Council for International Organizations of Medical Sciences

2nd meeting of the CIOMS Working Group on Clinical Research in Resource-limited Settings (CRRLS)

27–28 March 2018, Geneva, Switzerland

Minutes (web)

Meeting objectives 1
Introduction 1
Focus of work 1
Guiding principles 2
Obstacles 2
Enabling environment 4
Discussion on the nature/structure of the report 7
Date of next meeting 8
Participants 8

Meeting objectives

Following the 1st meeting three working groups were established, each of which would address particular aspects of clinical research in resource-limited settings as highlighted in the minutes of the first meeting. The objective of the current meeting was to transition from the brainstorming phase to identify/prioritize key elements that could be the main scope of the final document.

Introduction

The meeting was introduced by Dr. L. Rägo. It was noted that some members that attended the first meeting were not able to participate in this meeting, while new members had joined the group.

Before the participants engaged in the group work Prof. H (Bert) G.M. Leufkens made a presentation on the spatial dynamics of clinical trials in resource-limited settings.

Focus of work

The 3 working sub-groups proceeded to report the main conclusions from the first meeting. The discussion that followed raised the issue if it was appropriate (or not) to focus the future work on the "**minimal requirements**" necessary to conduct clinical research in resource-limited settings. It was concluded that this approach should not be followed, instead, the focus of the work should be on:

A. Mapping the fundamental **guiding principles** underlying clinical research in resource-limited settings
B. Identifying the **obstacles** that impact on attaining an optimal clinical research capability
C. Addressing issues that should be considered as key towards creating an **enabling environment** to conduct clinical research in in resource-limited settings.

With this premise the three working subgroups engaged in individual discussions that were reported on the second day of the meeting. The conclusions are summarized in the table below.

Guiding principles

- The expected risk/benefit analysis of the research should drive the requirements.
- Whilst the ethical principles guiding the conduct of clinical research are universal, health standards are different because of health inequity, and so the guidelines and requirements for the conduct of clinical research may differ depending on circumstances.
- Good quality ethical research needs to be encouraged and facilitated to narrow the health gap.
- All clinical research should be justified and should have local relevance. Whether simple or complex clinical research, this research should be designed, conducted, analyzed and interpreted following the highest standards.
- The degree of detail and precision pursued during clinical research should be commensurate with the scientific objectives pursued.

Obstacles[1]

The three subgroups identified the following obstacles:

Participant-related

Group 1
- Cultural and linguistic barriers; illiteracy
- Travel taking many hours or even days for the patient or family
- Inability of the family to afford travel, drugs, or time away from occupation
- Compensation may be disproportionate to usual income

Group 2
- Low levels of literacy and research culture (lack of community engagement guidelines?)
- Perception of reimbursement -> CIOMS guidelines 13 / applicability to resource-limited setting and see how to change

Standard of care-related

Group 1
- Low standard of care (or different standard of care compared to wealthy settings)
- Insurance companies excluding some countries
- Lack of anthropometric and laboratory normal values
- Many diseases go undiagnosed; no autopsy culture
- Traditional medicine is widely used, may produce toxicity, - probably interacts with other medical practices and is not well studied
- Gender imbalance
- High rates of chronic infections and anaemia

Group 2
- Different standard of care – prevents research to be conducted in some countries / comparator: should we revise the concept of multicentre studies?

Group 3
- Lack of clear rationale for “local” clinical trials
- Preconceptions:
    - That innovation and clinical trials in low resource settings are not compatible
    - Impossibility of conducting clinical research within health system structures.

