Sex differences in health research and clinical guideline development
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Chapter 4

INTEGRATING A GENDER PERSPECTIVE INTO THE DEVELOPMENT OF CLINICAL GUIDELINES: A TRAINING COURSE FOR GUIDELINE DEVELOPERS

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Dutch guideline-developing organizations do not focus systematically on differences between men and women when developing guidelines, even though there is increasing evidence that being male or female may have an effect on health and health outcomes. In collaboration with two prominent Dutch guideline-developing organizations, we designed a training course to encourage systematic attention to sex differences in guideline development procedures.

The course is targeted towards guideline developers. Its aims are to improve awareness concerning the relevance of considering sex differences in the guideline development process, as well as the competence and skills necessary for putting this into practice. The design and teaching methods of the course are based on adult learning styles and principles of changing provider behaviour. It was adjusted to the working methods of guideline organizations. The course was taught to, and evaluated by, a group of staff members from two guideline organizations in the Netherlands.

The course consists of five modules, each of which corresponds to a key step in the guideline development process. The participants rated the training course positively on content, programme, and trainers. Their written comments suggest that the course met its objectives.

The training course is the first to address sex differences in guideline development. Results from the pilot test suggest that the course achieved its objectives. Because its modules and teaching methods of the course are widely transferable, the course could be useful for many organizations that are involved in developing guidelines. Follow-up studies are needed to assess the long-term effect of the course on the actions of guideline developers and its utility in other settings.
Chapter 4

INCORPORATING A GENDER PERSPECTIVE INTO THE DEVELOPMENT OF CLINICAL GUIDELINES: A TRAINING COURSE FOR GUIDELINE DEVELOPERS

BACKGROUND

Clinical-practice guidelines are important tools for improving patient care. They provide recommendations concerning optimal strategies for prevention, diagnosis, and treatment of specific clinical conditions. They are usually developed under the auspices of a guideline organization by a group of experts (which sometimes includes patients) representing a user group. Guideline organizations in many countries use a similar standard methodology for developing guidelines, including the following stages: formulation of key questions; formulation of a search strategy for locating relevant literature; critical appraisal of selected literature; and phrasing of recommendations for clinical practice. Quality criteria for the development of guidelines are formulated in the Appraisal of Guidelines, REsearch and Evaluation (AGREE) Instrument, which was designed by an international group of researchers and experts in guideline development. One criterion involves the target population of the guideline, which should be specifically described. The AGREE instrument mentions gender as one of the items that may be considered in such descriptions.

In the past, women were often underrepresented among the subjects participating in clinical health research, based on the belief that males and females have the same biology, except with regard to the reproductive system. In the 1980s, scientists and women’s health activists began to express concerns about this approach, as it could hamper an accurate understanding of the impact of biological sex factors or socially constructed gender factors on health and disease. Impeding this type of understanding could lead to less appropriate health care services for both sexes. Health research funding organizations in several countries responded to this situation by adapting their policies. For example, the US National Institutes of Health have required that men, women, and minorities should be adequately represented in clinical studies since 1993. In recent years, the number of published studies addressing sex and gender differences in aetiology, diagnosis, treatment, and prevention has increased considerably.
If quality of care for both women and men is to be improved, it is essential that the new body of evidence concerning sex and gender differences be taken into consideration when developing clinical guidelines. This conforms to the Global Platform of Action, which was adopted at the Fourth World Conference on Women in Beijing in 1995 and which is now being implemented through legislation in many countries across the world. Article 105 of the Treaty states the following: “In addressing inequalities in health status and unequal access to and inadequate health-care services for women and men, governments and other actors should promote an active and visible policy of mainstreaming a gender perspective in all policies and programs, so that, before decisions are taken, an analysis is made for women and men, respectively.”

In the Netherlands, two guideline organizations have longstanding experience with guideline development. The Dutch Institute for Healthcare Improvement (CBO) has been developing multidisciplinary guidelines since 1981, and the Dutch College of General Practitioners (NHG) has been developing guidelines for general practitioners since 1989. Both organizations use an internationally accepted methodology for developing guidelines; this methodology is reflected in the handbooks they have published.

