RESEARCH ETHICS

Gender equality in the work of local research ethics committees in Europe: a study of practice in five countries

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Background: Funding organisations and research ethics committees (RECs) should play a part in strengthening attention to gender equality in clinical research. In the research policy of European Union (EU), funding measures have been taken to realise this, but such measures are lacking in the EU policy regarding RECs.
Objective: To explore how RECs in Austria, Germany, Ireland, The Netherlands and Sweden deal with gender equality issues by asking two questions: (1) Do existing procedures promote representation of women and gender expertise in the committee? (2) How are sex and gender issues dealt with in protocol evaluation?
Methods: Two RECs were selected from each country. Data were obtained through interviews with key informants and content analysis of relevant documents (regulations, guidelines and review tools in use in 2003).
Results: All countries have rules (mostly informal) to ensure the presence of women on RECs; gender expertise is not required. Drug study protocols are carefully evaluated, sometimes on a formal basis, as regards the inclusion of women of childbearing age. The reason for excluding either one of the sexes or including specific groups of women or making a gender-specific risk–benefit analysis are investigated by some RECs. Such measures are, however, neither defined in the regulations nor integrated in review tools.
Conclusions: The RECs investigated in five European member states are found to pay limited attention to gender equality in their working methods and, in particular in protocol evaluation. Policy and regulations of EU are needed to strengthen attention to gender equality in the work of RECs.

Clinical research has a crucial role in the provision of high-quality care. It provides healthcare professionals with information on optimal strategies for the prevention, diagnosis and treatment of health problems. Public funding organisations and local research ethics committees (RECs) have a key role in the assessment of quality in clinical studies. Although the funding organisations evaluate the proposals according to scientific standards and relevance, RECs assess their ethical soundness, guided by the principles of respect for people and their autonomy, doing no harm, doing good and justice.[1]

It was assumed for many years that, apart from the reproductive system, there were few differences between men and women that affected health. Clinical studies on conditions that affect both men and women were mostly conducted with male research participants and were not designed to identify differences between men and women or relevant subgroups. It has, however, been recognised since the 1990s that marked differences exist in patterns of health and in conditions that affect both men and women: some conditions are more prevalent or more serious in one sex than the other, have distinct risk factors for men and for women or require different interventions.[2 3] These differences may stem from specific biological characteristics of women and men (reproductive, genetic, hormonal and metabolic features; sex), or from differences in socially constructed variations in the daily lives of men and women (gender), which interact in complex ways.[3–8] In addition, it has been suggested that the earlier research bias with relation to men without considering possible differences between the sexes has created gaps in our knowledge, both of disease management in women[2 3 9 10] and of how gender affects health.[6 10–12] To fill these gaps, researchers should consider both women and men and design their studies with sensitivity to sex and gender factors.[3–5 8 9 13 14]

In response to a concern that such lack of information may hamper optimal healthcare to both men and women, public funding organisations in several countries have adapted their rules for research applications. For example, supported by a mandate from the US Congress, the US National Institutes of Health required since 1993 that men and women should both be adequately represented in clinical studies and that research designs should permit valid and meaningful analysis of differences between the sexes.[15] More recently, the European Union (EU) has made a clear commitment to promote gender equality in research funded by the EU by aiming at balanced participation of male and female scientists in projects (40% women) and attention to gender in the research content.[16] With respect to the attention to gender, study proposals must consider the needs and interests of women as much as those of men. In the sixth Framework Programme, which started in 2002, applicants for projects in the life sciences were asked to describe and justify the composition of the study population according to sex and to integrate attention to sex and gender issues, whenever relevant, in the objectives and methods of their research projects.[16]

The revised National Institutes of Health policy presented real challenges to the institutional reviews boards, which are responsible for the ethical review in the US, on how to carry out the ethical assessment of study protocols. Until 1993, the work of the institutional review boards was guided by the ethics of protectionism, often resulting in the exclusion of women, especially pregnant women or women of childbearing age, from research to protect them and their unborn children from potential harm.[14] The new regulations also instructed the boards to examine issues of justice and equitable selection of

Abbreviations: EU, European Union; REC, research ethics committee

participants.[17] A new balance had to be found, with less emphasis on protection and more on inclusion: to be fair in the selection of research participants, a study should include all relevant groups, including women, unless there are sound scientific reasons for not doing so. Furthermore, the study design should be attuned to the specific needs of the groups included, to avoid an unfair distribution of benefits and burdens.[8 17–19]