[1] *The bullet points in this section were categorized under different headings post hoc to improve readability. The categorization does not originate from the discussion and was not part of the agreed working minutes.*

Health care system-related

Group 1
- Low resource hospitals or health facilities without adequate facilities
- Low doctor to patient ratio
- Lack of availability of staff time for Research
- Lack of experienced staff conducting Research
- Poorly resourced infrastructure so that sophisticated biology/ laboratory/ imaging etc. cannot be easily done

Political

Group 1
- «Political landscape»
- Corruption
- Ethical review may be inconsistent and vulnerable to political interference

Regulatory

Group 1
- Lack of clear guidelines/ competencies/ process for the authorization of clinical trials (what body for what type of research) both for approvals by ethics commissions (ECs) and national regulatory authorities (NRAs) as well as drug importation and shipment samples – same for pharmacovigilance (PV)
- PV reporting rules not necessarily adapted to the purpose of signal detection and not often not harmonized during multicenter studies
- For migrants / refugees / displaced persons there may be no responsible bodies competent to approve research protocols
- Drug importation can be very difficult, expensive and slow
- Export of clinical samples to another country may be prohibited or difficult
- Placebo often not available / accepted

Group 2
- Regulatory bodies and ECs are not always present and/or functional . Bureaucracy.
- Several layers of reviews conducted, including local reviews;
- Lack of resources -> protected time for regulators who are not full-time employees
- Data and material transfer is challenging. Needs enabling regulation/consent

Methodology-related

Group 3
- Exclusion criteria: often irrelevant in context (pregnancy testing, age in children)
- Stepwise (phase 1, 2, 3, 4) product research structure not always the most appropriate

Enabling environment[2]

Participant-related

Group 2
- Perception on reimbursement on undue inducement: see CIOMS Ethical Guideline 13
- Very general, can be used in all settings – propose some contributions.
- For now left out to EC. Based on minimum wage but could be based on time inconvenience: develop guidelines on technical aspects to consider (number of procedures, time inconvenience..)
- Informed consent: RECs and NRAs should unpack risks adequately - transparency on decision-making is required
- Discuss more living wage rather than minimum

Group 3
- Introduce social and behavioral research early on (and identify funding)

Standard of care-related

Group 2
- If a study is conducted in a low- or middle-income country (LMIC), there should be an intention to register the product in that country? But not always possible for academia

Group 3
- Innovation: can be an enabling framework: repurposing / better formulations / Promoting e-health technologies for research as enabling research overall

Health care system-related

Group 1
- Increase equitable and fair partnerships … local researchers/ academia/ industry/ PDPs/ government/ donor institutions: ensuring core support for sustained clinical research & training platforms (increase volume -> sustainability) (could be measurable output)
- Supporting initiatives for open access to data repositories (e.g WWARN, http://www.wwarn.org): Supporting researchers to provide their data

Group 3
- More extensive use of real world evidence, i.e. how to conduct research in the field / within the existing health system – would help to build competencies and sustainable capabilities: embedding CR in the health system

Political

Group 1
- Build trust and «educate» governments that have an obligation to create an enabling environment for research that will benefit their population.
- Encourage mutually beneficial international collaboration
- Explain the benefits of research: increases health systems competencies
  > Show value of research as economic value for all (health/business): increase demand

Group 2
- Make sure that policy makers will receive results in a comprehensible way

Regulatory

Group 1
- Promoting collaborative EC/NRA processes for clinical trials- build on AVAREF as well as WHO collaborative/ facilitated procedures

Group 2
- Propose best practices for NRAs / research ethics committees (RECs) / consider pooling resources (between ECs and NRAs) – address multiple reviews … consider regional reviews – request amendment to laws and regulations to allow for collaborative procedures, such as the African Vaccine Regulatory Forum (AVAREF) (check publications and show the added value) BUT THIS REQUIRES FUNDING … Building reliance ….

[2] *The bullet points in this section were categorized under different headings post hoc to improve readability. The categorization does not originate from the discussion and was not part of the agreed working minutes.*

- Share risk-benefit information between regulators
- Provide human resources to regulatory bodies by governments («empty chair syndrome») – build on African Medicines Regulatory Harmonisation (AMRH)?

