Sex and gender considerations in research: the role of research ethics guidelines and research ethics committees

Meeting Report

02 February 2023
Geneva, Switzerland

On 2 February 2023, a meeting was co-hosted by Council for International Organizations of Medical Sciences (CIOMS) and GENDRO[1]. The meeting invited relevant stakeholders from Geneva and its environs belonging to international research groups, international ethics committees, pharmaceutical industry, not-for-profit and non-governmental organizations, guideline makers and gender experts, (See Annex 1 - List of Participants). The objective of the meeting was to present the results of a recently published scoping review on the considerations of sex and gender dimensions by research ethics committees and to initiate a discussion on the role of research ethics committees (RECs) and research ethics guidelines in addressing the gender bias in research, (See Annex 2 – Agenda).

The meeting was opened by the President of CIOMS, Herve Le Louët, and chaired by Shirin Heidari, President of GENDRO and Lembit Rägo, Secretary-General of CIOMS.

Herve Le Louët acknowledged the continuing lack of attention to sex and gender considerations in health research, and the possible contributions of the different stakeholders of health research in addressing the gaps. He hoped that the meeting participants would be able to agree on the role that Research Ethics Committees (RECs) could play in addressing gender biases in health research and reach consensus on the next steps, which could then be taken forward by CIOMS, GENDRO and other relevant organizations and groups.

Lembit Rägo, in his introductory remarks hoped that the presentation of the scoping review would initiate discussions on the role of RECs in strengthening sex and gender considerations in health research. A key question to the meeting participants was whether a review and revision of current CIOMS research ethics guidelines with a view to better incorporate sex and gender dimensions in health research would be warranted. Shirin Heidari, in her opening

[1] (CIOMS) is an international non-governmental organization (NGO) based in Geneva, whose mission is to advance health through guidance on health research and policy including ethics, medical product development and safety.
GENDRO is an international non-for-profit association, based in Geneva, with the mission to advance equity through the integration of sex and gender dimensions in research across disciplines.

statement pointed to the growing evidence of the importance of sex and gender[2] as determinants of health, which go beyond the biological differences between the sexes. Based on their sex and gender orientation there is evidence that people have different experiences within the health system and differential access to health services. She then introduced her organization - GENDRO – whose mission is to advance equity through the integration of sex and gender dimensions in research across disciplines.

Following a "tour de table", the meeting opened with the following introductory presentation by Dr Heidari.

Dr Heidari's presentation noted that despite consensus on the importance of sex and gender as determinants of health, health researchers have been slow to incorporate these considerations in research protocols and conduct as a matter of routine. For example not only is there a persistent underrepresentation of women in health research, but gender blind research, by not paying attention to gender roles and norms, ignores the differential access and uptake of health services by different groups of people, based on their gender role. She emphasized that it is not only an issue of inclusion of men and women in trials, rather the need for collection and reporting of data disaggregated by sex and a meaningful sex and gender based analysis. She illustrated the implications by providing the examples of drug withdrawals in the US. According to a report by FDA, between 1997 and 2010, out of ten drugs that were withdrawn from the US market, eight were withdrawn due to greater harms observed in women in post-marketing data.

Dr Heidari however noted that researchers alone do not bear the responsibility for ensuring that sex and/or gender considerations are incorporated adequately into health research. Across the path from conceptualization of ideas to publication of results, several gatekeepers are responsible to ensure that research is nurtured, funded, conducted and findings disseminated according to the highest established standards of ethics and rigour. These gatekeepers are research institutions, research funding bodies, research ethics committees, drug regulators, academic journal and other research or clinical governance bodies, and as parts of the health research system, they work together to achieve a common goal (Figure 1). In their gatekeeping function, by deciding what research is funded and obtains ethical approval, and what is published, these actors play a pivotal role in defining quality, rigour and ultimately, what constitutes knowledge.

[2] According to WHO, sex refers to the different biological and physiological characteristics of females, males and intersex persons, such as chromosomes, hormones and reproductive organs while gender refers to the characteristics of women, men, girls and boys that are socially constructed. This includes norms, behaviours and roles associated with being a woman, man, girl or boy, as well as relationships with each other. As a social construct, gender varies from society to society and can change over time.

