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Improving sex and gender equity in research protocols: the new SAGER-swissethics recommendations

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Introduction

For several decades, the majority of experimental and clinical studies have been conducted using male cells, animals, and human subjects [1, 2]. It was assumed that the sexes were biologically identical, leading to the incorrect extrapolation of findings from male to female subjects. While the exclusion of women may be justifiable in some cases, such as that of women of childbearing age due to risks of congenital defects in the foetus, in many instances justification has been insufficient or unjustified. The exclusion of women in cardiovascular research has led to guidelines and management that are not adapted to their specificities. This contributes to the poorer prognosis observed in women under 50 years, who have a higher risk of death when hospitalised after acute coronary syndrome [3]. These disparities in care management suggest implicit bias or even covert discrimination in risk assessment. Another concern is the tendency towards so-called biological reductionism, where differences between men and women are reduced to biological mechanisms (hormonal, genetic), ignoring behavioural or social dimensions. This has led to an imbalance in scientific knowledge, as evidenced by numerous historical studies that have justified the inferiority of women on the basis of erroneous anatomophysiological beliefs [4]. Furthermore, sex and gender are often considered as binary variables (female/male, women/men) in research. A proportion of the population has variations in sexual development; hormone levels may fluctuate and are not produced uniformly between and within groups. Therefore, sex should be considered a proxy based on multiple dimensions (sex hormone levels, gonads, and genetics). Gender operates both at the individual level, through self-identification and expression, and at the structural level, through gender norms that shape roles and relationships within institutions and society. These in turn modulate exposure to risk (e.g., to domestic violence), health-related behaviours (e.g., diet and smoking) and access to care (e.g., health-seeking behaviour and financial access) [5]. Furthermore, gender identity manifests along a continuum and can change over time, as reflected by the growing recognition of gender diversity [6]. People who do not conform to normative expectations of sexual orientation, gender identity and expression, or sex characteristics are at an increased risk of discrimination. This often leads to health inequalities and poorer access to health care. It is therefore crucial to consider the influences of both biological sex and gender as multidimensional variables in health research [7]. Depending on the research objectives, consideration of the influence of sex/gender on health should go beyond the sex assigned at birth, including information on self-reported gender identity, gender norms and roles, and, where relevant, hormone levels or variations in sexual development.

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The roles of research ethics committees

One of the roles of research ethics committees is to ensure that Swiss law on research involving human subjects is respected. Article 6 of the Human Research Act states that "*Nobody is to be subjected to discrimination in connection with research. With regard to the selection of participants in particular, no group of persons shall be disproportionately included in or excluded from research without good reason.*" At the beginning of 2024, the Federal Council adopted amendments to the ordinances, in particular Article 4a of the Ordinance on Clinical Trials, which emphasises the importance of including relevant groups of participants, representative of the target population in terms of sex and age. Any exclusion or under-representation of relevant groups of participants should be clearly justified. In addition, any research project is ethically justified only if

it is of high scientific quality and integrity, if it complies with the legal framework, and if the risk/benefit ratio for the individual is acceptable.

Globally, issues of representativeness and the use of procedures to improve the diversity and inclusivity of study populations are often insufficiently addressed [8]. The US National Institutes of Health has mandated the inclusion of women in clinical trials since 1993, but in practice, this has been poorly implemented [9, 10]. In 2016, the Sex and Gender Equity in Research (SAGER) guidelines were developed to aid researchers in considering these dimensions in study design, conduct, analysis and reporting; editors were meanwhile encouraged to evaluate manuscripts submitted for publication on their adequate consideration of sex and gender dimensions, or reasonable justification for lack thereof [11]. However, despite the widespread dissemination of the SAGER guidelines, many investigators tend to ignore or dismiss the issue [12], both in the development of study design and the definition of study populations, and in methods of analysis, interpretation, and publication of data and results. Research ethics committees therefore have an important role to play in the review of submitted research protocols as gatekeepers for the integration of sex and gender issues [12] when relevant and appropriate [13]. In this context, the swissethics National Board decided in 2023 to set up a working group to draft new recommendations, hereafter referred to as the "*SAGER-swissethics recommendations*". The purpose of this paper is to inform the Swiss health research community about the importance of considering the influence of sex and gender in research.

Development and dissemination of the SAGER-swissethics recommendations

A working group, consisting of six representatives from different Swiss research ethics committees and two experts in gender medicine, was set up in September 2023. The group searched textbooks, bibliographic databases, reference lists, and personal files for relevant material. The group met five times remotely between September 2023 and January 2024 to develop new recommendations based on the SAGER guidelines [11]. These were presented in two documents (a complete and a short-form version) which were reviewed by external experts in gender medicine. A consensus on the final format was reached by the end of February 2024. The formalised documents were then presented to the swissethics Board on 26 March 2024 and were unanimously approved. The two documents are now available on the swissethics website [14] and include a checklist to be used by researchers before submitting their research protocol and by research ethics committee members during the evaluation process. In addition, reminders on the relevance of sex and gender issues have been incorporated into appropriate sections of the protocol templates provided by swissethics, which guide researchers in the development of their research plan, and other information documents [15].

