

European Gender Medicine Network - EUGenMed

Roadmap for implementation of sex and gender into biomedicine and health research in Europe

The overall objective of EUGenMed is to improve the health of European citizens, women and men, by improving biomedical and health research through a sex and gender (S&G) sensitive approach. For this purpose we will develop a Roadmap to implement sex and gender into European biomedicine and health research. The Roadmap is the main output of the EUGenMed Project.

Definition – the Roadmap

The Roadmap includes all steps of the EUGenMed project, all materials that were discussed and generated during the project in a true spirit of openness, transparency and inclusiveness and a number of suggested implementation steps that shall take place after finishing the project. The core element of the Roadmap is a comprehensive document that summarizes the findings of four workshops in a precise and coherent manner with a number of appendixes in different formats (flyers, ppt sets), as well as recommendations for implementation of sex and gender aspects in biomedicine and health research for different target audiences.

The Roadmap was developed in four workshops, in specific areas that were chosen in a complementary manner to cover important fields in biomedicine and health research: clinical medicine and pharmacology, public health and prevention, basic research, medicines regulation and medical education. The workshop (WS) themes were developed in such a way as to support each other. However, WS documents will be written so that they can be used and understood on their own. They will be made available to the target groups/stakeholders soon after the conference. The entire Roadmap with supporting materials will be published at the EUGenMed website (www.eugenmed.eu).

