3rd meeting of the CIOMS Working Group on Clinical Research in Resource-limited Settings (CRRLS)

8–9 October 2018, Tallinn, Estonia

Minutes (web)

Meeting objectives

- Open pre-meeting (morning of Day 1): To consider lessons learned in Estonia and elsewhere with the use of electronic health records (E-HR) in clinical research
- Working Group meeting: To agree on an outline of the CIOMS guidance on clinical research in resource-limited settings and allocate specific sections to drafting teams.

Pre-meeting on use of electronic health records (E-HR) in research

Introduction

Dr Lembit Rägo, Secretary-General of CIOMS, opened the meeting and provided some background information about CIOMS[1] and its Working Group on Clinical Research in Resource-limited Settings. He emphasized that pragmatic guidance on the use of E-HR in research, based on lessons learned, is needed urgently as many countries are now building electronic health systems for the first time.

[1] Updated information is available at: http://cioms.ch

Dr Kalle Killar, Deputy Secretary General for E-Services Innovation and Development, Ministry of Social Affairs, welcomed the participants and made some opening remarks, highlighting that E-HR is a national priority for development purposes, building infrastructure that allows communication among different databases. A key objective is that of strengthening cooperation/communication among physicians, scientists and patients (data owners) in order to provide better health services.

The meeting participants then briefly introduced themselves. A list of participants is shown in **Annex 1**.

Presentations

Estonia has more than ten years of experience with electronic health records. Six presentations were made, highlighting experiences with electronic health records and their use for clinical research.

Estonian e-health Initiative: Focus on Electronic Health Records

Dr **Priit Tohver**, Adviser to E-Services Innovation and Development , Ministry of Social Affairs, Tallinn, Estonia

Dr Tohver outlined the development of Estonia's electronic health record (E-HR) databases, which started in 1995 with a collection of health billing records. Today the country's E-HR are widely and increasingly used for prescriptions, in clinical practice, and for detecting drug interactions and adverse events. Estonia has secure digital systems for e-health data, linked to individuals through the national ID number. Patients can opt out of granting access to their data for clinical care, but do not often do so. In principle, researchers thus have access to vast amounts of machine-legible and searchable electronic data. However, it is cumbersome to obtain access to the different databases, and most of the data are unstructured (free text), meaning that time-consuming review and interpretation are needed before some of it can be used in research. Dr Tohver concluded that cooperation between all stakeholders is imperative to improve the usability of E-HR for research given its potential for improved drug purchasing, policy making, real world evidence for drug safety, pharmacogenomics, etc.

Estonian Electronic Health Records for Clinical Research: A Viewpoint from Academia.

Professor **Irja Lutsar**, Tartu University, Tartu, Estonia

Professor Lutsar presented experiences with use of electronic health data for research, including specialized registers such as the Estonian HIV database (e-HIV). She highlighted the main challenges of using e-data for research and proposed future approaches to resolve them, including: collection of structured data instead of free text, early discussions with ethics committees and proactive seeking of informed consent for use of data in future research (the current process is cumbersome and less than 10% of patients provide consent), automatic data capture or self-entry by patients where possible, and inclusion of automatic links rather than double entries. In conclusion, Professor Lutsar emphasized that E-HR are more than an IT endeavour, that there is no "one-size-fits all" approach, and that clinical trial experts, regulators and ethicists should be involved upfront in designing E-HR systems. To achieve the full potential it is fundamental to have a political will, cooperation among all parties, and to collect structured data (following international standards) including data from registries.

Using E-HRs for clinical research: Quality matters

Professor **Dipak Kalra**, President, The European Institute for Innovation through Health Data (i~HD), University College of London, UK (via Webex).

Professor Kalra showed that E-HR are increasingly used world-wide for clinical documentation, providing real-world evidence that can support tracking of outcomes and decision-making. He described the

European Innovative Medicines Initiative (IMI), a (2008-2024) > 5 bn EUR partnership project between the European Commission and the European Federation of Pharmaceutical Industries and Associations (efpia), the EHR4CR project (2011-2016) providing a platform for trustworthy re-use of E-HR data to support innovation in clinical research and healthcare operations and secure re-use of health data to optimize clinical trials, the InSite service platform for queries on protocol feasibility, and the European Medical Information Framework (EMIF) project, which aims to develop common technical and governance solutions. The EMIF project highlighted the convergence of opportunities to address clinical research and healthcare. The European Institute for Innovation through Health Data (i~HD), a neutral body, brings stakeholders together to help create solutions focusing on healthcare, clinical trials and Big data. In response to questions Professor Kalra highlighted the need for global approaches, the usefulness of open-source technology, the value of consultation with all stakeholders, and the need for incremental approaches in systems design and introduction.