These documents provide definitions of sex and gender, explanations and illustrations of how sex and gender interact in health, disease and medicine [5, 7], and examples to illustrate why and when sex and gender dimensions are important and should be integrated. Researchers and research ethics committee members can follow the 13 items of the checklist (table 1), and if sex and/or gender integration is not considered in a proposal, this must be justified or the research protocol revised accordingly (items 1 to 3). It acknowledged that for some research questions, the consideration of sex and/or gender may not be relevant [8]. In the methods section (items 4 to 8), the study population should be shown to adequately represent the target population in all its diversity (item 4), with a minimum set of exclusion criteria (item 5). Researchers should define the measures taken to ensure an adequate representation of women or, in specific cases, how they will address the issue of participants belonging to the LGBTQI+ population (item 6). Authors are asked to specify whether stratified randomisation is planned or how the recruitment for specific target groups will be organised to minimise the risk of selection bias (item 6). For example, the participation of women of childbearing age can be improved by offering financial support for childcare during participants' study visits. The participation of sexual- and gender-diverse populations can be increased if recruitment is actively targeted, and if the communication used is sufficiently inclusive and context-appropriate. Involving representatives of sexual- and gender-diverse populations in the design of the research can help achieve these goals. With regard to the consideration of sex and gender, researchers are invited to anticipate the variables to be collected in the research plan in order to capture relevant sex and gender dimensions (item 7). For sex, the minimum information required is "sex assigned at birth"; however, this may be supplemented in some cases by the measurement of sex hormones, to approach sex as a continuous rather than binary variable. Where the issue of "gender dimensions" is relevant, the minimum required information is self-reported gender identity, using a multicategorical variable, with the option of accepting open responses (item 12). The statistical strategy should be well described and consistent with the considered dimensions: for example, if sex/gender analysis is planned, the statistical power must be appropriately adjusted (item 8). In projects involving small sub-groups, or where the assessment of sex/gender differences in research outcomes is not the primary objective, descriptive statistics may be sufficient. The informed consent should use inclusive language adapted to a diverse population (item 9) and be sufficiently explicit about the integration of sex and gender issues (item 10). In some research, participants may need to use contraceptives for legitimate reasons; this should be discussed transparently, and any related additional costs should be anticipated in the research budget (item 11). The final item on the checklist (item 13) concerns the publication and dissemination policy, and recommendations to adequately present sex- and gender-disaggregated data [11].

Limitations and perspectives

The dissemination of the SAGER-swissethics recommendations on the swissethics website [15] and the adaptation of research protocol templates are important steps towards a cultural change, aimed at sensitising the scientific research community to the importance and impact of sex and gender on health. The extent to which aspects of the checklist should be covered will of course depend on the objectives of each study, and researchers should not be too

Table 1:
The "checklist of issues" to be addressed in research protocols [14].

QUESTIONS		YES	NO	Comment for RECs
1. Topic of the study				
1	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	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*
3	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				
4	3.1. Is the study population correctly described regarding S/G (including sexual and gender diversity)?			*If no, ask for protocol's revision accordingly*
5	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*
6	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*
7	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*
8	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				
9	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*
10	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*
11	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*
12	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				
13	Do the publication and dissemination plans include the presentation of disaggregated results by S/G and SGD?			*If no, ask for protocol's revision*

dogmatic in applying the principles outlined above. However, passive dissemination of recommendations on a website may not be sufficient to bring about cultural change, and several complementary actions should be taken to promote the systematic consideration of sex and gender in health research. An initial additional action will be to engage research ethics committee members through the usual training sessions organised by Swiss research ethics committees. Research ethics committee members systematically referring to the checklist when reviewing research protocols, and providing critical feedback and advice to the investigators when warranted will constitute a further disseminative action in itself. Thirdly, training could be made available to the research community through the dissemination of short and practical tutorials on the swissethics website. Finally, sensitising the scientific staff of research ethics committees responsible for the initial reviews of research protocols is another measure that can be implemented in each research ethics committee.

In Switzerland, the development of the SAGER-swissethics recommendations is part of a range of actions aimed at reducing health inequalities in the Swiss health system. A recent report by the Swiss Federal Council, in response to the Fehlmann-Rielle postulate [17], emphasises the importance of sex and gender dimensions in various areas of health care, such as the development of new drugs, the promotion of health and well-being, the detection and management of health problems, and the training of health professionals. The integration of sex and gender issues in the undergraduate teaching of medical and nursing students is currently being supported by a Swiss inter-faculty initiative, funded by swissuniversities and supported by the Swiss Society for Gender Health [18]. The Gender Education in Medicine for Switzerland (GEMS) platform is one aspect of this swissuniversities project and aims to share teaching materials between all Swiss partner institutions [19]. Finally, the Swiss National Science Foundation launched in 2024 a National Research Programme on "Gender Medicine and Health" (NRP 83) to generate new knowledge on sex and gender aspects in health research, medicine and public health in Switzerland. The impact of the introduction of the SAGER-swissethics recommendations in combination with complementary measures should be properly evaluated in the future to assess their effectiveness.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *AGA*, *NK*, *AM*, *DN*, *PS* and *PAM*, are members of a Swiss research ethics committee. *CC* is president of the steering committee of NRP-83 "Gender Medicine and Health". *JS* contributed to the BAG/Fehlmann Rielle report as an external expert. *SH* has been the founding chair of EASE Gender Policy Committee and is the lead author of the SAGER guidelines. All other authors declare having no conflicts of interest related to the content of this manuscript.

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