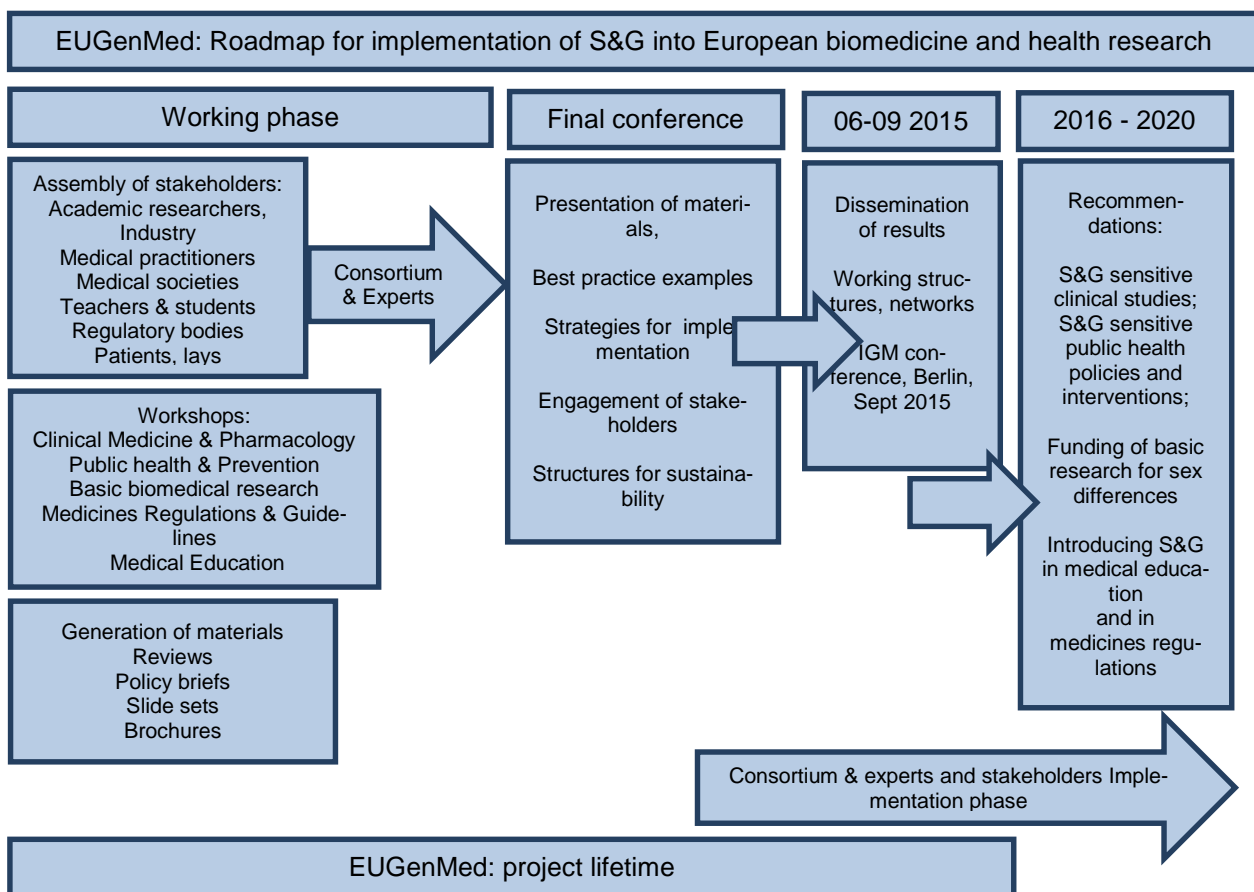


Fig 1: EUGenMed project roadmap

Overview on the EUGenMed steps leading to the elements of roadmap:

- **Assembly of Stakeholders and Target audiences, communication structure, networks**

Stakeholders in Gender Medicine or target audiences for our measures have been assembled by systematic searches and a large number of them has been involved in the kick-off conference and the four workshops: medical doctors and (bio) medical societies, researchers, teachers and students in academia, industry, pharmaceutical companies, science funding organizations, regulatory bodies, health policy makers, patient organisations, representatives of civil society and lay people.

Developing a roadmap strategy at the kick-off conference:

At the kick-off meeting we agreed a strategy with definition of focal areas of work, materials to be generated and target audiences. We defined our main working fields: clinical medicine and pharmacology, public health and prevention, basic biomedical research, medicines regulations and medical education and organized workshops in these fields.

- **Generation of Roadmap materials in four workshops (see appendix)**

The generation of roadmap materials, timelines and measures for implementation of sex and gender aspects in biomedicine and health research for different target audiences took place in four workshops. We choose cardiovascular diseases (CVD) as a topic for an overarching case study and it was therefore covered in all four workshops. As a result, publications will include

S&G differences in clinical CVD and in its treatment (WS 1), in its risk factors (WS 2), its pathophysiological bases (WS 3), in medicines regulations and in medical school teaching (WS 4). The WS outputs, available from our home page in form of reports, slide sets and policy briefs, will be presented and discussed at the final conference (see appendix) and will be published as papers.

- **Goals of the final conference**

The final EUGenMed conference will present the Roadmap and its different steps to the stakeholders, present the workshop findings and recommendations and discuss how we can all work together and with wider stakeholder groups to realize the EUGenMed goals after the project has finished.

- **Engagement of stakeholders**

We will engage stakeholders in the process of further communication and dissemination of results to reach our objectives agreed at the Kick-off conference. All stakeholders will be encouraged to take the recommendations forward in their field of action.

- **Structures for sustainability**

The project outline of EUGenMed asked for creating structures that will allow for sustainability of the project after the end of funding. We shall set up a working group that has the potential to generate new funding opportunities and continue to realize the recommendations of the roadmap. In the initial project we envisaged a European Gender Medicine Network, as the successor of EUGenMed. We will propose a structure to continue the EUGenMed work and involve an even wider groups of stakeholders.

- **Future steps towards implementation**

Continuation of group meetings and meetings with wider stakeholders in structures to be defined and ensure further publications, updated information and dissemination of papers, policy briefs, factsheets.

Providing free access to materials for dissemination and communication of gender aspects to others, including slide sets via homepage.

Inclusion of gender knowledge into medical teaching in as many institutions as possible by providing learning materials/modules for this purpose.

Cooperation with industry to include research for sex differences into their research and development.

Discussion with funding agencies to include sex and gender into their research calls.

Discussion with European agencies and institutions to include sex and gender into their guidelines and programs.

Appendix: Main workshop results

WS 1: Sex and gender in clinical medicine and pharmacology

Strategy

The EUGenMed WS 1.1 workshop group assembled 20 experts that have made significant contributions to the field of clinical gender medicine. They were identified in our kick-off conference and selected based on their previous contributions in the field and in order to cover a broad spectrum of topics of work and nationalities. The group acknowledged in intense discussions that in many diseases well-described differences in etiologies and clinical presentation exist between women and men. However, this knowledge is dispersed and incompletely translated into clinical practice and research programs. The highest density of evidence based knowledge is available for cardiovascular diseases (CVD). The EUGenMed WS 1.1 groups therefore decided to focus first on CVD and to summarize the gender related findings from the other disciplines under a different aspect.