Methodology-related

Group 1
- Training on methodology : increases cost efficiency
- Provide protocol & CRFs, ICD templates
- Use new digital technologies including research-adapted health records: define minimum essential standards (will facilitate remote monitoring -> cost saving!)

Group 3
- Use digital technologies to facilitate clinical research (fast)
- Ensure the relevance of exclusion criteria
- Encourage research in pregnant and pediatric populations should be developed: is there a need for adult data before starting children studies' – should we use epidemiology and benefit-risk analysis to justify … (CIOMS Ethical guidelines 19 for pregnancy)
- Create ownership (publications for example)

Strategic consideration to create an enabling environment for clinical research in resource-limited settings

In addition to what is outlined above, Group 3 introduced a strategic consideration to create an enabling environment for clinical research in resource-limited settings, focusing on some of the high level obstacles that they had identified previously:

1. **Questioning the clinical research paradigm**: reluctance to change the design and execution of clinical research according to pre-established phases of clinical trials: do we need a phase 1-2-3- and post-license studies in this order? What is the value of real-world evidence (RWE)? If a different approach is taken, this may mitigate the long timelines and costs. A process more focused on- risk-benefit appreciation taking into account:
    a. The needs of the populations to be studied (as appropriate for the indication);
    b. The burden of disease (morbidity and mortality);
    c. Pharmacokinetic (PK) studies in normal adult population in normal settings vs PK in local populations;
    d. Patient inclusion proportionate to the demographic characteristics: age (children/adults), frequency of pregnancy, other vulnerable populations; and
    e. Risk mitigation.
2. **Addressing feasibility for innovation in clinical research in low-resource settings** that currently is not happening because of lack of investment, or lack of appropriate capacity & training:
    a. To introduce innovative process for the conduct of research:
        i. Genetic characterization at population level in order to stratify populations for safety risk assessment, for early and better diagnosis, for early and adequate treatment.
        ii. E-technologies
        iii. Use of mobile devices

b. To introduce innovative products for:
    i. Patient diagnosis, adherence to treatment (e.g. HIV, TB, diabetes, etc.) and follow up.
    ii. Applications with public health impact: emerging epidemics, pandemics (patient, contacts, vaccination/treatment follow up).
    iii. Innovative approaches for treatment of primary disease and post-treatment follow up (e.g. leprosy, anti-microbial resistance).

3. **Integrating clinical research into health systems** to complement clinical dedicated centres:
    a. Fostering a research environment within the health system.
    b. Engage communities by integrating and facilitating social and behavioral research into the various phases of clinical research.
    c. Engaging patients and communities in design of studies – building sustainable capacity for research, knowledge and partnerships.
    d. Revising the role of local researchers and investigators (leadership in the clinical trial design, its execution and resulting publications).

4. **Rationalization of local clinical studies**– moving the needle (to promote transparently needed research)
    a. Purposing local clinical research studies – avoiding unnecessary studies, when to do the right study in the right place(s) for the right purpose.
    b. Using facts and figures – genetic information, epidemiology, burden of disease, impact of intervention on population health.
    c. Challenge the current policy of requesting local studies without scientific merit.
    d. Clinical trial transparency – inform communities, academic centers, researchers - from access to protocols, registries to access to publications.

Funding and collaboration

Group 1 outlined the following enablers for sustainable funding:

- Funding by public/private groups – e.g. from charities instead of pharmaceutical companies:
  - Already exists and is a new opportunity for more research (WT, BMGF for WWARN, EDCTP)
  - Allows to have a holistic funding including more capacity building vs specific study-specific needs funded by industry
  - Allows independence of scientific choices? /
  - Would warrant sustainability more easily than if funded by industry (equipment legal obligations etc)
  - COULD CREATE A GLOBAL FUND FOR RESEARCH :
    - Train young researchers in clinical research and build career structure
    - Develop and maintain lab equipment and logistics and quality assurance support
    - Establish rules to maintain records of quality assurance (HR + labs)
    - Creation of regional networks could reduce the need for unnecessary & systematic local trials (and engage with regulators)
    - Needs continuous core support, i.e. funding from: Governments: Probably Ministers of Education/ Research; and
      Industry (needs incentive)

