

Session reports: Session 1.4: Medicines Regulation and Medical Education

Chairs

Hildrun Sundseth (European Institute of Women's Health [EIWH], Belgium) and **Petra Verdonk** (VU University Medical Center, Netherlands)

Discussants

Medicines Regulation

Thorsten Vetter (European Medicines Agency, United Kingdom), **Marco Stramba-Badiale** (IRCCS Istituto Auxologico Italiano, Italy), **Ingrid Klingmann** (European Forum for Good Clinical Practice [EFGCP], Belgium), **Christiane Druml** (Medical University of Vienna, Austria)

Medical Education

Katrín Fjeldsted (Standing Committee of European Doctors [CPME], Iceland), **Margarete Hochleitner** (Medical University Innsbruck, Austria), **Ute Seeland** (Charité - Universitätsmedizin Berlin Germany), **Kristina Mickeviciute** (European Medical Students Association, Lithuania)

Rapporteur: **Kristin Semancik** (European Institute of Women's Health, Ireland)

Context

Medicines Regulation

Thorsten Vetter presented the European Medicines Agency's (EMA) marketing authorisation procedures. He explained that in the past Phase I/II registration trials were comprised of mainly healthy males 18-35 years old. US Food and Drug Administration (FDA) guidelines of 1977 excluded premenopausal women from early phase clinical trials; the trial population was therefore not very representative. In the 1990s young women were excluded from HIV trials, so the FDA took steps to facilitate their inclusion. With regard to EMA Marketing Authorisation, the percentage of patients by sex who participated in pivotal clinical studies for the authorisation of new medicinal products tended to reflect the prevalence of the disease in men and women. Analysis of all products, which received marketing authorisation in the EU between January 2000 and December 2003 showed that there seemed to be no or only negligible gender bias. However, there was an under-representation of women in hypertension and diabetes trials, while there was an over-representation of women in rheumatoid arthritis and allergy trials. Importantly a FDA report published in August 2013 on the collection, analysis, and availability of demographic subgroup data analysing all applications approved by the Center of Drug Evaluation and Research during 2011 suggests that the percentage of patients by sex who participated in clinical studies tended to reflect the prevalence of the disease in men and women. As most if not all of these applications draw on data from global development programmes, these data can be assumed to closely reflect the situation in Europe.

Thorsten Vetter stated that a possible underrepresentation of women in clinical trials might occur for various reasons. Possibly, many of the cited studies are not registration/confirmatory trials. Women may be more difficult to recruit and retain due to reasons such as family/carer role, different risk perception from men, recruitment/cohort issues (particularly in USA where many trials are done through veterans health administration, Medicare access, with bias toward male populations). The vulnerability mind-set seems to still prevail among investigators; legitimate protection needs to be balanced with possible collection of important data in women. Powered subgroup analysis require increased sample size; improved morbidity/mortality in many important disease areas (e.g. cardiovascular) translate into decreased event rates requiring increased sample sizes in outcome trials which could allow for a broadened data base with a view to sex/gender. However feasibility is clearly

an important challenge. The New Clinical Trials Regulation to enter into force in 2016 takes into account both age and gender.

Marco Stramba-Badiale discussed how gender differences in the clinical presentation of cardiovascular diseases (CVD) have been demonstrated and some therapeutic options may not be equally effective and safe in men and women. Furthermore, sex differences in pharmacokinetics, pharmacodynamics and physiology may contribute to a different response to cardiovascular drugs in women when compared with men. Women, for many years, have been underrepresented in randomized clinical trials for CVD. The majority of therapeutic interventions were tested for safety and efficacy in male populations. He cited some reasons: the lower occurrence of outcomes in females may affect the costs of the study; the reluctance of women to be enrolled, due to their misperception of risk of CVD; and difficulties in terms of transportation or support for the follow-up visits for women.

Ingrid Klingmann explained that 100% of humankind is affected by pregnancy, but there is almost no guidance on women who become pregnant during a trial. Women are underrepresented in clinical trials, especially in the early stages. Most medicines are contraindicated during pregnancy. Clinical trials have become ultraconservative, and yet 90% of pregnant women actually use medicines. There are hardly any clinical trials in pregnant women and other ways of systematic data collection about medicines in pregnancy are not established. The different provisions in the new Clinical Trials Regulation will encourage the performance of clinical trials in and for pregnant women.