Results

We briefly summarized our major findings related to CVD: Ischemic heart disease in the presence of non-obstructed epicardial coronary arteries is more common in women than in men. Diagnostic algorithms for coronary artery disease (CAD) that perform well in men are less suitable for low and median risk middle-aged women. Tako tsubo syndrome and spontaneous coronary artery dissection endanger predominantly women and may be related to hormonal changes. Remodelling in myocardial hypertrophy and HF differs in women and men, with more concentric hypertrophy and less fibrosis in women. Women have unique biological life events, menopause, pregnancy, breastfeeding which may alter their risk of CVD and response to therapies.

Sex differences in pharmacology is a major issue. Sex differences in pharmacokinetics determine bioavailability of CV drugs. Sex differences in pharmacodynamics may be based, among other factors, on sex specific ion channel expression and regulation. Even so a number of differences are well known they are incompletely integrated into drug development and testing.

The group contributed to five policy briefs that are coordinated by the European Institute of Women's Health (EIWH). We suggested inclusion of some the facts listed above for CVD in a more general manner, e.g. stroke occurs more frequently and with a different pathophysiology in women, diabetes is a more severe risk factor for CVD in women than in men, that asthma and lung cancer have different risk factors and manifestations in women and men.

In conclusion, we provided evidence that a more stringent consideration of S&G differences in CVD will lead to better understanding of pathophysiology and more personalized therapeutic approaches. We provide data suggesting that gender specific mechanisms play a role in many other diseases than CVD and just need more gender sensitive analysis.

Workshop outcomes and further steps towards implementation

The participants recognized the necessity to communicate their knowledge to a broader scientific community, to present findings at congresses, to publish summaries, to present knowledge to medical societies and be included in their guidelines and to include knowledge to medical students and health care professionals in a structured manner. As a consequence, they decided to publish 2 papers and to contribute to the *eGender learning* programme that is built for medical students and HC professionals. Sessions were submitted and accepted for the ESC congress London 2015. Furthermore, cardiovascular disease was integrated into the IGM congress September 2015 in Berlin. Next steps may be submission of sessions to OSSD congress 2016 and ESC 2016.

- Publication: Gender in CVD, V. Regitz-Zagrosek et al, submitted
- Publication: Transdisciplinary criteria for the inclusion of sex and gender into diagnostic algorithms, Oertelt Prigione et al, in preparation
- Contributions to ESC meeting 2015 London; 3 sessions with gender topics in clinical field
- Planning sessions at congress of the International Society for Gender Medicine in Berlin, Sept 2015 (www.igmcongress.com/)
- Submitting sessions with cardiovascular gender topics for OSSD 2016, DGK 2016, ESC 2016
- Contributions to 5 policy briefs on CVD, Stroke, Diabetes, Asthma and Lung Cancer

WS 2: Sex and gender in public health and prevention

Strategy

In accordance with the general structure of the project, WS 2 was also designed to include the largest possible number of stakeholders in the field. This appears most significant for the field of public health, which includes practitioners from diverse backgrounds, and fields of activity. Hence, a significant additional effort was made to identify and invite experts beyond the participants of the kick-off conference. The WS included 22 participants covering all stakeholder areas (researchers, policy-makers, politicians, advocacy groups, funding bodies, WHO and European Commission representatives, media and communication actors).

The workshop was then structured into two main blocks, one on knowledge, where available but frequently unstructured information was to be assembled and one on implementation, where diverse experiences and expectations were summarized and analyzed to produce a systematic catalogue of practical steps for the use in different public health domains. Furthermore, the process of generating this knowledge and 'doing gender medicine' was also analyzed, paying particular attention to the ways in which sex and gender are redefined in this process.

