles for revision:**

- Reconcile any specific recommendations in the sections with the overarching Recommendations avoid redundancies and contradictions
- Consider whether and how to explain technical terms (Glossary? Footnotes?)
- Appendices should be no more than 2-3 pages, and complementary to the main text. For now, lead authors should shorten the draft appendices if needed and identify the parts to be moved to the main text. The actual re-structuring and any grouping of appendices will be taken forward in a subsequent revision by the chapter leads and an editorial team (yet to be formed).
- *Post-TC note from CIOMS: Please keep the only those comments and tracked changes in the text that are under discussion (i.e.accept agreed tracked edits and delete previous comments).*

*****For constructive comments** (suggestions from Pol and Ames): Please (1) read the entire section before commenting, and (2) provide concrete comments, where possible propose actual wording.

Minutes of discussions

1. Opening

Lembit Rägo welcomed the group and introduced two new WG participants: Marie Valentin (WHO) and Isobel Lakatos (Genentech, replacing Puneet Arora). Bert Leufkens then took the chair.

Previous meeting minutes, agenda

The **minutes** of the 5th WG meeting, held in Merida, Spain, on 8-9 October 2019, were circulated on 21 October to the WG, for comment by 1 November. Comments were addressed and the amended 5th WG meeting minutes posted on the CIOMS website. No further comments or objections were raised at the TC. The minutes are thus considered accepted.

The **agenda** for the call was adopted with modified timing to enable PoI to lead the discussion on Chapter 2 from 16:30 h.

Initial general remarks on the draft report

- The overall title will be adapted when it is clearer whether the document focuses more on policy guidance or on practical advice for implementation.
- Overlap with 2016 CIOMS ethical guidelines should be avoided throughout; instead these guidelines should be referenced, and a minimum of relevant included as needed.

2. Synthesis and recommendations

These two sections have been drafted as agreed at the 5th WG meeting. They may be placed upfront as an Executive Summary, with the Recommendations repeated at the end of the main text. In addition, more technical, concrete recommendations may be included in the chapters and appendices.

Note: In the draft of 22 April these sections are duplicated, with different versions shown at the beginning and at the end of the main text. The text at the beginning is the updated one.

Suggestions from WG

- Add "funders" to the second target group for the recommendations, "Research community and sponsors". (And a WG member commented via Zoom chat: *I think that most African governments are not interested in funding research. Most research is funded by external organisations)*
- Add recommendations about benefits for patients in terms of access to innovative health products (including compassionate use)
- Emphasize the need to include all age groups in clinical trials, including children (*Kalle to provide wording*)

▶ ***WG:*** *send comments to CIOMS*

▶ ***Lead authors of chapters/appendices:*** *Ensure that any recommendations included in their sections are consistent with, and complementary to, the overarching Recommendations*

3. Chapters 1-3

Chapter 1, Introduction and problem statement

Report-back (Aita)

The revisions to this section entailed some restructuring with a clear problem statement at the end, balanced focus across clinical trial types, and a description of "resource-limited settings". Aita asked for WG comments on the structure of Chapter 1 and any missing elements.

Discussion

In addition to cholera, Ebola and Zika, Chapter 1 should include some initial experiences with COVID-19 research (ref: Lancet paper on global COVID-19 research coalition). Participants made various points related to COVID-19.

- The public health effects and logistic challenges of COVID-19 are disproportionately large in RLS.
- Treatments being studied are mainly repurposed drugs, not new ones.
- There is a need for clinical trials on Covid-19 mortality and underlying diseases (including communicable ones) in RLS, e.g. sub-Saharan Africa
- Uniform, stringent research standards should be upheld even in emergencies
- Governments should set up health systems structures and governance frameworks that can ensure preparedness and timely response.
- Need for a preparedness "toolbox", with standardized study protocols, enabling comparison and pooling of results across trials
- Need to avoid redundant studies in all settings (not only RLS)
- "Territorial" research ethics committees all want to have their say, delaying reviews
- Urgency of research to prevent use of non-validated treatments
- Challenge of coordinating all players globally.

It is too early to comment on COVID-19, but the report will include some basic principles to do with emergencies in general (e.g. prompt ethical review, making needed material available etc.)

▶ ***WG members will send feedback on Chapter 1 to Aita over the next few weeks.***

Chapter 2, Principles of clinical research

Report-back (Pol)

Previous comments on this chapter have been addressed, except for Section 2.3 where some language from CIOMS 2016 ethical guidelines will be included.