Medical Education

Petra Verdonk (VU University Medical Center) defined the context of gender medicine in medical education. She explained how S&G are hardly integrated in medical education, taking a “bikini model” that mainly focuses on reproductive health. Beyond reproduction, S&G in education mainly focuses on “established knowledge” like cardiology, rarely teaching gender issues such as partner violence. A large issue is that many different bodies are involved in medical education at multiple levels, such as governments, physician associations, local universities, etc. Although the Bologna Declaration aims towards more harmonisation in both undergraduate and graduate programmes across countries, but it is mostly focused on workforce mobility, comparability of degrees and not uniformity of teaching. When S&G is integrated into medical education, there are different approaches: single courses (sometimes electives), or integrated (mainstreaming throughout the curriculum).

Katrín Fjeldsted explained that high quality education and training is fundamental for high quality healthcare. Professional knowledge, skills and competences must be updated continuously. Education and training at all levels must respect ethical codes and enshrine up-to-date evidence-base for practice and treatment. There is a moral and ethical obligation to counteract avoidable health inequalities, which can be caused by a variety of factors, including gender. Historically, there has been a male-bias in medical education and training that needs to be corrected. CPME needs assistance from experts to better incorporate S&G into their activities.

Kristina Mickeviciute explained that medical students are well trained in individualized and patient-centered medical care, however they are not trained in the concept of S&G influences on the health and well being of patients. She argued that if we are looking for better health care, we should start with integrating S&G into medical education. The way tomorrow’s physician is trained, will define the quality of the health care in the very near future.

Examples of best practice/existing gaps

Medicines Regulation

Thorsten Vetter identified knowledge gaps in three critical groups: older women, who comprise the majority of older, multi-morbid patients, which the EMA Geriatric Medicines Strategy is addressing; a strategy for pregnant and lactating women, the vulnerable subject is the embryo/foetus/baby (e.g. IMI PROTECT is investigating new methodologies to obtain large sets of observational data in pregnant women); and sex-genetically linked issues, which require sufficient sample size for detection, and personalised medicine initiatives.

Marco Stramba-Badiale discussed the European Heart Health Strategy under the EuroHeart Project, which included a work package on women and CVD. It aimed to address the issue of gender representation in CVD research by collecting information on clinical trials and registries in Europe and identifying potential gender differences in the primary outcomes of clinical trials, as well as in the current clinical practice and in the Guidelines of European Scientific Societies.

Christiane Druml stated that the Ethics Committee of the Medical University of Vienna has issued guidelines for the inclusion of women in clinical research projects already in 2004. Furthermore, the Austrian Bioethics Commission is considering gender aspects as a crossover issue in all its decisions and in 2008 has published a recommendation with gender reference for Ethics Committees and Clinical Studies. Also In 2008, the Italian National Bioethics Committee published its recommendations, "Pharmacological trials on women."

Medical Education

Petra Verdonk gave examples of initiatives that integrate S&G into medical education at local, national, European levels including Umea in Sweden, Charité Berlin, Innsbruck, a Dutch nation-wide project, and the EUGiM EU-project. She stated that education materials and textbooks existing in the Netherlands, for example, were hard to transfer from curriculum to curriculum even within one country.

Petra Verdonk cited various difficulties to integrating S&G into medical education including: resources and money; political support, including from deans, directors; a lack of S&G experts in every medical school; open-minded faculty; the presence of local change agents to own issues; and the time-consuming nature of changing curriculum. Sustainability is also an issue—once S&G is into programmes, it is frequently removed during the next reform.

Margarete Hochleitner reported on gender medicine being incorporated into the medical curricula at Innsbruck Medical University. She outlined the compulsory and elective lectures in the field of gender medicine at her university. Through a series of classes, courses, modules, the university trains future doctors and researchers systematically in the field of Gender Medicine. These classes are compulsory. Gender Medicines is also incorporated into other school curriculum like nursing. It is also included in all examinations. Other tools, like posters about gender medicine courses, are distributed to clinics and institutes to reach out to a wide circle of medical doctors.