Results

Non-Communicable Diseases (NCDs) such as cardiovascular diseases (CVD), cancers, chronic respiratory diseases and diabetes, are a major global health concern and the leading cause of premature death (more than 40% of them occurring before the age of 70 years) and disease burden, both worldwide and in Europe. Modifiable risk factors, such as tobacco smoking, unhealthy diet, physical inactivity and alcohol use contribute to the majority of NCDs. Adopting an integrative approach to health and a broad understanding of risk factors, we chose to not only focus on these modifiable risk factors, but also on mental health due to its strong relations with NCDs, on obesity insofar as it is both a condition and a risk factor, and on work which is both a protective and a risk factor. Addressing highly prevalent and relevant NCD risk factors is a significant public health and primary prevention topic, relevant for a large range of conditions. Gender-sensitive interventions are likely to contribute to an increased efficiency of interventions.

For women and men, most NCD risk factors show distinct associations with NCDs, such as with CVD, and population attributable risks differ considerably for men and women. Furthermore, from a life course perspective, first manifestations of cardiovascular diseases differ in men and women, with men being more likely to develop coronary heart disease as a first event, while women are more likely to have cerebrovascular disease or heart failure as their first event, which may be explained partly by a different lifetime pattern of risk factors.

Risk factors have to be conceptualised as influenced by factors intersecting with sex and gender, relating them to culturally driven gender norms, socio-economic position, behavioural factors, genetic make-up, levels of susceptibility, exposure time to risk factors, differences in knowledge and risk perceptions, access to health care and health care seeking patterns, health systems responses (control and management).

Major publications, even when displaying detailed sex-specific data, do not address sex and gender aspects, and there is a paucity of sex- and gender-specific recommendations for prevention. Likewise, although a number of gender sensitive Public Health Policies have been developed and implemented in the last two decades (WHO, 2012; UN General Assembly, 1997), research on impact and efficiency of such approaches and on risk factor control and management is very scarce and there is a lack of critical discussion on methodology of gender-sensitised interventions.

The workshop brought together the best evidence concerning sex and gender aspects of NCD risk factors, identified examples of effective interventions, pointed out current research gaps and formulated steps for implementation in public health practice that will be discussed with stakeholders.

Workshop outcomes and further steps towards implementation

Within the WSs the need for differentiated approaches to implementation was emphasized and all stakeholders agreed upon the need for a concerted systemic and multi-level approach. Significant current hurdles are represented by an insufficient coordination between research, politics and organizations hampering concerted actions on well-defined priorities within the field of sex and gender research and practice. Based on written and oral feedback from all involved stakeholders, structured steps for the implementation at different process levels are being assembled in order to initiate, advance or finalize the implementation of gender-sensitive policy and practice in public health.

- Publication: Sex and gender aspects of risk factors for non-communicable diseases across Europe, V. Elisabeth Zemp-Stutz, Ineke Klinge et al, in preparation
- Publication: Doing gender medicine: Reflections on sex and gender in medicine and public health, Lucie Dalibert, in preparation
- Publication: Implementation steps towards gender-sensitive policy and practice, Sabine Oertelt-Prigione, in preparation
- Planning sessions at congress of the International Society for Gender Medicine in Berlin, Sept 2015 (www.igmcongress.com/)
- Submitting abstracts to Gender Summit 2015, EUPHA 2016 and EASST 2016.

WS 3: Sex differences in basic research

Strategy

The EUGenMed WS 1.3 workshop group assembled 20 experts that have made significant contributions to the field of sex differences in basic research and were identified in our kick-off conference, with the aim to assure of broad coverage of different topics and views from different European nations. The group acknowledged in intense discussions that in a large number of animal models and most cell culture systems, significant differences exist between male and female cells and animals. However, this knowledge is dispersed and incompletely translated into research programs and methodological difficulties hamper the progress. The group decided to develop concepts at 3 levels: improvement of knowledge, in methodology, and networking.

Results

With the consideration of sex differences in cells, tissues and organs basic research has reached an exciting new dimension. The individual clinical care of patients can only be as good as the knowledge brought up by basic research approaches which deal consciously with sex differences at genetic and molecular levels. Both the differences between the sexes and the alterations that arise with age are of great importance for a society with increasing life expectancy. On the other hand, determinants affecting the unborn child are of particular importance for basic researchers. An enormous number of questions regarding sex differences remain unanswered. Two main research questions are central: The first is about the contributions of sex chromosomes and sex hormones on sex differences in cellular function and the second deals with periods of susceptibility for cardiovascular risk factors.