A previous study, which examined the work of seven guideline working groups of the NHG and the CBO, revealed that these groups had paid little or no systematic attention to potentially relevant evidence on sex- and gender-related factors. This was reflected in the working methods that they used in the various stages of the guideline development process and in the final content of the guidelines. The study suggested several barriers to the systematic inclusion of evidence on sex-related and gender-related factors in the process of guideline development. These barriers are as follows:

1. The working groups were critical of the extensive evaluation of specific patient characteristics, as they aimed to develop recommendations for the general patient population.
2. The working groups lacked awareness that attention to sex-related or gender-related factors might improve the quality of guidelines.
3. The working groups also lacked competence regarding the identification and systematic evaluation of evidence on sex and gender differences, and the CBO and NHG handbooks for guideline developers lacked any comprehensive set of instructions on how to do this.

Based on the results of this study, both organizations decided to collaborate in a quality-improvement initiative to facilitate increased systematic attention to sex and gender differences during the guideline development process.

As an initial first step towards this end, we provided written recommendations for focusing on sex-specific evidence in the guideline development process, some of which were included in a new handbook for guideline developers published by CBO and NHG. Evidence from systematic reviews of professional behaviour change, however,
has shown that passive dissemination strategies (e.g., written information) are largely ineffective if they are not accompanied by more active approaches involving the target groups themselves (e.g., interactive educational approaches) 25, 26. The latter approaches are likely to be effective if they are used to challenge negative attitudes of professionals or to teach new skills 26.

For this reason, we designed a training course entitled ‘Attention to sex differences in guideline development’ for the staff members of CBO and NHG, who are charged with the task of providing methodological support to guideline working groups. This paper describes the course.

English language scientific literature commonly makes a theoretical distinction between the concepts of ‘sex’ and ‘gender’. The term ‘sex’ refers to biological and physiological characteristics that define men and women, while the term ‘gender’ refers to social characteristics that society attributes to the sexes. For example, gender affects the kind of health risks that men and women run and the type of health behaviours that they adopt or display 27. As is the case with many other languages, Dutch does not have two separate words for the concepts of sex and gender 28. In this article and in the description of the course, we therefore used the term ‘sex differences’ to designate differences between men and women. Details about the biological or social nature of these differences are provided only if they are relevant.

**Methods**

**Context**

The training course was developed by a psychologist and a librarian/trainer, two MD/epidemiologists and a social scientist, in close collaboration with the directors of the guideline development programmes of CBO and NHG. This group included experts in sex, gender, and health issues and in the methodology of guideline development.

**Aims**

The aim of the course is to facilitate the consideration and inclusion of relevant information on sex differences in the process of developing clinical guidelines. Based on the potential barriers identified in our earlier project, its specific aims are as follows:

1. To raise awareness concerning the relevance of attention to sex differences for clinical guidelines
2. To develop necessary competence (knowledge and skills) in the systematic consideration of sex differences in all steps of the guideline development process
3. To provide practical tools for facilitating the consideration of gender issues.
**TARGET GROUPS**

The course is designed for staff members of guideline organizations, guideline developers and teachers with prior experience in the principles of evidence-based medicine and evidence-based guideline development.

**OBJECTIVES**

By the end of the course, participants should have:

1. Greater understanding of why attention to sex differences may be relevant in guideline development
2. Skills for determining whether sex differences are relevant to the topic of a guideline and for phrasing sex-specific key questions
3. Sex-specific search terms for locating literature in Medline, Embase and PsycInfo
4. Information about other relevant sources for sex-specific information
5. Practical experience in focus on sex differences when appraising studies
6. Practical experience in the critical reading of reported subgroup analyses
7. Examples of various options for describing sex-specific information in guidelines.

**TRAINING METHODS**

Because the target group of the course consists of adults with substantial knowledge and experience in guideline development, the instructional methods of the course were designed to have the most impact and relevance to adult learners. Adult learners want to know why they need to learn something; they want to acquire knowledge and skills that adds to their experience; they learn from the experience of other learners, and they learn best when the topic is of immediate value to their practice 29. Because the experience of the course participants plays a large role in adult learning, learner-centered methods are more suitable than are teacher-centered methods 30, 31. Adult learning requires the trainer to adopt a moderating style and to use flexible methods that facilitate reflection and more specific learning 29.