A similar shift in focus is also visible in other national[20–23] and international[24–27] guidelines on research ethics. Besides ensuring that study participants are protected from harm, RECs should evaluate whether there is equitable representation of men and women[24–27] and whether burdens and benefits associated with participation are equitably distributed across the sexes.[24–26] Another issue is whether drug studies take possible sex differences in drug metabolism into consideration.[27] In addition, some guidelines mention that RECs must include both men and women as evaluators of research proposals.[24–26] Surprisingly enough, however, the recently adopted directive of the EU on clinical research, which is intended to harmonise the working methods of RECs in the member states, does not contain any reference to sex or gender. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relates to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

To provide a firmer basis for decision making, there is a need to know how much attention is paid to gender equality in the existing procedures of RECs in member states of the EU. To this end, we conducted an exploratory study in Austria, Germany, Ireland, The Netherlands and Sweden in which the following questions were asked: Do existing formal or informal arrangements require a REC to include women or an expert on health-related sex and gender issues on the committee? Do existing formal and/or informal arrangements for the evaluation of research protocols pay attention to sex and gender factors in the design and conduct of a study?

MATERIALS AND METHODS

In each of the five participating countries, three key informants were interviewed to answer the research questions. One key informant was selected for his or her expertise on the national laws and regulations regarding RECs. The other two (one male and one female) informants represented two RECs, and were selected for their expertise on current procedures and practices (throughout this article, we use R1 and R2 to distinguish between the two RECs in each country).

The RECs selected in each country had all reviewed a substantial number of protocols. Of course, this number depends on the level of research and the rules for review in the country concerned. Hence, the number of protocols reviewed by the selected RECs ranged from about 40 a year in Ireland to about 500 in Sweden. In the selection of RECs, we also tried to take into account possible variations in a country's regulatory framework. In Germany, for instance, there are two systems of ethical review—one set by the Chamber of Physicians and the other by the universities. We selected one REC from each review system.

One member of each REC, who had longstanding experience of the committee's work, was invited for an interview. Most of them were chairpersons or scientific secretaries or had held such a position in the past.

The interviewers used structured questionnaires or topic lists.

Firstly, the informants on the regulatory framework were asked to name and comment on documents (in particular national laws and regulations) that described the formal procedures guiding the work of RECs in their country. The informants from the RECs complemented this list with specific local guidelines and tools for review. All these documents were subsequently collected.

Secondly, the informants from the RECs were asked to describe the composition of their committee, the evaluation of research protocols and the decision-making process regarding the approval or rejection of protocols. They were asked whether sex was a criterion for committee membership and how much attention was paid to potentially relevant sex and gender differences in the evaluation of the study protocols. Some questions focused on the requirements laid down in the committee's formal rules and regulations, and others focused on what was actually done in practice.

We collected the data in the second half of 2003. The interviews were conducted by the coauthors ER, DH, NM, CJM and MN for Austria, Germany, Ireland, The Netherlands and Sweden, respectively. The interviews were audiotaped with the permission of the informants and transcribed verbatim. The informants could check the transcripts for correctness if they so wished.

The data were analysed as follows. Firstly, the rules and regulations of the RECs were screened for direct and indirect references to sex and gender factors by looking for the words ''female'', ''male'', ''woman/women'', ''man/men'', ''sex'' and ''gender'' (or their equivalents in the non-English-speaking countries). Paragraphs in which these words occurred were summarised briefly. Details of the numbers of men and women in the selected RECs were taken from official documents.

Secondly, the information from the informants from RECs on how attention to gender equality was incorporated in their actual work was summarised in two sections relating to (1) selection or recruitment of committee members and (2) protocol evaluation. Ethical approval for the present study was required only in Sweden, where all RECs gave their consent. In the other countries, this type of study did not require ethical review. Table 1 shows each country's definition of the type of research that requires review.