WG suggestions

- Make it clearer for the uninitiated reader what prompted the creation of guidelines and subsequent changes to them.
- How are these principles seen and applied in RLS?
- The document should emphasize the importance of keeping up uniform stringent standards, and find ways to do good quality research even when literal application to ICH guidelines is not possible.
- Clinical studies should address local public health needs, but are at the same time subject to criticism because they are perceived to be conducted according to lower standards.

It was confirmed that this section should provide the link between the *Background/problem statement* and the practical *Obstacles/enablers,* setting out the history and evolution of principles on how to do good research. Addressing the needs of vulnerable populations is mentioned at the end of Section 2.1.2. in response to a comment from Nick.

The lead author of Section 2.8 invited the WG to comment on that section, which deals with conducting research in RLS according to stringent standards that enable an appropriate benefit-risk assessment for the specific local situation. The section heading may be reworded to apply beyond "exceptional situations".

▶ ***PoI will provide a revised chapter for further comment by the WG.***

Chapter 3, Obstacles and enablers

Report-back (Nick, Jerry)

The chapter has been revised as agreed at the 5th WG meeting. Still to be added are cross-references to other chapters, and some initial examples related to COVID-19. The report could give practical examples of needed supplies, e.g. protective equipment, emphasizing the need for a basic standard of care as the first pre-requisite for conducting a clinical trial. Some more focus may need to be placed on the enablers – although the obstacles can be "daunting".

WG suggestions

- There are examples of low-resource countries that manage to maintain good study sites for research, these are enablers.
- Stress the responsibility of governments to create an enabling environment.
- Mention the role of international organizations (e.g. BMGF), e.g. where there is no government

▶ ***Nick will provide a revised version within the next week, to be circulated to the WG for further (final?) comments.***

4. Appendices

Appendix 1: Vulnerable populations (Lead author: Roli)

Valuable additions have been received from Ames and Nick. This is a very comprehensive appendix which needs to be shortened and integrated with the main text.

▶ ***Roli will provide a shortened Appendix 1 in the next few weeks, highlighting the parts that should be moved to the main text, for further comment by the WG.***

Overall the appendices currently differ in terms of length, style and format. There is a need to make them more uniform: (introduction, "meat of the problem", conclusion). From a general discussion on appendices the following principles emerged:

- The main concepts should be presented in the main text.
- Appendices should be no more than 2-3 pages in length. They are secondary to the main text, complementing it with more in-depth information and/or illustrative examples.
- Certain appendices deal with similar subjects and may be grouped (e.g. Appendices 1, 4 and 6; Appendices 2 and 3).

▶ ***At this stage the lead authors should shorten appendices if needed and identify parts to be moved to the main text. In a next step, editing and restructuring will be taken forward by Chapter leads and a smaller editorial team (yet to be formed).***

Appendix 2: Digital technologies in clinical research in RLS (Lead author: Luc)

Comments received for this appendix have been addressed. It now needs to be linked to the main text, for example as an "Enabler" in Chapter 3. This appendix could be grouped with

Appendix 3 on electronic health records (at a later stage, see general discussion under Appendix 1 above)

WG suggestions:

- Include COVID-19 experience that digital platforms are not only enablers but that they can create obstacles (fragmentation, some "messy stuff" out there)

▶ ***Luc will provide a revised Appendix 2 for further comment by the WG.***

Appendix 3: Electronic health records (lead author: Lembit)

This appendix has been circulated for comments to the WG and to additional experts[1] who participated in the open session on Electronic health records (EHR) held on 8 October 2018 at the beginning of the 4th WG meeting in Tallinn. An important objective of the appendix is to encourage countries that are now setting up EHR systems to design these in such a way that they can be used as a source of data for research.

WG suggestions

- Move this Appendix to the main text as a separate, stand-alone chapter as it deals with a core topic.
- Explain that "databases" exist in all countries, regardless of whether or not they are using certain specific technologies
- Seek input from WHO or other capacity-building initiatives for implementation of e-health structures.
  It was noted that the WHO pharmacovigilance programme has received increased requests for assistance with digital systems due to COVID-19, the team may be able to provide input.

Appendix 4: Paediatrics (Lead author: Kalle)

Chapters 2 and 3 are now advanced enough for this appendix to be linked with them. Further comments from the WG are also welcome.

▶ ***Kalle will revise the appendix to reconcile it with the main text avoiding duplication, and to address comments received from the WG.***

Appendix 5: Outbreaks (lead author: Jerry)

This currently focuses on Ebola; concise information on lessons learned from other outbreaks (cholera, Zika, COVID-19) will be added. Further comments and pointers to references and/or examples are invited from the WG.