**PILOT TESTING OF THE COURSE**

The course includes a collective evaluation of what has been learned. For the purpose of our project, participants were also asked to complete questionnaires in order to evaluate the programme, trainers and content of the course along a ten-point scale (with 1 indicating very poor and 10 indicating very good) and to indicate three learning points. These learning points were coded according to the seven objectives of the course, using the MAXqda2 program for data analysis.
RESULTS

DESIGN

The course consists of five modules: an introductory module that discusses the purpose of the course and four modules that correspond to the various stages in the process of guideline development (assessment of the scope of and phrasing key questions for a guideline, searching literature, critical appraisal of evidence, and phrasing of recommendations). The topics of these modules are quite similar to those addressed in the introductory course on guideline development that is offered by the CBO. This format was chosen because educational approaches are most likely to facilitate behaviour change in professionals when they are tailored to the attitudes, knowledge, skills, habits, and routines of the target group. Moreover, the selected format also facilitates the incorporation of this course or parts of it into the regular training programmes of the guideline organizations.

The main role of the trainers in our course is to facilitate adult learning. Corresponding to the principles of adult learning, we have chosen a combination of training techniques, tailored to the following specific objectives:
1. Group and subgroup discussions to facilitate reflection on the participants’ own attitudes regarding the relevance of sex differences to guideline development, and for the purpose of developing ideas and concepts
2. Short instructions by the trainer, assignments, as well as group and subgroup reflection about the assignments to facilitate more specific learning about incorporating attention to sex differences into the various stages of guideline development.

Educational materials consisted of a course manual for participants and trainers, including a set of tools, a Power-Point presentation to guide the course and introduce each new topic, and a flipchart. The course was designed to be taught in two afternoon sessions of two to three hours each. The participants were asked to review the course materials in advance of each session.

CONTENT

The training course consists of five modules (see Appendix for a detailed description of the modules of the training course).

Module one is the introduction to the training course; its purpose is to increase awareness of the potential relevance of integrating attention to sex differences into the guideline development process. The module consists of two parts. It starts with an icebreaker to assess and discuss the opinions of the training-course participants regarding the potential relevance of paying attention to sex differences. The second part consists of a brief lecture by the trainer, explaining the scope, aims, and objectives of the training course, followed by an introduction about a number of key concepts. The module
ends with a group discussion, facilitated by the trainer, to elicit reflection on the course programme and the key concepts.

Each subsequent module corresponds to one of key steps in the guideline development method:

Module two addresses the following questions: How can potentially relevant sex differences be assessed with respect to the topic of the guideline? Which type of key questions would allow sufficient attention to these differences? The module starts with a group discussion, in which the participants are asked to provide examples of questions that could be used to assess sex differences related to the general topics that are addressed in guidelines (e.g. epidemiology, aetiology, diagnosis, pharmacotherapy). They are subsequently provided with a tool containing examples of sex-specific questions and research evidence according to the main topic areas of clinical guidelines. Participants are then asked to complete two assignments using this tool. First, they are asked to reflect on whether any of these questions would be helpful in formulating potentially relevant sex-specific key questions for a guideline on which they have worked. Second, they are asked to explore whether and how key questions formulated in an existing guideline should be rephrased into sex-specific questions. Both assignments are completed by subgroups of two participants. The module concludes with a short plenary discussion about the results of the assignments.

Module three addresses the following question: Which literature search strategies may allow the identification of potentially relevant literature on sex differences? This module provides written tools for locating published studies on sex differences. Examples of relevant databases are provided, along with the specific search terms that are relevant for the most commonly used bibliographic databases in biomedicine (i.e. Medline, Embase, PsycInfo). The trainer provides examples of how the tools can be used. If internet facilities are available, a training assignment may be given that involves using the tools.

Module four addresses the following question: How can we assess whether the retrieved studies provide relevant information about sex differences? This module starts with an introduction by the trainer of a written tool that provides examples of specific questions regarding sex differences that may be relevant for the critical appraisal of research publications. Participants are divided into subgroups and given an assignment in which they must apply the tool by assessing the abstracts of selected publications. The results of the assignment are discussed in a plenary session. The participants subsequently receive plenary instruction about a written tool for assessing sex-specific information within articles. Specific attention is paid to assessing the quality of the statistical methods used in studies (subgroup analysis). Each participant then receives an individual assignment to apply this tool to the methodology sections of a number of selected publications. The module concludes with a plenary assessment and group discussion of the results of this assignment.
Module five addresses the following question: How can information on sex differences be integrated into the final guideline document? The trainer introduces this topic by providing examples of various ways of presenting relevant information on sex differences in guidelines. A group discussion follows to facilitate reflection on whether and how the participants could use such examples in their daily practice.

**Pilot testing of the course**

Draft versions of the course were tested and discussed with three experts in guideline development and teaching. The training course was given in two sessions in March and April 2005 at the offices of the CBO and the NHG. The first session covered Modules one through three; the second session covered the remaining two modules. An interval of two weeks was included between the two sessions, during which the participants were encouraged to complete assignments or engage in reflection.

