Council for International Organizations of Medical Sciences

1st meeting of the CIOMS Working Group on Clinical Research in Resource-limited Settings (CRRLS)

20–21 November 2017, Geneva, Switzerland

Minutes (web)

CIOMS background

(adapted from CIOMS homepage: http://www.cioms.ch)

"The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.

In 2013, the membership of CIOMS included 49 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences and medical research councils. The main objectives of CIOMS are:

- To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;
- To maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO; and
- To serve the scientific interests of the international biomedical community in general.

To achieve its objectives, CIOMS has initiated and coordinates the following main long-term programmes:

- Bioethics
- Health Policy, Ethics and Human Values - An International Dialogue
- Drug Development and Use
- International Nomenclature of Diseases"

CIOMS working groups are typically planned for three years, focusing on a specific topic. Operating model includes two face-to-face meetings per year, and regular subgroup meetings in between. CIOMS secretariat provides logistical support and helps coordinating activities.

Meeting objectives

- Identify key challenges to focus on
- Develop WG business plan
- Set up subgroups to address key topics
- Identify other key initiatives to interact with

Introductory session

Short introductory presentations on CIOMS by CIOMS Secretary-General was followed with "around the table" statements from participants' perspective (academia, product R&D /industry, and regulatory) on their concerns regarding Clinical Research in Resource-limited settings (CRRLS). The following issues were flagged:

- understanding of the role of the principal investigator as a researcher;
- communication on clinical research: address awareness issues
- patient informed consent (length, language);
- clarity on the study benefits for the subjects and community;
- ethical approval (multiple ethical applications, validation of scientific and regulatory context, timing);
- need to address genetic information (and DNA storage) as key factor in patient protection;
  - address custodianship and ownership of samples
- addressing children (and other vulnerable/specific populations (elderly, obese, pregnant, …);
- quality of research (academic , industry), same standards;
- high level of requirements for clinical research making it unaffordable for LIC; need to understand costs;
- issues on capacity building for clinical research;
- missing tools, feasibility to apply new study methodologies and e-health tools (data transfer/integrity) learn from other initiatives to avoid previous pitfalls;
- ethical, social, economic and cultural factors for country specific studies; mention of not overprotecting patients form studies therefore leaving them behind new options; Issue of affordability;
- incidental findings, management of safety (PV) within local context;
- patient reimbursement and their impact on the study outcome;
- variability of "standard care" among different settings; issues with placebo controlled studies in such settings;
- clinical studies under emergency situations;
- LIC medicines regulatory challenges (guidelines, funding, political interference, "learning while doing", building technical capacity);
- civil society engagement/participation;
- need to support post-approval effectiveness studies as well including measuring drug levels.

Brainstorming

Following the "around the table" statements three sub-groups were established (each with representatives from industry, academia, and regulatory agencies) with the task to highlight/develop the key topics to be considered as the scope of the WG on Clinical Research in Resource-Limited Settings. Their contributions are shown below.

Subgroup 1

The group focused on identifying and reducing the obstacles to allow increase of clinical investigations in Low Resource Settings. These obstacles can be categorized as practical or ethical. For the purposes of this working group the subgroup focused on the practical obstacles.

Cost analysis: One method to identify the obstacles is to analyze where the majority of costs of conducting clinical investigations are; this may be indicative of where the obstacles are.

"Minimal requirements" to conduct clinical trials: The group should identify what these are, and in which situations there is a propensity to go above and beyond those minimal requirements. This will help to design clinical investigations that fit the needs of the patient population we are studying. Looking retrospectively at the pooled malaria trial data provide indications as to what data have been collected that are not useful/needed. Having a central database of local clinical trials, including PI's and clinical trial sites, may help to avoid duplication of effort and identify those sites that meet the criteria to conduct quality clinical trials across industry and academia.

Ways of monitoring: The subgroup also discussed the benefits of having the ability to measure drug levels post-trial, keeping patient DNA to retrospectively look at any safety trends or unique occurrences and the potential challenges this may pose. It was noted that historically HIV trials have presented many challenges, and these were all overcome in time; this may be a good case study for us to learn from.

Clinical trials (CTs) and standard of care: The subgroup discussed the importance of understanding the impact of clinical investigations on local standard of care. While the standard of care may be improved and a benefit of conducting local clinical investigations, there is also a potential for a falsely reported positive effect of an investigational drug product on patient health outcomes, when in fact this may be due to the inherent improved standard of care.