▶ ***Jerry will revise the appendix in line with comments received.***

Appendix 6: Women of childbearing age (Lead author: Nathalie)

This appendix is still to be drafted and will be based on a paper about to be published in PLoS (accepted version uploaded here), showing that women in RLS are excluded from clinical trials because they do not have access to effective contraception.

WG suggestions:

- Add information on pregnancy registries in the post-market phase

[1] Dipak Kalra European Institute for Innovation through Health Data (i~HD), and representatives of the medicines regulatory authority of Estonia

- Describe the challenges in getting informed consent in cultures where women cannot speak for themselves. Informed consent must then be given by the woman's father, her husband, or the—sometimes unknown— father of her unborn child.

▶ ***Nathalie will draft Appendix 6; seeking input from WG members on the above suggestions as needed.***

Appendix 7: Pharmacogenetics and personalized medicine (Lead author: Adrian)

The current draft describes what was prepared and presented by RIBEF researchers at the open session of the 5th WG meeting in Merida. The draft needs to be shortened to about 2-3 pages, selecting the relevant content.

▶ ***Adrian will revise Appendix 7 in line with the agreed format for the appendices.***

5. Glossary

Lembit asked participants to reflect whether a glossary should be included in the WG report. An alternative would be to explain certain technical terms in footnotes.

A cumulative glossary based on past CIOMS pharmacovigilance reports will be posted on the CIOMS website soon as a living document. If a glossary is to be compiled, the cumulative glossary would be a useful resource.

▶ ***The draft CIOMS cumulative pharmacovigilance glossary will be circulated to Chapter leads, for consideration how to deal with technical terms in the CRRLS draft.***

6. Any other business

It was suggested to:

- Mention diagnostics in the draft (currently it refers only to medicines and vaccines)
- Include some initial appreciation of the new reality that the COVID-19 pandemic will create for clinical research. Adrian gave examples from the WHO Solidarity trials[2]: having to approach very sick patients across protective barriers to get informed consent, and ensuring safe and efficient handling of infective samples.

7. Next steps / next meeting

A 6th and final face-to-face WG meeting will be held for the group to agree on next steps to finalize its report and discuss implementation strategies. The next face-to-face meeting is tentatively planned to be held in the week of 17 August, but may need to be changed to a remote format depending on how the COVID-19 situation will evolve.

The WG agreed to continue meeting regularly by teleconference. The next full WG teleconference will be held at the end of June

▶ ***CIOMS will circulate a Doodle for the June video call.***

[2] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

8. Participants

* = new WG member

WG Chair	Bert **Leufkens** (Utrecht University)
CIOMS	Lembit **Rägo** Janis **Lazdins-Helds** Monika **Zweygarth**
Academia/ research	Ames **Dhai** (Steve Biko Institute/ University of Witwatersrand) Kalle **Hoppu** (Pediatric Clinical Pharmacology Section, IUPHAR) Samia **Hurst** (University Geneva) Walter **Jaoko** (DNDI/ University Nairobi) –*intermittently, bad connection* Gustavo **Kesselring** (IFAPP) Adrian **LLerena** (Universidad of Extremadura) Irja **Lutsar** (University of Tartu) – *from 16:40* Roli **Mathur** (Indian Council of Medical Research) Aita **Signorell** (Swiss Tropical & Public Health Institute) Nick **White** (Wellcome Trust)
Product R & D	Elly **Kourany-Lefoll** (Merck Germany) Satu **Kujala** (Oy Medfiles) Luc **Kuykens** (Sanofi) Aude **Le Roux** (Sanofi) Florent **Mbo** (DNDI Regional HAT Platform) –*intermittently, bad connection* Rosanne **Rotondo** (Novartis) – *until 16:30* Nathalie **Strub Wourgaft** (DNDI) – *from 16:40* Pol **Vandenbroucke** (Pfizer)
Regulators	Christoph **Conrad** (Paul-Ehrlich-Institut, Germany) Jerry **Pierson** (formerly: NIAID Division of Clinical Research)
WHO Regulatory systems strengthening	Samvel **Azatyan** – *until 17:00* *Marie **Valentin**

Apologies: Ruxandra **Draghia** (MSD)
Alambo **Mssusa** (Tanzania FDA)
*Isobel **Lakatos** (Roche/Genentech)
Honorio **Silva** (IFAPP) – unable to connect