Fourteen staff members participated in the pilot test. Twelve staff members participated the first session, and eleven staff members attended the second session. Nine of these participants attended both sessions. All participants completed the questionnaires, with the exception of one participant, who had to leave the last meeting early.

The content, programme and trainers were evaluated after the first session (n = 12). Course ratings varied from 7 to 9, inclusive, with means of 7.5, 7.8 and 8, respectively.

Learning points were evaluated after each session. In answer to the question of what they had learned from the course, participants noted forty-five statements on 22 evaluation forms. Table 1 shows how the statements were coded. Next to the seven objectives of the course, an additional theme emerged during the analysis: ‘general methodology for integrating attention to sex differences in guidelines’. This theme referred to the practical applicability of the sex-specific methodology learned in the training course. Fourteen of the statements referred to this theme. Five statements referred to other topics that neither referred to one of the other objectives/themes nor raised another new theme. One of the forty-five statements had a double coding, and one statement had a quadruple coding.

Eleven of the statements expressed that participants had learned skills other than or in addition to those related to a sex-specific approach to guideline development. Nine of these statements referred specifically to the utility of the module on the critical reading of subgroup analysis.
**Table 1:** Pilot test: Learning points of the course

<table>
<thead>
<tr>
<th>Course objectives</th>
<th>Module*</th>
<th>Number of statements</th>
<th>Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Greater understanding of why attention to sex differences may be relevant in guideline development</td>
<td>1</td>
<td>14</td>
<td>“Gender does matter, but other forms of diversity can be relevant as well. It is right to consider these matters throughout the development process.”</td>
</tr>
<tr>
<td>2. Skills for determining whether sex differences are relevant to the topic of a guideline and for phrasing sex-specific questions</td>
<td>2</td>
<td>4</td>
<td>With reference to the tool: “assessing with the help of criteria rather than ‘unquestioningly doubling’ key questions by gender”.</td>
</tr>
<tr>
<td>3. Sex-specific search terms for locating literature in Medline, Embase and PsycInfo</td>
<td>3</td>
<td>4</td>
<td>“It is good to know that there are sex-specific search filters”.</td>
</tr>
<tr>
<td>4. Information about other relevant sources for sex-specific information</td>
<td>3</td>
<td>1</td>
<td>“sources and knowledge”</td>
</tr>
<tr>
<td>5. Practical experience in how to focus on sex differences when appraising studies</td>
<td>4</td>
<td>4</td>
<td>“sex-specific checklist for literature assessment”</td>
</tr>
<tr>
<td>6. Practical experience in the critical reading of reported subgroup analyses</td>
<td>4</td>
<td>10</td>
<td>“very clear explanation of subgroup analysis”</td>
</tr>
<tr>
<td>7. Examples of various options for describing sex-specific information in guidelines</td>
<td>5</td>
<td>2</td>
<td>“different ways of including it in the guideline”</td>
</tr>
</tbody>
</table>

**Other codes**

| General methodology for integrating attention to sex differences in guidelines      | 1-5     | 14                   | “specific practical leads with which to work”                        |
| Other                                                                             | 1-5     | 5                    | “Discussion about the homework: the correct answers that were provided were too strict. It has to be put into perspective that the parts that I assessed as right were not obviously false”. |
| Total                                                                            |         | 58                   |                                                                      |

* Modules 1 to 3 were covered in the first session; the second session covered Modules 4 and 5. Statements from 12 evaluations of the first session and 10 evaluations of the second session.

**Discussion**

This paper describes an educational course that was designed to help guideline development organizations consider sex differences in the design of clinical practice guidelines. The course targeted experts in evidence-based guideline development. Educational theories emphasize the importance of tailoring educational interventions to the needs and specific characteristics of the target groups. For this reason, the format of the course (five modules) follows the common stages in the process of guideline development and it uses a variety of educational strategies that have proven useful in supporting adult learning. A previous study in two Dutch guideline organizations suggests...
that the barriers that impede guideline developers from considering sex differences in guideline development include lack of awareness and lack of the knowledge and skills that are necessary to implement such consideration. Therefore, the objectives, content and educational strategies of the course were aimed at raising awareness and stimulating the development of practical skills.