Subgroup 2

The overall concept should be to focus on "Minimum Requirements".

Increase awareness of clinical trials (CTs): This topic should be included. Overall concept: Focus on "Minimum Requirements". Need to include or focus on medical practitioners, including pharmacists and others. Not only focus on benefits but also on risks, clinical trials are experiments after all. Difference between clinical research vs. access to care

Delays in emergency situations: This topic should be included. Consult WHO guidelines first and fill gaps. How to do an expedited review; How to do the ethics review.

Environment for CTs in non-emergency situations: This topic should be included. Concept of centers of excellence/clinical research units. Education and training recommendations. Need for certification or not? Discuss systems failures and learn from them/address them. Recommendations for capacity-building and roles of different stakeholders in this regard.

E-health and registries: This topic should be included. Focus on needs for clinical research. Provide standards on what to record. Provide guidance for what countries will need. Discuss links between databases. Formulate requirements for national/regional databases. Discuss need for unified registry of clinical trials.

Requirements for local trials: This topic should be included. Define in which situations they would be required. Build on ICH E5.

Other topics to include in the guidance

- Special populations (children, obese, aged, frail, pregnant women and those taking contraception, immuno-suppressed). Identify gaps
- Ownership/custodianship of tissue samples and data, and use of anonymized data
- Discuss responsibilities of the different stakeholders
- Legal status of children: check CIOMS guidelines and address gaps
- Reimbursement for trials: look at 2016 CIOMS ethical guideline and address any gaps
- Recommendations for long term safety monitoring

Subgroup 3

Topics that the subgroup feels should be included in the CIOMS Working Group roadmap:

Communication about benefits: Explore how to address communication about social and health benefits of product development research and how best to engage local population and other stakeholders (health care professionals, researchers). The population needs to understand the CT goals. An understanding of how they could benefit from the investigations is key, in particular for trials which can only be conducted in specific populations (e.g. malaria in Africa). The subgroup is not expecting uniform recommendations, but rather guidelines to increase acceptance.

Emergencies: Recommendations on how to handle emergency situations beyond the priorities identify by WHO. Learn from the past (Ebola and Zika experience). Include cholera and other recurrent disease outbreaks (plague in Madagascar)

Training (ethical and scientific) is key for health care professionals, the population, and local regulators. This must be supported by reliable technologies for import and export of trial material and data.

Collection of relevant clinical information (e-health record) in a timely, precise and effective manner. This requires key technologies as mentioned above. Lessons learned in other countries should be considered to build on experience and avoid repeating mistakes.

Research in "own communities", striking a balance between scientific research interest and feasibility for genotyping local population. Consider specific findings (comorbidities and other features) that may influence reaction to treatment, as well as cultural influences.

Engagement with local authorities to define good timing for local trials.

Vulnerable populations (children, women in certain circumstances, refugees etc…): Guidelines to allow them to consent. Balance: protection should not prevent people to participate in CT from which they could benefit. Determine how much extrapolation could be used depending on the circumstances.

Access to innovative medicines: Technology /infrastructure issue (availability of technology to accommodate new innovation in healthcare); time for approval after CT

CT trial fit with population needs: Targeted population should benefit from the treatment/health solution tested during the CT. The design of the trial should be adapted to the context without compromising high ethical standards. The medical solution should remain accessible after the CT (price, technology etc).

Plenary discussion

Based on the group brainstorming sessions, in plenary discussions the key points/topics were further identified and expanded, yielding a collection of topics. These topics were then allocated to the groups (see next section).

Key topics to be developed by each subgroup

Further discussions focused on consolidating the topics developed and adjudicating writing responsibilities within three sub-groups. Key topics to be developed are as shown below. Some topics were selected by more than one subgroup (SG)