RESULTS

The regulatory framework for RECs varied from country to country (table 1). The Netherlands has a special law on the ethical review of research protocols by RECs. In the other four countries, ethical review is regulated by laws and regulations about medical products or clinical research in combination with specific regulations from the institution a REC is affiliated with (table 1). The type of research that requires evaluation varies from experimental studies only (Austria, Ireland) to all sorts of experimental and observational studies in humans (The Netherlands, Sweden). Some countries have national guidelines or manuals for ethical review, based on laws and regulations (Ireland, The Netherlands, Sweden). In all countries, locally developed regulations and tools for review define how the actual review takes place. RECs in all countries use a mandatory application form that summarises important points for review as an evaluation tool (table 1).

As regards the composition of the committee, all selected RECs have informal arrangements, and in two countries (Austria, Ireland) even formal rules, to include at least some women (table 2). In practice, all RECs take sex into account when recruiting new members and all have women on board. All countries also have formal regulations on how the committee should be composed to ensure representation of certain kinds of expertises, such as biomedical and biometrical expertise, ethical and legal competence and expertise on issues regarding patients (data not shown). None of these regulations stipulate that committees should include an expert on sex and gender issues.

Table 1 Laws, regulations and other documents structuring the work of the REC in five European countries in 2003

	Country				
	Austria	**Germany**	**Ireland**	**The Netherlands**	**Sweden**
National or regional laws and regulations	Medicine Act, Medical Product or Device Act, Federal Hospital Act in addition, Regional Hospital Act (R1), University Act (R2)	Pharmaceutical Drug Law, Medical Products Law in addition, Chamber of Physicians Law (R1); Berlin University Law (R2)	Control of Clinical Trials Acts 1987 and 1990 (R2)*	Medical Research involving Human Subjects Act (1999)	University regulations concerning clinical trials, clinical drug trials (mandatory from the Medical Agency, drug companies, insurance), medical devices; Law regulating bio-banks; Personal Data Protection Act.
National guidelines and manuals	No such document exists	No such document exists	Guidelines on implementation of Clinical Trials Acts 1987 and 1990 (R2)	Manual of the Central Committee on Research involving human subjects. Committee was set up to supervise implementation of the Medical Research involving Human Subjets Act.	Guidelines for Ethical Review of Medical Research on Humans (Medical Research Council, 2000).
Type of research that requires review	Clinical trials of medicines, medical products or devices and application of new medical methods	Clinical trials in addition for R1: epidemiological studies, research with human gametes, artificial insemination or in vitro fertilisation with embryo tevaluation of suspected violations of pharmaceutical drug law.	Research involving human subjects, including behavioural research and alcohol and drug research. Law provides definition of clinical trials, categories of trials and exemptions.	Experimental and observational medical studies on humans, if physically or mentally burdensome to participants Exception: studies falling under the Population Screenings Act.	All studies in medicine on humans, except quality-assurance projects in medical practice, studies performed by students in basic medical training.
Local regulations	Local REC statute	Local REC statute	Local policy procedure manual	Local REC statute	Local REC statute
Review tools	Standardised application form from the Forum of Austrian RECs	Application form	Local protocol application form	Registration form Central Committee	National application form MRC, local working manual

REC, research ethic committee.
R1 and R2 refer to the two RECs in each country.
*Ireland R1 does not refer to the Control of Clinical Trials Acts. Composition of committee and protocol review are in accordance with Title 45 CFR part 46—Protection of Human Subjects, Revision November 2001 (Department of Health and Human Subjects, National Institutes of Health, and Office for Protection of Research Risks, USA), the Council for International Organizations of Medical Sciences—international ethical guidelines for biomedical research on human subjects, and the World Medical Association Declaration of Helsinki.

As regards protocol evaluation, it is reported that the review process used by all RECs selected includes due care to determine whether drug study protocols allow women of childbearing age to participate, the aim being to ensure that unborn children are protected from possible harm. Formal rules exist on this matter in Austria (pregnancy testing is obligatory) and Ireland (application form asks whether specific groups of women are included; table 3).

As regards the issue of men's and women's rights, the Swedish national guidelines for ethical review mention that men and women and their specific subpopulations should have equal rights to have their health problems studied and that this should be taken into account in the composition of the research population and the research design. The national manual of The Netherlands also states briefly that attention should be paid to gender during the selection of study participants and the evaluation of risks and burden (table 3).