Experience of Facilitating use of E-HRs for Clinical Research

Mr **Sulev Reisberg**, Tartu University, Tartu, Estonia

Mr Reisberg presented his experiences from software development for national health registries and the Estonian biobank as well as from health data analysis and design of tools for post-marketing studies (single protocol/common tools), pharmacogenomics and personalized medicine. The E-HR in Estonia are collected centrally, using HL7, ISO and ATC standards and terminologies. Much of the data is entered as free text, which is not only difficult to extract and analyse, but may delay the granting of access by researchers as it could contain confidential information. Mr Reisberg highlighted the need for correct standardized E-HR, central common standards, recording facts that include timing of intervention, emphasize differences for different diseases, better agreements and easier procedures for data extraction keeping in mind funding, privacy and commercial issues. He made suggestions for improving data quality and protecting patients' privacy, and recommended that data analytic specialists should be involved from the point of data entry, recognizing that research is part of the system.

Secondary use of E-HR in clinical research: regulatory and academic thinking around the globe

Dr **Alar Irs**, Chief Medical Officer, State Agency of Medicines, CHMP member, Cardiologist at Tartu University Hospital, Tartu, Estonia

Dr Irs looked at the perspectives of regulators and scientists on using E-HR, which were initially created in Estonia for administrative purposes. He mentioned the difficulty of interpreting results, given that data entry is not mandatory and it is unknown what data are missing. Patient consent to data access is currently assumed for clinical care use, but this does not cover for use in research. Dr Irs referred to new FDA guidance on E-HR that aims to increase data quality and interoperability of systems, and noted that future electronic systems must be built with scientific and analytical perspectives in mind. In the discussion, participants took up the topic of patient consent and agreed that simple yet balanced solutions are needed to protect data and privacy without unduly hindering research. It was also noted that in low resource settings, countries that are strengthening their medicines regulatory systems should build E-HRs at the same time.

Using e-Health Databases for Clinical Research: Opportunities and Challenges.

Mr **Priit Raspel**, Centre of Health and Wellbeing Infosystems (TEHIK), Tallinn, Estonia

Mr Raspel described the architecture of the Estonian Health Information System and data issuance for different users. The overall Health and Welfare Information system centre also includes data on social

security and the labour market. He went on to outline infrastructural and procedural improvements envisaged under the project "Health Sense" for faster provision of better health data to stakeholders. The challenges he highlighted were: building an appropriate environment, changing laws, creating regulations for data protection, building a dynamic process for data issuing, and concluding agreements between data owners and Health Information Systems. The main focus should be on data quality and efficacy in data processing to reduce delays.

Lessons learned

The presentations and questions highlighted some recurring themes on the benefits and challenges when using electronic health records for research. Benefits include the large number of cases covered and availability of data, in principle. Challenges include patient consent issues, onerous procedures for researchers to access data, the difficulty to interpret these data as they are not necessarily complete (data entry not being mandatory) and often unstructured, with many free-text fields. As a result, extraction of relevant information tends to be time-consuming and costly. A fundamental lesson learned from the Estonian experience is the need for multidisciplinary cooperation in designing and using E-HR.

Working Group meeting

Reflections on pre-meeting

In opening the WG meeting, Dr Rägo encouraged the WG members to provide their feedback on the pre-meeting. The participants expressed their appreciation of the presentations made, and reflected on some success factors for better data quality, relevance and access in clinical research in a broad sense, including post-marketing surveillance. They noted that, going forward, there is a need for:

- Cooperation at the global level,
- common data models, e.g. OMOP,
- common standards (e.g. ISO, C-DISC),
- structured databases with relevant content,
- intuitive, fast and accurate data capture (e.g. automatic, self-entry by patients),
- inclusion of pharmacogenomics,
- incremental approaches to system development,
- engagement of the public, raising awareness of the social value of research,
- simple, balanced systems for obtaining informed consent, and
- good specifications for, and oversight of, outsourced work.

As many countries are now drafting e-health records for the first time, there is a unique opportunity to communicate the lessons learned by other countries to governments and donors. It was agreed that this should be done in an appendix to the proposed CIOMS guidance. A subgroup was identified to draft this appendix. WHO WG members may be approached to provide input on whether E-HR are being considered within WHO's health system strengthening activities, and whether the profile of clinical records is considered to serve product development.

