SEX AND GENDER IN RESARCH INVOLVING HUMANS ACCORDING TO THE HRA

RECOMMENDATIONS FOR THE ETHICAL REVIEW OF RESEARCH PROJECTS

Introduction: general considerations

The issue of sex and gender (referred to as *"sex/gender"*) in biomedical research has recently gained significant attention among researchers and clinicians [1-4] and also by the creation of a new National Research Program on "Gender Medicine and Health" announced on June 2nd 2023. There is a growing recognition [1, 2, 5] of addressing sex/gender in research involving humans according to the HRA, which reflects the need for equity and justice from the conception of the research project to the participant selection and the analysis and presentation of research findings. This should impact on how Research Ethics Committee (REC) review the documents that are submitted [5] and how those documents are drafted.

In the past few years it is generally agreed upon that biomedical research should strive to include participants from diverse sex/gender backgrounds whenever relevant[1]. In addition, the issue of sex/gender is only briefly mentioned in the BASEC templates. Despite this development, there is still a persistent underrepresentation of women and sexual and gender diverse persons (SGD, see definition below). This contradicts art. 6 par. 2 HRA and the declaration of Helsinki, which states (art 13) that "*Groups that are underrepresented in medical research should be provided appropriate access to participation in research*[6]. More broadly there is insufficient integration of sex/gender issues in biomedical research: many investigators tend to ignore or dismiss this topic [7], not only in the way they develop their design and define the study population, but also in how they analyse, interpret and publish their data and results.

Consequently, it is suggested that protocols and related documents submitted to Swiss RECs thoroughly refer to sex/gender in the future. This formulation highlights the fact that the concept of sex/gender is inherently intersectional (interconnected nature of social categorizations) and requires an understanding of both the biological and societal factors and their dynamic interplay to advance health equity [8]. This document presents the main aspects of the issue of sex/gender and provides a concrete approach as how to assess documents submitted to RECs. It will be updated regularly.

Definitions

To deliver a comprehensive message to all members of the REC, a definition on the different terms used is needed [1, 3, 5, 7, 9].

Sex relates to the biological attributes that distinguish male and female, based on chromosomal identification, reproductive organs, hormonal exposure. However, a number of studies have shown that the distinction between male and female is far more complex and not reduced to a binary view that the sex category would suggest, for example in the case of individuals with variation of sex development (intersex)... *Sex assigned at birth* refers to the sex (male, female, intersex) assigned to a child at birth, most often based on the child's external anatomy [10]. In health research, sex

[1] Building upon this understanding, a milestone was reached in 2020 when Peter Kleist (KEK Zürich) proposed recommendations on sex and gender equitable research, which were put on the Swissethics website. This former document is now replaced by the present one.

assigned at birth is often used as a proxy for sex, as readily available through administrative documents.

Gender refers to the roles, behaviours, expressions and identities built socially among girls, women, boys, men, and gender diverse people. Gender operates at different levels influencing health of individuals. For example, the distribution of power and resources in a given society (structural level) affects access to care; gendered social norms influence health behaviours such as risk taking or health-seeking behaviour, but also exposure to health risks and hazards in relation to the gendered division of labour (interactional level). Finally, gender operates through the process of self-identification and expression of gender (individual level). In addition, gender identity manifests itself along a continuum and can change over time, reflecting the growing recognition of sexual and gender diversity (SGD), and of individuals defining themselves as LGBT+ or LGBTQQIP2SAA (lesbian, gay, bisexual, transgender, queer, questioning, intersex, pansexual, two-spirit (2S), androgynous, and asexual), or included in the new SOGIESC definition [11][2].