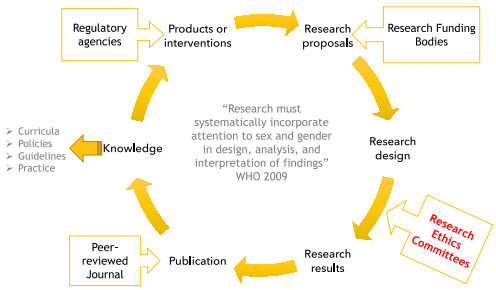

Figure 1: Stakeholders in the development, conduct and publication of research

Figure 2: The Health Research System

In recent years, several efforts have aimed to address the gender gap in research by engaging key gate keepers of the health research system. In 2016, the introduction of the Sex and Gender Equity in Research (SAGER) guidelines by the Gender Policy Committee of the European Association of Science Editors, provided journal editors with an effective tool to improve reporting of sex and gender considerations in research they publish. Research funding agencies, some of whom have endorsed the SAGER guidelines, have introduced similar principles in their funding applications. Noting that another gatekeeper relevant to the health research system are the RECs, Dr Heidari wondered if the development of guidelines similar to SAGER guidelines for RECs could bridge the gaps and harmonize efforts across the research system.

Following these introductory remarks, Abha Saxena, an independent Bioethics Advisor, and co-author of a scoping review published in 2022 by GENDRO's working group on gender and research ethics (established in 2019) presented its outcome.

In her presentation, Dr Saxena reiterated that to understand why women continue to be under-represented in research and why gender-related data is not sufficiently available, it is essential to view health research through a systems lens and to focus on all the players of the health research system (Figure 2). She pointed out that the lack of attention to women and gender issues is not only a scientific concern; it also raises ethical concerns related to justice, autonomy and beneficence. Whether or not RECs pay adequate attention to this ethical concern was the objective of the scoping review published in 2022.[3] The question that the authors attempted to answer was "To what extent do RECs deliberate (in their review and discussions of research protocols) on sex and gender dimensions, for example, through requiring equal participation of men and women in research and considering the gendered aspects of inclusion, risk and vulnerability of research participants". The authors also gathered data from the literature regarding the gender balance of RECs.

[3] Saxena A, Lasher E, Somerville C, Heidari S. Considerations of sex and gender dimensions by research ethics committees: a scoping review. Int Health. 2022 Nov 1;14(6):554-561. doi: 10.1093/inthealth/ihab093.

Using a predefined search string relevant to the questions, 56 articles that met the inclusion and exclusion criteria were analysed in the scoping review. A majority of these articles were published after 2010 and by authors in high income countries. Only 40 articles were based on primary data collection (surveys, focus group discussion, ethnography, observations of REC meetings, and/or analysis of their outputs). Of these, 27 publications described the issues raised by RECs during review of protocols and 16 articles described the composition and expertise of RECs. The remaining articles were commentaries, philosophical analyses, or reviews of published literature.

Presenting the findings of the scoping review, Dr Saxena informed the meeting participants that the scoping review identified a gap in literature related to the information on review practices of Research Ethics Committees (RECs). In addition, the scoping review demonstrated a lack of evidence on the awareness among RECs of the importance of sex and gender related considerations in health research and a paucity of information on gender-related training provided to RECs. Published studies also demonstrated an under-representation of women on RECs.

Dr Saxena further elaborated on the findings of the scoping review:

1. Sex and gender concerns were often not explicitly mentioned by RECs or researchers as being relevant nor were they considered in the evaluation of research protocols by RECs. Survey respondents of several studies often identified representativeness of the research participants as being important, noting cultural, linguistic, socioeconomic and geographic variables as being relevant, but not gender. The REC outputs focused on principles of autonomy, beneficence or ethics as harm and benefits and voiced concerns around fair participation. REC outputs also mentioned inclusion criteria, recruitment criteria, representativeness, legitimacy and appropriate risk benefit analysis. However, fairness in relation to inclusion of women or sex and gender considerations were not *specifically* described in REC outputs nor were terms such as equitable recruitment, equitable distribution of risks and benefits, or justice. Similarly, some articles described vulnerability as a principle that is relevant to RECs, but the discussions did not include gender considerations, and in two papers, vulnerability was reported to be a rationale used by RECs for *not* approving studies on women in particular situations (gender based violence), or excluding pregnant women from research relevant to their health needs. One article reported the lack of regulation or guidelines for RECs on equitable inclusion of men and women in research, or on equitable distribution of risks and benefits across male and female participants.