Dr Bert Leufkens then took the chair.

Approval of 2nd meeting minutes

The minutes of the 2nd Working Group meeting were approved. It was confirmed that the proposed guidance will provide strategic directions for policy-makers, but the recommendations should be useful for any stakeholders wishing to support good quality research in RLS. Clear, simple language and messages, and balanced consideration of the benefits and risks of CRRLS are key, complementing the 2016 CIOMS ethical guidance[2].

Presentations from subgroups

At the 2nd Meeting, it had been agreed that the report should include the following: (a) Problem Statement; (b) Guiding principles; (c) Obstacles and (d) Enablers; followed by (e) Recommendations, and that each sub working group should produce a document containing the key elements identified under (a) to (d) above, to be reconciled by an editorial board (to be constituted).

The final document will highlight key aspects through appendices. The following topics for possible appendices were considered at the 3rd Meeting: Electronic health systems/records; digital health; vulnerable individuals and groups; paediatrics; innovation; outbreaks, and pharmacogenetics (see also **Annex 2**).

Each of the three subgroups presented the texts that they had drafted in the lead-up to the 3rd Meeting. The following points were raised in the discussions of the draft texts, confirming or complementing the topics identified during earlier meetings:

- Governance / leadership: Governments' responsibility to create a conducive environment for research benefitting their citizens; due consideration of local structures (e.g. buy-in by community leaders, chiefs); and potential instability of the political "ecosystem", which can change overnight. Promotion of an inter-sectorial (health, education, economics, trade) approach when designing / implementing clinical research
- Ethical issues: Useful information is found in the CIOMS 2009 and 2016 guidance and will be complemented to cover the gaps. Dr Rägo informed participants that CIOMS is considering to establish a new Working Group on healthy volunteers in clinical trials. CIOMS will circulate the draft concept paper to the members of the CRRLS WG.
- Funding: Need for innovative approaches; e.g. Global Fund for research, social funding
- Capacity-building and knowledge transfer: Need for more inclusion of research-related topics (e.g. GCP, ethics) in medical curricula; trend towards regulatory networking (example: the WHO African Vaccine Regulatory Forum, AVAREF, served as a collaborative platform during the Ebola outbreak).
- Clinical trials: Relevant topics include, among others, innovation e.g. through new mobile technologies; clinical trials versus real-world evidence; the need for transparency/registries, rationalization of studies to avoid duplication, responsible sharing of protocols and data; availability of standards for analysis; and availability of GLP-certified laboratories.
- Universal health coverage: how to integrate research with existing health systems
- Emergencies (definition?): Need for rapid, unbureaucratic pathways and for prioritization of applications to facilitate progress of promising products.

[2] International ethical guidelines for health-related research involving humans. CIOMS: 2016. Freely available at: https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/

- Clinical research as a networking activity
- Consideration of the applicability/relevance of existing guidelines for Clinical research in resource limited settings.

Proposed table of contents and allocation of sections

The WG decided that it will now move to the writing stage of the CIOMS guidance. Designated sub-teams will draft specific sections for comment by the full WG.

The participants agreed on a draft table of contents for the proposed guidance and its appendices (see **Annex 2**) and allocated the writing of sections to WG members based on expertise and willingness to contribute.

Breakout sessions

The newly formed drafting teams discussed the content of their allocated sections in break-out sessions and briefly reported back to the full Working Group on the topics intended to be covered. Some of the topics mentioned are listed below. The lists are not exhaustive; the sub-teams will harvest material from their existing texts and meeting minutes as appropriate.

Group 3 – Rationale and problem statement

- Health care needs
- Need for clinical data in lower- and middle income countries
- Raising awareness about the social value of research
- Social, ethical and regulatory challenges
- Conducive environment for solid research
- Need for appropriate regulatory framework throughout the product lifecycle
- Outbreaks (examples – e.g. Ebola)
- Introduce the concept of vulnerable individuals and groups; children

Group 2 - Principles of clinical research

- Registries of clinical trials, enabling patients to access treatment[3]
- Responsible sharing of clinical data (access to clinical trial data and results)
- Combating "ethics dumping"[4]
- Need for capacity-building among ethics committees and regulators reviewing clinical trials
- Importance of good study design

Group 1 – Obstacles and enablers

- Distinction between short-term and aspirational long-term research
- Lifting excess bureaucracy
- Need to boost funding