Basic research feeds directly into drug development. CV drug development is getting more and more difficult and costly. We need new approaches to replace the "one size fits all" model by targeted, sex specific approaches that will lead to an improved and S&G sensitive understanding.

The WS discussed possible underlying mechanisms like the interaction between sex chromosomes and sex hormones with respect to sex differences in gene regulation depending on genetic variants and epigenetic processes. Examples for translational approaches were mentioned like the development of anti-arrhythmic drugs based on proteomic results concerning sex differences of ion channel expression leading to arrhythmias. Furthermore participants made reference to the progress in developing modified estrogen receptor drugs (SERMs) and the sex specific effects of PDE 5 inhibitors.

The discussants agreed that methodology is a major issue. They discussed the use of primary cells and cell lines of both sexes for in vitro experiments, use of animals of both sexes in disease models, transgene- or knock-out animal models genetically unique to sex, use the four core genotype (FCG) mice to provide insights into the action of sex chromosomes and perform micro array sequencing, RNA sequencing and GWAS with respect to both sexes.

The group discussed basic research aspects that could play a role in CVD, stroke, diabetes and lung cancer and contributed them as open needs for further research to the policy briefs.

Workshop outcomes and further steps towards implementation

The participants recognized the necessity to communicate their knowledge to a broader scientific community, to present findings at congresses, to publish summaries and to enter knowledge into guidelines. The vision is to act together with the International Society of Gender Medicine (IGM), the Canadian Heart Research Centre (CHRC) and the American Organization for the Study of Sex Differences (OSSD). S&G should be integrated in basic research projects, as in RADOX. The group decided to publish a review paper S&G specific data and methods in basic research. In the preparatory phase, sessions were submitted to the European Society of Cardiology (ESC) congress and 1 session with gender specific basic research topics will be held at ESC in London. Furthermore, sex differences in basic research were integrated into the IGM congress September 2015 in Berlin. Next steps may be submission of sessions to OSSD congress 2016 and the basic research congresses of ESC 2016 and AHA (BCVS).

- Publication: Gender in Basic research, V Regitz-Zagrosek et al in preparation
- Contributions to ESC meeting 2015 London; a sessions with basic research gender topics
- Planning sessions at congress of the International Society for Gender Medicine in Berlin, Sept 2015 (www.igmcongress.com/): epigenetic mechanisms in sex differences, sex differences in cells,
- Submitting sessions with basic research topics for OSSD 2016, IGM 2017
- Contributions to 5 policy briefs on CVD, Stroke, Diabetes, Asthma and lung cancer

WS 4a: Medical Education

Strategy

The EUGenMed workshop 4a and 4b brought together over 40 experts from a broad range of stakeholders: representatives from the regulatory body, the European Medicines Agency; national Ethics committees; European Good Clinical Practice organisation; Commission officials; healthcare professionals in various disciplines from the European and national level; patient organisations, academics and researchers in education and communication; and the pharmaceutical industry.

Results

The Workshop 4a acknowledged that over the last 10 years the importance of sex and gender in medical research and treatment of medical conditions has been increasingly recognised. However, the need for integration of this knowledge into medical education curriculum still remains a challenge. Acknowledging the impact of sex and gender differences, increases the quality of health care provision. A patient-centred evidence-based sex and gender perspective is required throughout medical curricula including graduate programmes, medical programmes, nursing, rehabilitation, and pharmacy, continuing medical education and continuing nursing education across Europe.

Cardiovascular disease (CVD): Traditionally regarded as a male disease, CVD is the number one killer of women worldwide. The risk of CVD in women is still often underestimated in the medical community and in women themselves. Incorporating information generated from the growing discipline of sex and gender based medicine in educational and training programmes improves access to high quality health care and thereby will improve patient outcomes.

The regulation of medical education in Europe is the responsibility of individual Member States not the European Union (EU). The European Commission has passed legislation relevant to the medical community, such as the mutual recognition of professional qualifications, and is participating in a number of efforts to synchronize the education systems across Europe. However, detailed regulation as well as the assessment and evaluation of curricula remains the remit of individual Member States which has its own set of standards and regulations for medical education.