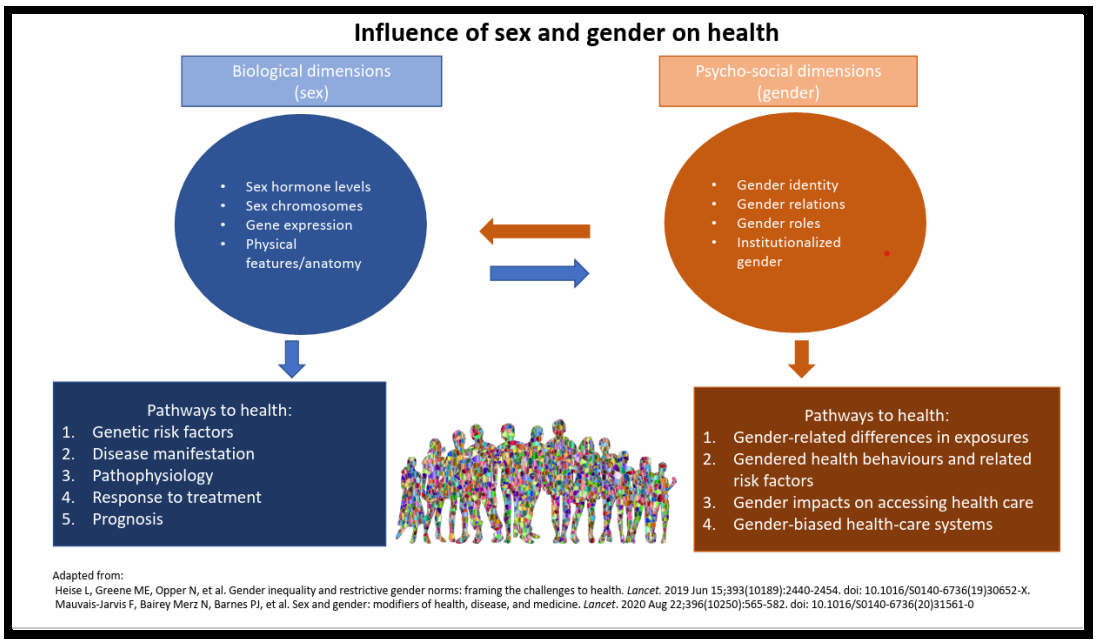
Sex and gender interplay

As outlined in a recent publications[11, 12]:

- ✓ Biological sex impacts the physiological functioning of the body as well as the clinical manifestations or response to treatment, due to variance in the individuals' genetic and hormonal status.
- ✓ Epigenetic modifications can modulate the expression of biological sex.
- ✓ The patients' perception of disease, help-seeking behaviour or access to or use of health care can be affected by gender construct.
- ✓ The patients' sex and gender can influence the behaviour of health care providers, such as the way they investigate and treat their patients.

The figure below illustrates the inter-relation between sex and gender in health, diseases, and medicine [12, 13].

[2] *SOGIESC* is a new acronym for sexual orientation (SO), gender identity and gender expression (GIE) and sex characteristics (SC) that may progressively replace other acronyms. SOGIESC diverse persons have one or more SOGIESC characteristics placing them outside socially or culturally mainstream categories. They share an increased risk to be exposed to stigma and discrimination because they depart from restrictive sex and gender norms. This frequently results in specific health care and public health needs.



Why and when do sex/gender matter?

There are projects for which the component of sex/gender may not be relevant. *If this seems irrelevant or proves impossible, the principal investigator should provide convincing arguments for avoiding the exploration of sex/gender in her/his/their research protocol*.

However, most of the time, the issue of sex/gender in all submitted documents is appropriate and applicable. Here are a few examples:

- In many retrospective studies and most prospective studies, the issue of the recruitment process and sample composition must be assessed in terms of an equitable representation of women and men, including participants expressing sexual and gender diversity, or reasons not to do so should be provided when relevant.
- In prospective research projects, especially in randomised clinical controlled trials (RCTs), the issue of contraception and pregnancy should be adequately dealt with. For instance, it is irrelevant to request contraception from a lesbian woman living in a stable relationship with her female partner.

Recommendations to the presidency, scientific collaborators and members of RECs

Protocols

All protocols and other documents should be systematically appraised according to the introduction above. All Swiss RECs are asked to incorporate the following guiding principle – inspired by the SAGER guidelines [14][3] in the review process performed by the presidency and the scientific secretariats. In addition, all Swiss RECs must provide this document to all REC members for their information and use.