None of the RECs we studied, however, have any stipulations in their local regulations or review tools requiring the ethics of justice to be taken into consideration in their review processes. In other words, none of the committees are required to evaluate whether men and women are sufficiently included in the study

Table 2 Gender equality in the composition and recruitment, of RECs as laid down in legal and other documents and as observed in practice

	Country				
	Austria	**Germany**	**Ireland**	**The Netherlands**	**Sweden**
National or regional laws and regulations	Women and men must be included.	No	No	No	No
National guidelines and manuals	No such document exists.	No such document exists.	Membership should, as far as possible, contain both sexes.	No	No
Local regulations	REC should include women (R1 and R2).	No	Membership must include women (R1).	No	No
Practice	Chair looks for women to succeed departing members (R1), representative body intends to recruit women (R2).	Women must be included in reproduction working group—1 of 6 working groups (R1)	Committee must include both men and women in as representative a manner as possible (R1), not much emphasis on recruiting both sexes (R2).	At least one woman in the committee, following Food and Drug Administration rules; departing person seeks successor of same sex and expertise (R1).	Include both women and men in context of general endeavour to ensure equal opportunity (R1).
Actual composition: No of. women/total (%)	R1, 4/16 (25%) R2, 21/83 (25%)	R1, 17/41 (41%) R2, 5/19 (26%)	R1, 1/6 (17%) R2, 4/12 (33%)	R1, 4/12 (33%) R2, 5/14 (36%)	R1, 7/22 (32%) R2, 2/14 (14%)

REC, research ethic committee.
Findings for selected RECs in five European countries in 2003.
R1 and R2 refer to the two RECs in each country.

Table 3 Gender equality in protocol evaluation as laid down in legal and other documents and as observed in practice

	Country				
	Austria	**Germany**	**Ireland**	**The Netherlands**	**Sweden**
National or regional laws and regulations	Pregnancy testing before start of study obligatory for women of childbearing age in drug trials.	No	No	No	No
National guidelines and manuals	No such document exists.	No such document exists.	No	Use of contraceptives prescribed when necessary; gender considered as a feature of study population.†	Exclusion of certain groups of women; inclusion of both sexes to enable investigation specific problems.‡
Local regulations	No	No	Use of contraceptives prescribed when necessary for women of childbearing age	No	No
Review tools	No	No	Inclusion of women of childbearing age or pregnant women (application form; R1 and R2).*	No	No
Review practice	Special attention given to pregnancy-related risks for women and inclusion of women in study population (R2).	Special attention given to women in drug studies.	Women of childbearing potential are considered as a vulnerable population.	Women given special consideration in drug studies; when one sex is excluded or different criteria set for male and female participants, researcher must justify decision (R2).	Women given special consideration in drug studies; inclusion of both sexes, gender-specific risk–benefit analysis, and other aspects of design; information to patients (R1 and R2).§

Findings for selected RECs in five European countries in 2003.

R1 and R2 refer to the two RECs in each country.

*Ireland R2: application form asks for the following information: scientific justification, negative teratogenic studies, have subjects been warned that the fetus may be damaged, initial negative pregnancy test, recommended forms of contraception to be taken until the drug is cleared from the system, have those unlikely to follow contraceptive advice been excluded, have subjects been asked to notify investigator if pregnancy is suspected.

†The Netherlands Central Committee Manual: gender is mentioned as a characteristic of the study population. As such it needs to be taken into account in the selection criteria for the research population and when looking at risks and burden for the selected research population.

‡Sweden medical research council guidelines: choice of study participants (risk of negative discrimination of certain groups such as pregnant women or women in menopause) and principle of justice (both sexes must have the possibility of participating in research projects so their specific problems will receive attention).

§Sweden R1: screens research protocols for unfair exclusion of one of the sexes; expressions in the information leaflets for possible participants that are offensive to women or to men. Sweden R2: attention to gender aspects in all steps of the review: information to patients, research questions and study design, the population, ethical principals, risk–benefit analysis.

population as long as there are no potential harms. Furthermore, none of the committees had rules or review tools that require them to evaluate whether the potential benefits and risks associated with the study are equitably distributed across male and female participants.

Nevertheless, the informants from both Swedish committees stated that their committees often pay attention to gender-specific issues in the actual review process, even apart from the matter of participant inclusion. One committee also carries out an analysis of the potential benefits and risks of participation in the study for both sexes (see footnote §, table 3). In the other countries, some informants state that their committees pay some attention to the inclusion of both sexes in the study population or other aspects related to a study participant's sex (Austria R2, The Netherlands R2 in table 3).