2. There was generally poor gender balance in the RECs and a lack of gender expertise in the committees. On the composition of RECs, the scoping review demonstrated that most RECs described in literature included more men than women, with men often hierarchically in more senior positions. One paper that reviewed national laws, regulations and guidelines from five European countries found that while most required a representation of women, none required an equal or balanced representation, and gender expertise was not a requirement.

3. The literature on the topic of sex and gender considerations by RECs is limited though lack of studies on this aspect does not necessarily mean that these issues are not considered. Thus, more research is required to understand whether and how RECs consider gender issues in their discussions.

Several papers included in the scoping review also noted that RECs are reticent to share information about how they function, what they discuss and the content of the ethical review. They are also reluctant to be evaluated for performance. These areas may merit further investigation. The scoping review found that the few evaluation frameworks for RECs mentioned in literature were also gender blind.

Three papers in the scoping review highlighted the potential role of RECs in promoting integration of sex and gender considerations in health research, by requiring researchers to describe sex and gender related dimensions in the protocol, including a sample size that allows for sex (and gender, where relevant) disaggregated analysis, and describing a plan for such analysis. The authors of these papers also recommended that RECs should be trained on sex- and gender related ethical concerns. Other ideas described in literature included the development of checklists, decision trees and guidelines on the issue, including more women on RECS as well as including gender expertise on RECs.

In her concluding slide, Dr Saxena summarised that based on the analysis of the scoping review, the authors of the scoping review were of the opinion that because the concept of fair participation hides the reality that within groups of potential participants to whom fairness is owed (e.g. older people, lower socioeconomic groups, ethnic minorities, etc.) women are often more disadvantaged than men, and often under-represented, therefore, sex and gender as variables are particularly important to comment on independently when reviewing research. As such, RECs have a responsibility to be cognizant of intersectional sex and gender dynamics, gender biases in research and the ethical implications thereof. This will enable them to promote inclusion of sex and gender dimensions in health research at an early stage. Development of guidelines, tools and evaluation criteria for inclusion of sex and gender dimensions in research can support RECs in this endeavour. Dr Saxena further noted that the literature on the topic of sex and gender considerations by RECs is limited and lack of studies on this aspect does not necessarily mean that these issues are not considered by RECs. Therefore more research is needed to determine whether (and how) RECs consider sex and gender related issues when reviewing research protocols.

Dr Saxena then put up the following questions on the screen to guide the discussion that followed:

- Of the many aspects of fairness in research participation (age, sex, gender, race, ethnicity, disability, etc.), is it fair to single out sex/gender as a variable over other variables?
- Do ethics guidelines and ethics committees have a role to play in supporting gender sensitive research?
- Should ethics guidelines include an explicit guidance/ recommendation on sex/gender sensitive research that covers not only recruitment criteria, but also gender inclusive sample size and sex/ gender sensitive data analysis?

- Should REC tool kits, checklists, evaluation frameworks be explicitly gender sensitive?
- Should REC training modules be specifically gender focused (favouring gender issues over other issues related to age, ethnicity, disability, etc.)?

General Discussion

The discussion was opened by reiterating the objectives of the meeting on the role of RECs and research ethics guidelines and whether development of specific guidelines, tools and evaluation criteria for inclusion of sex and gender dimensions in research can support RECs to address the concern. It was also reiterated several times that while the focus of the meeting is on the role of RECs, it is critical to recognise and emphasise the responsibility of several other stakeholders, including investigators, sponsors and funders (including public and private funders), regulatory agencies, industry (medical device, pharmaceutical and diagnostics), not-for-profit and non-governmental organizations supporting or conducting health research to address the sex and gender biases in a systematic way.

Several REC member participants acknowledged that RECs may be reviewing sex and gender aspects of research protocols, but often not explicitly. There was further a recognition that the deliberations of RECs are often not transparent, since most RECs do not minute them, so even if sex and gender related issues are discussed they may not be documented. All participants agreed that while more research on REC practices and discussions is needed, development of guidance for RECs on consideration of sex and gender issues during review of research would be relevant. At the same time, it was acknowledged that RECs were just one cog in the health research system.