Subgroup 1

- "Minimum requirements" on the quality of data on clinical studies pre-approval versus post approval e.g. requirements for large pragmatic trials that will influence policy change in the future **(also SG2)**
  - harmonisation issues are similar for pre-registration –example: good laboratory practices (GLP), PK requirements
  - all is about implementation of the Good clinical practices (GCP) requirements, plus an enabling environment
- Creating an enabling environment for clinical trials **(also SG2)**
  - Infrastructure, capacity, certification recommendation on training requirements for all **(also SG3)**
  - Clinical laboratory value reference ranges
  - Mapping
  - Need for basic background education at the University level on clinical research (nurses, doctors …)**(also SG3)**
  - Community advisory board (CAB)
- Communicating the value of research for health to patients, civil society, taking into account social context
- Identify cost components that may result in barriers to the conduct of research: identify common costing rules between sponsors to avoid different costs (will facilitate review … acceptance by funding agencies) … and later add to minimum requirements – including reimbursement
- Communication with HA (health authorities?) during the life cycle of CTs
- How can we measure the impact of clinical research (CR) and feedback to HA
- How research contributes to strengthening health systems (from safety monitoring to pharmacovigilance)

Subgroup 2

- Applicability of general principles about guidance(why … what for … scope) on study consent and participant privacy (+setting of priorities at country level + social context of research)
- Are there different standards for research? "Me-too's" versus true innovations. Standard should be context-specific, but not double standard. Are there different regulatory standards?
- "Minimum requirements" on the quality of data on clinical studies pre-approval versus post approval e.g. requirements for large pragmatic trials that will influence policy change in the future
  - harmonisation issues are similar for pre-registration –example: good laboratory practices (GLP), PK requirements
  - all is about implementation of the Good clinical practices (GCP) requirements, plus an enabling environment
- Unmet needs and priority settings: promote this at the country level
- Responsibility of different stakeholders
  Researchers (other responsibilities, to negotiate about implementation, to take results and channel them for policy change, i.e. advocacy)
  Governments: providing health care vs defaulting to industry
- Creating an enabling environment for clinical trials (**also SG1**)
  - Infrastructure, capacity, certification recommendation on training requirements for all (also **SG3**)
  - Clinical laboratory value reference ranges
  - Mapping
  - Need for basic background education at the University level on clinical research (nurses, doctors …) (also **SG3**)
  - Community advisory board (CAB)
- Harmonize Investigators' sponsored trials: how this represents a particular burden for LMIC
- Addressing fraud in CTs?
- Engagement with local regulatory authorities (when, what is needed «locally») and requirements for «local trials»
- Clinical research vs access to care. What happens after clinical research?
- Understanding social context of research during International studies (legacy of colonisation, gender issues, bribing practices)

Subgroup 3

- Clinical trials in emergency situations (to be addressed linking to other existing initiatives such as the WHO initiative on R&D preparedness for epidemic outbreaks) in specific populations
- Addressing vulnerable population as well as new population (obese, elderly …) but also not forgetting children
- Collection of research information as a whole (sites, data, new methodologies) as a public good in order to:
  - Promote research collaboration within region (engaging countries that currently are not performing any research)
  - Discuss collaboration on «background intelligence» … (phase I baseline data – slow fast metabolisers … ECGs …)

- Use, collection (incl. DNA) and sharing of data. Data protection, limitation of request (examples of exaggeration …). Databases, centralizing registries? …)
  - Ownership: biological specimen and data : move to the notion of custodianship –
  - Promote safer use of drugs worldwide: study better population drug metabolism profile
  - Conduct more bioequivalence/ bioavailability studies (will improve value of generic drugs)
  - Drug levels should be measured (Electronic health records - learning from errors: anonymisation methodology)
- Acknowledge new advances in research: gene therapy, immune therapies ….as complex research. Value of research to access them …
- Promote cooperation and collaboration between ethics committees (within country) and NRAs; development of some supra-national facilitating process for resource-limited settings (**also SG2**)

Key topics (not yet addressed by any subgroup)

Reference to existing CIOMS, WHO and ICH existing guidelines (should we check what has been already well addressed and challenge/not?)

Final discussion

It was agreed that in the interim period before the next meeting of the working group, subgroup coordinators will lead the compilation of the draft for the 3 writing groups. They will interact with the members of their respective groups to commit from each of them the writing of given sections from the adjudicated topics in order to have material (drafts) for the development of the core document. It should focus on robust recommendations. Perspectives more bound to change over time should go in appendices.

Recommendations in the report will not have binding character, but will reflect consensus opinion of the CIOMS group.

Audience of the paper will be across public stakeholders, regulatory bodies, investigators and practitioners.

A project platform, e.g. SharePoint, Dropbox etc. is desirable. The CIOMS Secretariat may be able to help with that.

Date of next meeting

The next face-to-face meeting will be held on 27–28 March 2018 in Geneva.

Participants

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