There is no direct mandate to coordinate medical education at an EU-level. However, most Member States collaborate in the Bologna Process and are bound by EU Directive 2005/36/EC to provide some form of regulation. The inclusion of vocabulary such as "socio-economic realities" and the "social surrounding of the human beings" in EU Directive 2005/36/EC highlights an existing awareness to combine the clinical component of medical education with social and cultural questions. Sex and gender and diversity awareness must be included in the dialogue.

There are different approaches to integrate sex and gender into medical education: single courses (sometimes electives) or integrated (mainstreaming throughout the curriculum) or both. Sex, gender and diversity must be included in final objectives of programmes, as part of accreditation, in quality criteria and considered by visitation committees. Consequently a multilevel approach is needed and experts must work with each other.

In the final Roadmap conference we will discuss with key stakeholders how best to integrate sex and gender into medical and health professional curricula. Recommendations from the workshop on medical education will be presented for discussion and agreement at the final EUGenMed conference.

Suggested next Steps

- Develop a policy paper on sex and gender in medical education. Generate accessible and inclusive publications.
- Set up a European stakeholder group on sex and gender in medical education.
- Educate teachers on the importance of integrating sex and gender into medical education. Encourage interactive education.
- Work with students to integrate sex and gender in medical education, improving medical education. Adjust curricula to improve content, focusing on well-being.
- Improve communication of the importance of sex and gender in medical education, expanding to a wide audience. Develop a clear definition of "medical education."
- Promote the diffusion of best practice of integrating sex and gender into medical education using evidence to improve patient outcomes.
- Hold a symposium on sex and gender in medical education

WS 4 b: Medicines Regulation

This Workshop discussed how to translate the scientific evidence from sex and gender research into regulatory practice. Information collected from experts in the different EUGenMed workshops suggests that translating the evidence from Sex and Gender research into regulatory practice will lead to more effective, safe and targeted medicines for all.

The Workshop identified gaps in robust analysis and available information how medicines work in women. There is a lack of data from the current medicines approval process on 50% of the population - women.

Ever since the Thalidomide tragedy in the late 1950s, there has been a reluctance to include women in clinical trials. The male body has been the norm. According to Health Canada *“The general assumption prevailed that women did not differ from men except where their reproductive organs were concerned and data obtained from clinical research involving men could simply be extrapolated to women.”*

Medicines are safer and more effective for everyone when clinical research includes diverse population groups of all ages. Even today, women are underrepresented in many clinical trials and if included, robust analysis is often lacking, a prime example is CVD. It is also known that women metabolize medicines differently; a recent concrete example is the sleeping pill Ambien. The US Food and Drug Administration (FDA) halved the dose for women, after the drug had been on the market for 20 years.

The new EU Clinical Trials Regulation No 536/2015 is a major step forward as it has amended the legal conditions under which clinical trials will have to be conducted in the future. As of its implementation date May 2016, the population groups for whom the medicines are intended must be included in the trial and, if certain groups have been excluded this must be justified.

Workshop outcomes and further steps towards implementation:

In the final Roadmap conference we will discuss with EMA representatives and other key stakeholders how to improve sex and gender analysis when the Agency implements the new Clinical Trials Regulation and will make this information publicly available on the EU Portal and Clinical Trial database.

Suggested next steps

- National Ethics committees to develop guidelines that require the inclusion of women in clinical research, utilising insights from the good practice example from the Medical University of Vienna.
- IMI-2 initiative to bring together researchers, pharmaceutical industry, the European Medicines Agency (EMA) and other key stakeholders to develop a robust methodology for subgroup analysis according to gender and age, addressing existing barriers to recruitment and retention of women and older people in clinical trials.
- EMA together with key stakeholders to draft guidelines for the analysis of sex and gender differences in clinical trials (examples Health Canada, FDA guidelines).
- EMA to follow FDA Snapshot initiative to make sex and age-specific data available and transparent
- For already existing medicines improve rigorous sex- and age-specific pharmacovigilance reporting.
- Request collection of post-marketing data for medicines use in pregnant women and develop common rules for pregnancy exposure registries.