The following guidelines provide some concrete examples based on published papers to illustrate the importance of integrating sex/gender in the research questions or when it would be important to integrate it (look at the flowchart on page 6).

[3] On March 4th 2024, the World Health Organization has officially disclosed the adoption of the SAGER guidelines

Topic of the study **:** Given the nature of the research, are sex/gender and sexual diversity issues relevant and do the reviewers need to focus on specific aspects in all documents? If NOT, explain why.

The British Whitehall study including male British civil servants began in 1967 and studied the association between social class and mortality from a wide range of diseases. The second British Whitehall II study (1985 -1988) included men and women (6900 men, 3414 women) aged 35-55 found interesting differences but also similarities between men and women. For example, job satisfaction explained 68% of the association between job insecurity and self-rated health in women, but only 36% in men[15].

Title: Does the title mention the issue of sex/gender and SGD, especially if only one sex is included, or if the aim of the study is to focus on gender issues?

A recently published study assessed the efficacy of postexposure doxycycline to prevent bacterial STI in men who have sex with men. The sample included 96% men and 4% transgender women or gender-diverse persons but this was not specified in the title of the paper [16].

Introduction Does the introductory scientific review mention the issue of sex/gender and/or SGD and address the potential importance of these concepts within the context of the study? Do the objectives of the study include statements on sex/gender if appropriate? In some instances, the issue of intersex individuals should be explicitly raised.

Some authors report that coronary artery diseases (CAD) have different pathophysiology between women and men due to different anatomopathological presentation related to sex; others argued that there is no sex difference rather some inequities in the care management of CAD between women and men (gender inequalities) [17].

Methods:

- *sample*: Is sex/gender equity secured and is sex and gender diversity documented and how? If not, why? If men or women or SGD persons are excluded, are the reasons for such an exclusion provided? How is the recruitment performed to allow for a fair distribution of sex/gender? Is there any threat to selection biases identified and how is it addressed?

Women represent globally >50% of the population living with HIV. A 2016 systematic review demonstrated that women represented only 19.2% of participants involved in antiretroviral therapy (ART) studies, 38.1% of those participating in HIV vaccine studies, and a paltry 11.1% of those taking part in HIV cure studies [18].

- *gathering of data*: Does the process of obtaining the data ensure an adequate distribution of women and men? Does the collection of data ensure an equitable representation of men women and other SGD persons?

The question of contraceptive use in clinical trials was shown to be differently applied between men and women (inclusion of women requiring up to four counter-signatures to confirm the contraceptive use whereas no signatures were required for men), thus providing selection bias in the study population [19].

- *statistical analyses*: Do the planned analyses consider the issue of sex/gender and SGD? will the data be disaggregated by sex/gender and, if applicable, subgroups among the sexual and gender diversity (expected differences versus similarities)? Is the study sufficiently powered to be able to assess some sex/gender differences? For clinical trials, is it planned to report adverse events separately by sex/gender?

It was possible to conduct robust sex-specific analyses to assess the association between obesity and risk of heart failure among participants of the Framingham Heart Study thanks to a large sample size (n>5000)[20].

- *If applicable*: Is the issue of pregnancy test(s) and of contraception covered for both participants and partners? The exclusion of women or transgender men of childbearing age should be systematically justified.

Different requirements for the use of contraceptives by men and women lead to burdens that were disproportionate in women than in men [19].

- *If applicable*: Does the protocol mention financial or organizational measures to support the participation of children' caregivers?

- *If applicable: S*ome trials may have consequences in terms of fertility (e.g. if abnormalities of reproductive organs or function have been observed in former experimentation on animals). In such situations, including patients of reproductive age in a clinical trial need to be carefully discussed (risk-benefit evaluation).