Ute Seeland discussed how the EUGiM-based curriculum has been implemented as an elective module into the Master Program Health & Society of the Berlin School of Public Health. There has been a systematic integration of S&G aspects throughout the medical curriculum at the Charité-Berlin. Gender-specific courses or courses with integrated S&G aspects are compulsory for all students and assessed in the examinations.

Steps for action

Suggested strategic approaches to improve implementation of S&G

Medicines Regulation

Marco Stramba-Badiale recommended that preventative and therapeutic interventions should be tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk. Clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis should be conducted, especially in the fields of ischemic heart disease, cholesterol-lowering therapy and heart failure. Enrollment criteria and follow-up duration should allow the inclusion of women at risk of developing cardiac events. A minimum enrollment for women should be ensured (e.g., maintain open enrollment for women until pre-specified proportion is reached). External barriers to the enrollment of women in clinical trials need to be addressed, and in particular transportation difficulties for follow-up visits. Regulatory agencies must be urged to adopt strict rules on the inclusion of women in clinical trials and a systematic gender analysis.

Ingrid Klingmann explained that 100% of humankind is affected by pregnancy, but there is almost no guidance on how to best protect women who become pregnant during a trial. Women are underrepresented in clinical trials, especially in the early trial stages. Most medicines are contraindicated during pregnancy, yet 90% of pregnant women actually use medicines. There are hardly any clinical trials in pregnant women and other ways of systematic data collection about medicines in pregnancy are not established. The new provisions in the upcoming Clinical Trials Regulation on benefit-risk assessment, informed consent process, patient and embryo protection as well as use of data in pregnancy situations in clinical trials will encourage the performance of clinical trials in and for pregnant women.

Christiane Druml stated that national advisory bodies, like Bioethics Committees, should strive to include gender issues to raise awareness on a national level.

Medical Education

Petra Verdonk suggested that with regard to medical education, S&G must be included in final objectives of programmes, as part of accreditation, in quality criteria and considered by visitation committees. Experts much work with those in power on boards, Ministers of Health, Ministers of Education, alliances with deans and directors of schools, student organisations, patient organisations and presidents of physician associations to integrate S&G into medical education and training.

Katrín Fjeldsted asked for guidance from S&G experts to help organisations, such as CPME, to integrate S&G into education, training and development, but do not know where to start. **Kristina Mickeviciute**, encouraged the EUGenMed to work with medical students and their associations as many training doctors are willing and eager to incorporate S&G into their practice in order to be better doctors.

Ute Seeland recommended that gender-specific courses should be required in medical training for all students. A list of teachers should be assembled to increase quality standards. She stated that eLearning is the future; “eGender Medicine” is a flexible tool to spread S&G knowledge in Europe providing eLearning material for eight internal disciplines.

Summarizing the discussions, **Hildrun Sundseth** stated that the new EU Clinical Trials legislation entering into force in 2016 would require women and older people to be included in clinical trials. Also it contains provisions for clinical trials in pregnant women. As this is now a legal requirement, EUGenMed has an opportunity to provide useful guidance how the regulatory process could be improved to take S&G considerations into account. She stressed the importance that results of the EUGenMED research feed into the implementation guidelines for the new legislation to improve medicines treatment for both men and women, and ensure that this knowledge is also included in the training of the medical professions to the benefit of male and female patients and society in general.

Tentative implications for workshop planning

- Topics: medicines regulation and medical education need to be split into two separate sessions for the workshop due to the unique nature of each topic.
- Special audiences to be invited: regulatory agencies, government officials, academics, university deans and directors, journalists, media, patient organisations, Research foundations and Institutes, doctor organisations, medical student organisation, other medical professional organisations, hospital and nurses associations, academics, industry, clinical trials research organisations, ethics committees, Innovative Medicines Initiative, EUPATI (European Patients Academy)
- Specific strategies for communication: write briefing document, reviews in scientific journals, suggestions for guidelines to include S&G in medical school education, provide S&G input for new Clinical Trials Regulation
- Satisfy specific needs of roadmap (discussion ongoing)
- Date and location: February 2015 in Brussels, Belgium (TBC)
- Chairs: **Hildrun Sundseth** (European Institute of Women's Health) and **Petra Verdonk** (VU University Medical Center)