In the discussion, the following points and initiatives were highlighted:

- Ensuring sustainability of infrastructure is essential: are there any existing initiatives? -> NEPAD could be an example for funding: e.g. setting up cooperation between Gabon & German University & Ouagadougou for the conduct of clinical trials (CTs)
- Difficulty to convince funders to participate to a Global Funding Initiative? BUT
  - Could synergize calls for proposal based on common goals
  - Have a common database
  - See the Coalition for Epidemic Preparedness Innovations (CEPI) as a model: coalition of goals, BMGF + Wellcome Trust + Norway, Japan, Germany, India, the EU, and others. However a model to achieve sustainability is still in development.
- Innovative Medicines Initiative (IMI) call to build infrastructure to support clinical trials, including in low income settings
- European and Developing Countries Clinical Trials Partnership (EDCTP), Horizon 2020 program, etc.
- A WHO plan of action had proposed to establish a global fund to support R&D, but this was opposed by developed countries. The efforts resulted in the Global Health R&D Observatory.
- International Rare Disease Research Consortium (IRDiRC): http://www.irdirc.org/
- Maintaining quality is one of the attractive components for all stakeholders.

Discussion on the nature/structure of the report

A discussion on the scope and target users and structure of the final document followed.

Audience

The final report of the working group may be targeted towards RESEARCHERS or POLICY MAKERS.

If for researchers, administrators of research infrastructures, funders: the report should provide the following:

i) Processes oriented for researcher – the document should be process-wise from conception to delivery of goods. Publications are already available for investigators, including for LMIC.

ii) Strategy-oriented– what are the big issues in research in limited resource settings: scientific, political, ethical, practical. Should have a clear problem statement. Policy makers – for informing them on removing obstacles, including priorities to consider.

If for policy makers the report should emphasize that system is broken; things are not functional; whatever is the system now, it has a potential to grow, to improve. Selling the concept of change involves stating that there is a problem. It should highlight the obstacles and propose solutions how to create an enabling environment.

The discussion concluded that the primary audience would be policy makers. From this discussion also emerged that the document could have a strategic as well as process oriented scope. The strategic component would be captured within the problem statement and the guiding principles and the process scope would be reflected within the identification of the obstacles and the enabling factors.

Key elements

a) Problem statement

i) Explain why research is needed in LMICs and show that it is not occurring (CIOMS Guideline) + concept paper addresses this - explain value of research – extend and amend as appropriate (public health – economy) – fill the gap of health disparities.

ii) No matter which research system exists, it has potential to grow.

iii) Address it scientifically and in a logical manner, so there is a good oversight and topics are placed into a strategic proposal for policy makers. Politicians have to have options, but not too many. We need to highlight the impact of doing nothing, and in the same time propose practical issues.

b) **Guiding principles**: as discussed (see above) Include "boxes", figures, annexes, references.
c) **Benefit-risk analysis** / trade-offs are important to underline. We need to include the reasoning behind this balance, including the difference between doing and not doing research.
d) **Educate governments and gain their trust**. If asking for funding, one needs to make it really important to them.
e) **Emphasize that addressing health disparities involves research**.

Structure

a) Problem Statement – strategic
b) Guiding principles – strategic
c) Obstacles – process
d) Enablers – process
e) Conclusions and recommendations

Regular report is about 60-75 pages, including appendices.

As a work process it was recognized that within the above framework and structure each sub working group should produce a document containing the key elements that they have identified. Thereafter an editorial board (to be constituted) will reconcile the three contributions.

Date of next meeting

The next face-to-face meeting was scheduled for 8-9 October 2018 in Tallinn, Estonia.

Participants

***** = new members

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