Because we did not assess the long-term effects of the training course, we do not know whether the participants’ behaviour has changed. Nevertheless, the statements on what the participants had learned from the course reflect themes that are considered important conditions for behavioural change among professionals in the literature on quality improvement in healthcare. The results of the evaluation of the pilot test suggest that the current design of the training course is successful in achieving its objectives. We are currently conducting a follow-up study to assess whether and how the participants are implementing the knowledge and skills that they acquired in the course in their guideline development practice. The findings of this study will provide information concerning whether the training course needs further improvements.

Conclusion

Clinical guidelines are often used as tools for quality improvement in clinical practice. According to international treaties on gender equality, guideline organizations are charged with the task of ensuring that evidence on sex differences is considered in guidelines. Active educational approaches seem to be an effective way to raise awareness of innovations among professionals. Our training course is the first to address sex differences in guideline development. Because the modules and the teaching methods are widely transferable, the training course could be useful for many organizations that are active in guideline development.

Acknowledgements

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12. Bekker MH: Investigating gender within health research is more than sex disaggregation of data: a Multi-Facet Gender and Health Model. Psych Health Med 2003, 8:231-244.


Appendix - Description of the modules of the training course
‘Attention to sex differences in guideline development’

Module 1 (Introduction): Relevance of sex differences for clinical guidelines; scope and purpose of the training course

Topic: Why could it be relevant to pay attention to sex differences in guideline development?

Icebreaker

The module opens with an icebreaker. The participants are presented with the following exercise: Please indicate how you view the relevance of paying attention to sex differences in guideline development by locating yourself at either end of the wall in this room. If you locate yourself on the left side, this means you find it very irrelevant. If you locate yourself on the right side, this means you find it very relevant. Please explain why you have chosen a particular position.

Introduction by the trainer

The trainer introduces the course as follows: The task of guideline developers is to identify and evaluate the most relevant information concerning particular topics of guidelines by systematically asking and answering a number of questions. Most guidelines thus far focus on the general patient population. It is becoming increasingly recognized, that health disparities may exist between or among groups of patients (e.g., according to age, socioeconomic status, ethnicity or gender). The aim of this training course is to provide background information and practical tools that may be useful, should you want to address health disparities in guideline development. The training course focuses on differences between men and women. In recent years, it has become increasingly acknowledged that being a man or a woman may have an important impact on individual health, as well as on the aetiology, signs, symptoms, and course of diseases. It can also affect diagnosis, prognosis, treatment, or response to diagnostics and treatment modalities. Some of these effects are related to the fact that men and women have different biological characteristics that are caused by genetic and physiological differences. In the literature, such differences are known as sex differences. These effects, however, can also be related to the fact that men and women have different social and culturally constructed characteristics, which may lead to differences in lifestyle, living conditions, norms and values. The literature refers to these types of differences as gender differences. For the sake of simplicity, this course uses the term ‘sex differences’ to refer to both biological and socially constructed differences.
Those who are not familiar with sex and/or gender differences in health may not know how to identify and evaluate potentially relevant information on differences between men and women. This training course is meant to facilitate this task. It consists of a number of modules that correspond to the steps that are commonly used in guideline development. For each step, we discuss ways in which to address differences between men and women (modules two through five).

By the end of the course, participants should have:
1. Greater understanding of why attention to sex differences may be relevant in guideline development
2. Skills for determining whether sex differences are relevant to the topic of a guideline and for phrasing sex-specific key questions
3. Sex-specific search terms for locating literature in Medline, Embase and PsycInfo
4. Information about other relevant sources for sex-specific information
5. Practical experience in focus on sex differences when appraising studies
6. Practical experience in the critical reading of reported subgroup analyses
7. Examples of various options for describing sex-specific information in guidelines.

This module ends with a plenary discussion, facilitated by the trainer, to elicit reflection regarding the potential relevance of sex and gender factors for guideline development and the training programme.

Module 2: Assessing relevant sex differences related to the topic of the guideline and phrasing of sex-specific key questions

Topic: How can potentially relevant sex differences be assessed with respect to the topic of the guideline? What type of key questions would allow sufficient attention to these differences?

Introduction to this module: Guidelines are based on information from scientific literature. In order to locate information, it is necessary to phrase questions. This module discusses how questions can be phrased in order to find relevant information on sex differences. In the beginning stages of developing a guideline, sex differences can be considered by guideline groups as they trace bottlenecks in information regarding the topic of the guideline.

The module starts with a plenary discussion in which the participants are asked to provide examples of questions that could be used to assess sex differences.
related to the general topics that are addressed in guidelines (e.g., epidemiology, aetiology, diagnosis, pharmacotherapy).