Another important point raised was the strong linkage between RECs and regulatory health authorities, in particular in relation to research on investigational medicines which need to pass regulatory approval before being approved to be marketed. As such, it was recognised that any efforts encouraging appropriate consideration of sex and gender dimensions in drug trials should align with regulatory requirements.

In response to a question on whether sex and gender should be treated the same or as separate concepts, it was pointed out that sex is about biological differences (often between females and males, and specific consideration in relation to intersex individuals), and could influence drug metabolism, experience of adverse events, immunological responses to vaccine, among others. Gender differences can be due to gender norms and socioeconomic and cultural factors that can influence uptake, access, affordability, provider attitude and a wide range of issues, and can result in differential experience of women, men and people of diverse sexual orientation and gender identity expression (SOGIE). How any given research will address one or the other or both depends very much on the research question. It would also depend on the sex and gender related expertise within the team, or the availability of an expert on gender medicine who could advise researchers and drug developers on this aspect, including during the pre-clinical testing. It was clarified that the emphasis of developing guidance with regard to the ethics review of research using a sex and gender lens should not be prescriptive or instructing how research must be conducted. Rather the guidance should provide a rationale for the importance of these issues, encourage a more thoughtful reflection by RECs on research designs that capture sex and gender dimensions

where relevant, and require them to ask for transparent explanations of why certain populations were excluded. The guidance should also be about creating a dialogue between RECs and researchers on sex and gender related issues. It was also highlighted that not all research needs to be gender specific, but in certain cases, depending on the epidemiology of the disease, and the research question, the special needs of people of diverse sexual orientation and/or gender identities may merit dedicated research/ancillary studies to meaningfully capture their nuances and experiences and RECs need to be aware of the ethical concerns and contextual challenges related to these populations.

Other participants noted that methodologically, ensuring a sample size that is sufficiently powered to identify differences or confirm no differences between the sexes or among people of diverse SOGIE could be challenging, e.g. requiring sample size increase. RECs may be able to play a role by asking relevant questions such as whether sex or gender issues are relevant to the research question/s, or whether risk and benefits will affect men, women or people of diverse SOGIE differentially or whether research has equal social value for the different populations. They could also ask researchers – when relevant - to stratify the randomization by sex.

Participants of the meeting noted that in the case of drug development studies, RECs could require information on pre-clinical data from animal studies and cell/tissue data disaggregated by sex, evidence about possible sex differences or lack thereof, and assess research protocols in view of that. RECs could also require researchers to provide sex disaggregated data when reporting their studies, which could allow for future meta or pooled analyses, and or encourage sex and/or gender analysis to the extent possible. Sub-group analysis, even when not sufficiently powered, could be helpful in identifying signals that would merit future specific studies. A possible (quicker) solution to generate more data on sex differences could be retrospective analyses of data when disaggregation is available.

RECs can also raise awareness about these issues, especially when training researchers. One participant suggested that a research protocol should describe the challenges that the researchers are likely to face during recruitment, and possible solutions to facilitate an equitable participation by women and men or people of diverse SOGIE, if part of the research. RECs on their part must make themselves aware of the structural issues in the communities which can result in differential barriers to participation depending upon a person's age, sex, gender, ethnicity, race, socio-economic and literacy status. Meeting participants mentioned that pregnant women on whom there is paucity of data, are usually excluded from clinical trials. REC should ensure that either they are included in the research or dedicated clinical trials are planned. The meeting was informed about the endorsement by the ICH general assembly of a proposal for a new Efficacy Topic (E21) on "Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials" and the related Concept Paper outline, with an informal working group to be established by the end of 2022.[4] The members of this group also pointed out that the way in which clinical and other health related research is organized and operated may also need to be reviewed and reassessed with a gender lens, to remove gender-related barriers and allow equal access to

[4] https://admin.ich.org/sites/default/files/2022-07/ICH44_Athens_Assembly_Minutes_Meeting_Final_2022_0622.pdf

participation in research. One of the unanswered questions was whether guidance for RECs that review clinical research should be different from the guidance for RECs that review other health-related research such as socio-behavioural research studies.