For instances, in clinical trials of type 2 diabetes medications, exclusion criteria affecting women of childbearing potential are often disproportionate due to the low risk to the participant and foetus. These criteria have the potential to impede young women's access to clinical trials and may hinder the acquisition of clinical knowledge critical for improving the care of women with diabetes [21].

Other documents

ICFs: Does the layout of the information respect the epicene language, or is it written in an inclusive format? Does the information cover the study's aspect related to sex/gender or SGD appropriately? If applicable, is the issue of contraception and pregnancy fully and clearly presented?

Questionnaires, interviews: In addition to socio-demographic data, the questions asked in standardized questionnaires are often highly hetero-normative; thus, the prescriptions above apply to all documents that will be submitted to participants, especially when it comes to the inclusion of data pertaining to sex/gender.

Planned publications:

Will the results be presented considering potential variations across sex/gender or subgroups among the sexual and gender diversity, with appropriate discussion? If there are expected limitations to address such variations, does the protocol offer avenues to overcome these limitations?

A study assessed the one-year risk recurrence of acute coronary syndrome, including the use of a gender score, (tackling several dimensions of gender: stress, income, adherence to gender norms, gender roles). The outcome was not different when comparing men and women but a difference appeared when comparing participants with high feminine vs. neutral or high masculine gender score. Independently of their sex assigned at birth, those with high feminine score were at higher risk of relapse [22].

The flowchart on the next page, adapted from the SAGER guidelines[14], should inspire researchers as well as the professionals in charge of the review process

QUESTIONS	YES	NO	Comment for RECs
1. TOPIC OF THE STUDY			
Are sex/gender (S/G), respectively sexual and gender diversity (SGD) issues relevant to the topic and aim of the study?			***If the answer is no, check that it is justified***
If sex/gender issues are relevant to the topic/aim, please check all the following items			
2. INTRODUCTION			
2.1. Are S/G and SGD dimensions developed (genetic and/or biologic or social mechanisms at play)?			*If no, ask for protocol's revision accordingly*
2.2. If appropriate, do the objectives include the question on S/G and/or SGD?			*If no, ask for protocol's revision accordingly*
3. METHODS			
3.1. Is the study population correctly described regarding S/G (including sexual and gender diversity)?			*If no, ask for protocol's revision accordingly*
3.2. Eligibility criteria: does it ensure representativeness of all the S/G and SGD dimensions? Is there a selection bias regarding S/G distribution?			*If no, ask for protocol's revision accordingly*
3.3. Recruitment of participants: does the process of obtaining the data ensure an adequate distribution of S/G and SGD?			*If no, ask for protocol's revision accordingly*
3.4. Definition of S/G and SGD dimensions: do they capture sex dimensions (hormonal levels, gene expression, etc.) and/or gender dimensions (identities, norms…) and/or sexual orientation dimensions (sexual attraction, romantic attraction…)?			*If no, ask for protocol's revision accordingly*
3.5. Statistics (incl. sample size): if S/G and SGD are of primary interest, does the sample size estimation integrate this aspect? Are the statistical analyses appropriate?			*If no, ask for protocol's revision accordingly*
4. INFORMED CONSENT & OTHER DOCUMENTS			
4.1. Informed consent form & other documents: does the content of information respect the epicene language, or at least is written in an inclusive manner?			*If no, ask for ICF's revision*
4.2. Informed consent form: Does the information cover the study's aspect related to sex/gender and SGD appropriately?			*If no, ask for ICF's revision*
4.3. Informed consent form: If applicable, is the issue of contraception and pregnancy fully and clearly presented? does the document address the issue of potential extra costs that may deter women/parents to participate in the study, e.g. child care and custody			*If no, ask for protocol's and ICF's revision*
4.4. In questionnaires, interviews: is the language and content inclusive? is the possibility to cover the sexual and gender diversity open (e.g. in an open box)?			*If no, ask for documents' revision*
5. PUBLICATION AND DISSEMINATION POLICY			
Do the publication and dissemination plans include the presentation of disaggregated results by S/G and SGD ?			*If no, ask for protocol's revision*

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