[3] E.g. See the World RePORT open-access, interactive mapping database, hosted by the U.S. National Institutes of Health and managed through a steering committee of the agencies providing data: https://worldreport.nih.gov/app/#!/

[4] E.g. See the TRUST Project, which aims to foster adherence to high ethical standards in research globally and to counteract the practice of "Ethics dumping" or the application of double standards in research: http://trust-project.eu/

- Host governments: regulatory and legal framework, transparency, advocacy
- Infrastructural capacity: electricity, labs, standards, human resource
- Guidelines and review committee processes, trials, bureaucracy
- Financial support, interface with collaborators
- Clinical trial design
- Data sharing, material transfer agreements etc.
- Special situations, displaced persons
- Engaging participants
- Sponsors and funders (roles and responsibilities)

Conclusions

Process: The subteams will collaborate on appropriate e-platforms (to be agreed by each subteam) to draft their sections, for presentation to the WG at its 4th meeting. The CIOMS Secretariat will contact the members that did not attend the meeting, to link them up with subteam leads and involve them in the drafting. The Secretariat will also facilitate the collaboration and editing process as needed.

Date of next meeting

The next face-to-face meeting will be held in Geneva in late February or early March 2019 (date to be confirmed).

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Annex 1: List of participants

Working Group members

CIOMS	Janis **Lazdins**	Adviser
	Lembit **Rägo**	Secretary-General
	Monika **Zweygarth**	Technical writer
Regulators	Jerry **Pierson**	National Institutes of Health, U.S.
Academia/ Research	Ames **Dhai**	University of the Witwatersrand, Steve Biko Centre for Bioethics, Faculty of Health Sciences, Johannesburg, South Africa
	Kalle **Hoppu**	Children's Hospital, Helsinki University Hospital, and University of Helsinki, Finland
	Walter **Jaoko**	University of Nairobi, Department of Medical Microbiology, Nairobi, Kenya
	H. (Bert) G.M. **Leufkens**	Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, the Netherlands
	Irja **Lutsar**	University of Tartu, Estonia
	Roli **Mathur**	Indian Council of Medical Research, National Centre for Disease Informatics and Research, Bangalore, India
	Nick **White**	Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand & Wellcome Trust, London, United Kingdom
Product R&D	Puneet **Arora**	Roche
	Ruxandra **Draghia**	MSD, U.S.
	Elly **Kourany-Lefoll**	Merck KGaA, Global Health Institute, Coinsins, Switzerland
	Satu **Kujala**	Medfiles, Finland
	Luc **Kuykens**	Sanofi
	Danute **Ducinskiene** *(pre-meeting only)*	Pfizer *(delegated by Pol Vandenbroucke, WG member)*

Pre-meeting: Speakers and local invited guests

Speakers	Alar **Irs**	Chief Medical Officer, State Agency of Medicines, EMA CHMP member, Cardiologist at Tartu University Hospital, Tartu, Estonia
	Dipak **Kalra** *(via Webex)*	European Institute for Innovation through Health Data (i~HD), United Kingdom
	Kalle **Killar**	Deputy Secretary General for E-Services Innovation and Development, Ministry of Social Affairs, Estonia
	Irja **Lutsar** *(WG member)*	University of Tartu, Estonia
	Priit **Raspel**	Centre of Health and Wellbeing Infosystems (TEHIK), Estonia
	Sulev **Reisberg**	Tartu University, Estonia
	Priit **Tohver**	Adviser to E-Services Innovation and Development, Ministry of Social Affairs, Estonia
Local invited guests		
	Gerli **Aavik**	Social Welfare Department, Ministry of Social Affairs
	Sten Andreas **Ehrlich** *(apologies)*	Deputy Secretary General on Labour and Employment Policy, Ministry of Social Affairs
	Angela **Ivask**	Analysis and Statistics Department, Ministry of Social Affairs
	Arne **Kailas**	Employment Department, Ministry of Social Affairs
	Katrin **Kiisk**	Ravimiamet Estonian Medicines Regulatory Agency
	Raul **Kiivet** *(apologies)*	Department of Health Care Management, Tartu University