Some participants noted that sometimes investigators, research sponsors and funders prioritise a specific type of research that poses a challenge to carrying out proper sex and/or gender sensitive research. In such cases, a justification for doing so should be presented.

In relation to research ethics guidelines, most participants welcomed the idea of adapting the SAGER guidelines for use by RECs when providing an ethics review. Some participants claimed that the current ethics guidelines including the CIOMS *2016 International ethical guidelines for health-related research* involving humans are rather comprehensive; the challenges may be in the implementation of practices. There is, thus, no reason for a major revision of the current ethics guidelines. However, if a revision (e.g. of the CIOMS guidelines) were to take place (likely following the revision of the Helsinki declaration), it is important to seize the opportunity and ensure that sex and gender aspects are more explicitly included in the revisions.

Another idea that gained majority support was for CIOMS and other interested entities such as sponsors, research funders and research methodology course developers to raise awareness of the SAGER guidelines and also endorse and reference them. This would be beneficial to researchers and research teams, drug developers during initial trial design and clinical development plans, and facilitate the work of RECs. Another suggestion was for publishing an interpretative paper accompanying the endorsement of the SAGER guidelines which could expand on how the SAGER recommendations can be applied to the work of RECs.

Other proposals raised were development of implementation tools and instruments for RECs on “how to”, including specific ones for implementation research, health systems research, and social sciences. Another idea was incorporating relevant content on sex/gender in the online training instruments for RECs.

Cognisant of the non-representative nature of this group, participants discussed ways to disseminate any possible general guidance that the group may decide to formulate. Several proposals and opportunities were discussed: CIOMS confirmed that a working group on Good Governance Practices in Research Institutions was near finalisation, as was the work of the group on Recommended Standards of Education and Training for Health Professionals Participating in Medicines Development. Both co-organizers of this meeting could benefit from including relevant discussion and outcome from the workshop in their respective guidance. It was noted that the World Medical association (WMA) is in the process of updating the Declaration of Helsinki and the outcome of this meeting would surely feed into their discussions. The 2016 CIOMS guidelines, at the time of an update, could also take the outcome of this meeting into account. While the ICH GCP (E6) and other relevant E guidelines perhaps already contain language relevant to addressing sex and gender issues, it would be helpful to share the meeting report from this group with them. For example, in relation to drug development/industry trials, participants indicated that currently the product labels, e.g. Investigator Brochure(IB), Summary of product characteristics (SmPC),

United States packaging inserts (USPI), etc. do not have a specific section where relevance to gender or gender differences are depicted, even though health authorities, e.g. FDA have been advocating diversity in clinical trials for over a decade and very recently have released new guidelines to strengthen diversity which also include gender as one of the criteria.[5,6] Depending on the drug, current practice is that special populations may include the elderly, the paediatric, patients with hepatic and renal impairment, pregnant women and females/males of reproductive age. This categorization may miss the differences in safety and efficacy of drugs due to physiological and anthropometric differences in men and women that are unrelated to reproductive issues, and gender differences where relevant.

Concluding remarks

Overall, following fruitful discussion, there was a consensus among the meeting participants on the importance of addressing sex and gender dimensions in research and that RECs could play an active and important role, in collaboration and alignment with other gatekeepers of the research system. Guidelines including adaptation of the SAGER guidelines for RECs, training tools, decision charts and other tools could be helpful in enabling RECs to consider sex and gender related issues when providing an ethics review. This should include attention to the needs of and inclusion of pregnant and breast feeding women in health research, when relevant. There was a recognition that organizations like CIOMS, GENDRO, WHO, WMA and other organizations that support health research, could take this task forward but this work needs to go hand in hand with other efforts by other stakeholders in health-related research, including editors, funders, industry, regulatory bodies, normative agencies and research organizations. Potential research participants, including pregnant and breastfeeding women should also be enabled to provide inputs into how sex and gender considerations in health research could be strengthened.