DISCUSSION

In this study, we have explored how attention to gender equality was incorporated in the work of RECs in five European countries by considering the composition of these committees and the evaluation procedures they used. Overall, our results show that in 2003, ethical review committees paid only limited attention to gender equality in their method of working. Although it is considered important to have women on the committee, this is often not formalised in rules and regulations, and no attempts are made to have gender expertise on the committee. The main reason given for paying specific attention to female study participants in protocol evaluation is the ethical principle that pregnant women or women of childbearing age should be excluded from studies to protect unborn children from potential harm. An evaluation of equitable inclusion of women and men in studies is required neither in regulations nor in tools supporting ethical assessment procedures. This is also true for gender-specific analysis of risks and benefits associated with study participation. Only in Sweden do the national guidelines provide clear directions on these matters; the Swedish committees also paid the most attention to gender-related issues in their daily practice.

Our study was explorative in nature and we mapped the practices of only two RECs in each country by interviewing one representative from each committee. We selected our informants mainly on the basis of their knowledge of ethical review practices and of their country's ethical review system. We are confident that this procedure gives a reasonably accurate impression of how laws, regulations and tools that govern RECs deal with gender equality issues. A larger study group may have thrown more light on informal approaches to gender equality in ethical review procedures.

Some changes have taken place since we collected our data in 2003. A new law on the ethical review of biomedical research has come into force in Sweden. This law requires RECs to strive for equal representation of women and men in the committee once the criteria for expertise have been met. It also stipulates that study protocols must be evaluated for inclusion of both sexes, but does not demand attention to further sex and gender issues.[28] The German Pharmaceutical Drug Law, which structures the work of RECs, has recently been modified. One of the changes is that RECs must now consider the need for adequate participation of men and women in clinical studies.[29]

Despite the existence of a European policy on gender equality in health research funded by the EU, this policy is not reflected in the recently adopted EU directive on clinical research. The directive does not include recommendations on how to enhance gender equality in either the composition of the committee or protocol evaluation. Our study suggests that a policy on research ethics is needed to make attention to gender equality structural in the work of RECs, similar to policies that have been introduced in the US and in several other countries.[17 20–23]

In our opinion, the EU Directive on clinical research should also include provisions to enhance gender equality in ethical review of clinical research—both by encouraging equitable representation of men and women in RECs and by demanding that protocol evaluation should be more sensitive to gender-specific health needs and other possible sex and gender-specific differences. As a first step towards this, the EU Directorate for Research should initiate a debate among the relevant stakeholders in the disciplines of clinical research, research ethics and research policy to discuss the ramifications of greater attention to sex and gender in research content and ethical review, against the background of the need for equitable inclusion and equitable distribution of benefits and risks associated with study participation. Guidelines from other countries[17 20–23] and scholarly literature on the ethical review of clinical research[18 19] as well as literature on gender-sensitive research methods and practices[8 10 12 30 31] may serve as background information in this debate. It would be useful to organise similar debates in each member state. A concrete example of how RECs can pay attention to gender equality in protocol evaluation is the set of questions developed by the Liverpool School of Tropical Hygiene to ensure that gender issues are considered in clinical trials.[32]

Any improvement in the policy of the EU on ethical review of clinical research resulting from such debates must then be translated by each member state in its national or regional legislation and policies governing the working methods of local RECs. The application form for ethical review can also be an important means of focusing attention on gender equality in medical research and protocol evaluation, by requiring researchers to provide sex-specific and gender-specific data.

Furthermore, it is important to develop strategies to enhance the knowledge of REC members on how sex and gender affect health, and how these issues can be included in the design and conduct of clinical studies and the ethical assessment of study protocols. So far, only a few countries have a training system for REC members. Gender issues should be dealt with in these training systems, and the EU should help countries that do not have such training services for REC members to develop them. More work is also needed to encourage women to become members of RECs.

It should not be forgotten, however, that the ultimate objective is not to bring about policy changes but to improve the participation of women in health research both as evaluators and as study participants, and to ensure that those responsible for the design of research projects are more aware of the need to take sex and gender issues on board when considering the composition of study groups and research objectives.

Much work remains to be done to explore the content in human terms of gender equity in clinical research and to consolidate policy in this discipline. We believe, however, that our study helps in laying a solid foundation for future research in these directions.

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