Local invited guests (ct'd)	Agris **Koppel**	Head of Department of Health System Development, Ministry of Social Affairs
	Rait **Kuuse**	Deputy Secretary General on Social Policy, Ministry of Social Affairs
	Heli **Laarmann**	Head of Department of Public Health, Ministry of Social Affairs
	Eda **Lopato** *(apologies)*	Head of Department of Medicines, Ministry of Social Affairs
	Kaetlin **Luik**	Roche; Association of Pharmaceutical Manufacturers in Estonia
	Gerda **Mälk**	Department of Health Policy, Ministry of Social Affairs
	Kertti **Merimaa**	Health System Development Department, Ministry of Social Affairs
	Kristel **Niidas**	E-services Development and Innovation Policy, Ministry of Social Affairs
	Elen **Ohov**	European and International Co-ordination Department, Ministry of Social Affairs
	Elina **Osi**	Social Welfare Department, Ministry of Social Affairs
	Aigar **Ottas**	Clinical Research Centre, Tartu University and Tartu University Hospital
	Margit **Plakso** *(entire Day 1)*	Ravimiamet Estonian Medicines Regulatory Agency
	Rene **Randver**	Social Welfare Department, Ministry of Social Affairs
	Mare **Toompuu**	Health System Development Department, Ministry of Social Affairs
	Andrus **Treier**	E-services Development and Innovation Policy, Ministry of Social Affairs
	Maia **Uusküla**	Ravimiamet Estonian Medicines Regulatory Agency

Apologies

CIOMS	Hervé **Le Louet**	CIOMS President
WHO	Samvel **Azatyan**	WHO Regulatory Systems Strengthening (RSS) Team
	Vaseeharan **Sathiyamoorthy**	WHO Research, Ethics and Knowledge Uptake (REK) unit
Regulators	Christoph **Conrad**	Paul-Ehrlich-Institut, Germany
	Alambo **Mssusa**	Tanzania Food and Drugs Authority (TFDA), Dar es Salaam, Tanzania
Academia/ Research	Samia **Hurst**	University of Geneva, Switzerland
	Adrian **LLerena**	Universidad of Extremadura, Extremadura University Hospital and Medical School, Badajoz, Spain
Product R & D	Pierre **Dôme**	Merck KGaA, Global Health Institute
	Aude **Le Roux**	Sanofi – *company represented by Luc Kuykens*
	Florent **Mbo Kuikumbi**	DNDi, Regional HAT Platform, Kinshasa, Democratic Republic of the Congo
	Jutta **Reinhard-Rupp**	Merck Germany – *company represented by Elly Kourany-Lefoll*
	Rosanne **Rotondo**	Novartis
	Nathalie **Strub Wourgaft**	Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland
	Pol **Vandenbroucke**	Pfizer Inc. Chief Medical Office, New York, U.S.
	Estelle **Vester-Blokland**	Roche – *company represented by Puneet Arora*
	Raj **Long***	Bill & Melinda Gates Foundation

*New member

Annex 2: Draft table of content of proposed CIOMS guidance

As agreed at the 3rd Working Group meeting (working version, may evolve as drafting progresses)

Content

1. Abstract

2. Rationale & problem statement
    a. Background
    b. Social value of research in RLS (differentiate, short-long term benefits)
    c. Neglected diseases
    d. Challenges for implementation of current guidelines in RLS
    e. (Un)necessary CTs

3. Principles of clinical research (see intro 2009 guidelines and concept paper)
    a. Justification for deviations from ICH guidelines, including in emergencies

4. Obstacles and Enablers – illustrative cases
    a. Collaborations – interactions .. lack of trust
    b. Role of governments
    c. Unnecessary CTs , duplication
    d. E-health
    e. … Etc. *(look at previous work, group identified obstacles)*

5. Guidance (recommendations)
   Principles + explanatory notes – specify audience?
   Building trust
   Vulnerability (contextual, socio-economic e.g. child-headed households, gender-based …), „from exclusion to inclusion“ – health needs)

6. References

7. Appendices (size: ranging from approx. 1 to 5 pages)
    1) Vulnerable individuals and groups (including socio-economic challenges e.g. refugees, undue inducements, multiple participation by same individual in CTs..)
    2) Innovation in methods e.g. cluster randomized trials)
    3) Informed consent *(if needed, check what is needed in addition to CIOMS ethical guidelines, fit into chapters)*
    4) Digital health, (mobile technologies, telemedicine)
    5) Electronic health systems/records
    6) Paediatrics - *to be combined/linked with Appendix 1, Vulnerable individuals and groups?*
    7) Outbreaks, displaced populations
    8) Women of childbearing age (pregnancy…) - *to be combined/linked with Appendix 1, Vulnerable individuals and groups?*
    9) Genetic variations in populations (Justification of repeating CTs?) …, personalized medicine, … safety, diagnosis)

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