Way Forward

1. A meeting report will be made available on the web.
2. Principles and values that are key for the consideration of sex and gender issues in health research should be further clarified. There should also be a reflection on defining “fair participation” in research vis-à-vis variables such as age, race, ethnicity, socio-economic status versus sex and gender, and how to make balanced decisions with regard to fairness in research. This is not only a question of social value (an ethical concern) but also of good science.
3. The CIOMS working groups on Good Governance Practices in Research Institutions and Recommended Standards of Education and Training for Health Professionals Participating in Medicines Development will include some discussion from this group in their soon to be finalised reports.
4. CIOMS could consider making available sex and gender related resources both for researchers and research ethics committees on their website.

[5] FDA to require diversity plan for clinical trials (nature.com)

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations

5. CIOMS could consider developing a network for gender sensitive capacity strengthening for researchers and for RECs.
6. WMA has offered to raise awareness of sex and gender considerations in its discussions on updating the WMA Declaration of Helsinki guidelines.
7. Further steps should be taken for adapting the SAGER guidelines for RECs using a more representative process, and also to develop tools and checklists to aid RECs in paying attention to sex and gender issues when reviewing research.
8. Further research should be carried out on how RECs can contribute to strengthening appropriate inclusion of sex and gender considerations in health research.

Annex 1: List of Participants

Lembit Rägo	Secretary-General, CIOMS
Herve Le Louët	President, CIOMS
Abha Saxena	Independent Bioethics Adviser
Shirin Heidari	GENDRO
Clarisse Delorme	World Medical Association
Hans van Delden	Utrecht University
Dominique Sprumont	WMA/ EUREC
Aline Sigrist	Health and Gender Unit, Unisanté, Lausanne
Samia Hurst	Geneva University Medical School and Hospitals
Angèle Gayet-Ageron	Geneva University Medical School and Hospitals
Claire Somerville	Graduate Institute, Geneva
Lee Hibbard	Council of Europe
Andreas Reis	WHO, Health Systems and Innovation
Antonella Lavelanet	WHO, Sexual and Reproductive Health Research
Clara Moerman	Independent researcher
Joke Haafkens	Independent researcher
Srinivas Nammi	Novartis
Katrina Bramstedt	Roche
Raffaella Ravinetto	Chair of the Institutional Review Board, Antwerp Institute of Tropical Medicine, Belgium
Metin Gülmezoglu	Concept Foundation
Julie Archer	DNDi
Joelle Tanguy	DNDi
Emilie Alirol	FIND
Andrea Lucard	Medicines for Malaria Venture (MMV)
Anne Claire Marrast	Medicines for Malaria Venture (MMV)
Unable to attend	
Anna Coates	WHO, Sexual and Reproductive Health Research
Vasee Sathiyamoorthy	WHO, Health Systems and Innovation
Erin Kenney	WHO

Annex 2: Agenda of the Meeting

10:30	Welcome and Introduction - Opening remarks: by Hervé Le Louët, President, CIOMS; Lembit Rägo, Secretary-General, CIOMS; Shirin Heidari, President, GENDRO - Tour de Table - Selection of meeting officers (Chair/s and Rapporteur) - Adoption of the Agenda
10:40	**Setting the scene: sex and gender considerations in research; the role of RECs(10 min)** Shirin Heidari, President, GENDRO discussion
10:50	**Presentation of the results of the research on considerations of sex and gender dimensions by research ethics committees (30 min)** Abha Saxena, Independent Bioethics Adviser
10.20	**Q&A (10 min)**
11.30	**Short interventions from participants, including** - Academia/Researcher/Research organization perspectives - Industry perspectives - Ethics committee perspective - Funding agency perspective - Individual expert perspective
12.30-13.15	**Lunch**
13.15	**Discussion, including reflections on the interventions and discussion on gaps in existing ethics guidance documents and implementation practices:** - Potential need for strengthening research ethics guidelines regarding sex and gender considerations - Ways to improve ethical review practice considering systematically sex and gender consideration in ethical reviews and evaluations by research ethics committees (RECs) - Other issues
14.45-15.00	**Coffee / Tea**
15.00	**Discussion on way forward. Consensus on next steps, including** - Formulating short recommendations - A possible commentary jointly developed by CIOMS and GENDRO, co-authored by the attendees raising awareness about the role of RECs in advancing gender equity in research - Publishing a meeting report - Other
16.00	**End of Meeting**