To assess whether any sex differences are relevant to the topic of a given guideline, we provide a tool consisting of questions, arranged by theme, which can be addressed by the members of a guideline working group. In addition, we present matching evidence of sex differences. If any of these differences are thought to be relevant, key questions can be formulated that should subsequently be answered in the guidelines.

**Tool: Examples of sex-specific questions and research evidence according to the main topic areas of clinical guidelines**

**Life phase**
Questions regarding a person’s life phase (for instance adolescence, menopause or perimenopause) may be relevant to any of the following topics.

**Prevalence, epidemiology**
- Do men suffer from this health problem as often as women do?
- Can specific groups be distinguished within the sexes?
Example: The prevalence of psychological depression is higher among women than it is among men (ratio 2:1) 1.

**Co-morbidity**
- Are there differences between the sexes with respect to co-morbidity?

**Aetiology**
- Could differences in sex or gender influence the cause and development of symptoms?

**Risk profile**
- Are men and women subject to different risk factors?
- Are definitions of the risk factors the same for men as they are for women?
- Do men and women differ in behaviours that affect the onset or development of the disease?
- Are gender-specific aspects of socialization or personal history relevant to the development of the disease? (e.g., women are often more likely than men are to be victims of sexual abuse; men are more likely than women are to be war veterans.)

Example: In women, diabetes is a better predictor of cardiovascular disease than it is
in men. The risk of cardiovascular disease increases in a later stage in life for women than it does for men. (Women are ten years ‘behind’ men. A 60-year-old woman has approximately the same risk that a 50-year-old man has.) The age-related risk difference disappears for women who suffer from diabetes.

(Patho)physiology

• Is the (patho)physiology of the disease the same for men as it is for women?

Presentation of symptoms

• Is the presentation of symptoms subject to sex or gender differences?
• Does gender influence the point at which a person seeks help in the course of the disease?

Example: Women with acute coronary syndromes (ACS) are more likely than men are to present with symptoms that are considered atypical for ACS.

Diagnosis

• Are the instruments that are used for a diagnosis equally valid for men and for women (with regard to specificity, sensitivity, acceptation of the examination by the patient)?
• Are the criteria that are used for diagnosing the disease in men the same as those that are used for its diagnosis in women?

Example: Exercise ECG tests for diagnosing angina pectoris are more likely to yield false positive results for women than they are for men.

Prognosis, course of the disease

• Is the prognosis influenced by sex?

Example: The prognosis for melanoma is worse for men than it is for women.

Prevention

• Could any sex-specific or gender-specific aspects be relevant to the prevention of the disease?

Treatment

• Could sex-specific or gender-specific aspects influence treatment (i.e., type of treatment, patient preference for treatment, effectiveness of treatment, patient satisfaction, compliance)?
• Could sex or gender aspects influence rehabilitation?
Example: Women tend to discontinue rehabilitation treatment for heart attacks more often than men do.

**Pharmacotherapy**
- Has the medication been tested on both men and women?
- Do sex differences influence pharmacodynamics and kinetics?
- Is the therapeutic effect of the medication the same for men as it is for women?
- Is the optimal dose the same for men as it is for women?
- Are the side effects the same for men as they are for women?

Example: Alosetron is effective for women with non-constipated irritable bowel syndrome, but not for men.

**Sex hormones**
- Do sex hormones influence the development and course of symptoms?
- Do sex hormones influence the effectiveness of treatment (i.e., pharmacotherapy)?
- Do sex hormones interfere with establishing a diagnosis?
- How do puberty and menopause influence clinical presentation and treatment?

**Pregnancy, breastfeeding**
- Does pregnancy influence the course of the disease?
- Does pregnancy influence treatment (i.e., harm for mother or child)?
- What is the effect of the disease or treatment on breastfeeding?

Example: There is remission of the symptoms of rheumatoid arthritis during pregnancy.

**Advice and education**
- Are gender-specific aspects relevant for advice or education?

**Expectations of patient and doctor**
- Are patients’ expectations with regard to their doctors and treatment gender specific?
- Is the sex of the patient relevant for a doctor?

**Quality of life**
- Does the disease itself or its treatment have a different effect on the quality of life for men than it does on the quality of life for women (i.e., physical limitations, pain, work, relations)?
- Are there gender-specific aspects to the perception of the disease?
- Do gender-specific aspects influence the consequences of the disease or treatment?
for the private situation of the patient (e.g., care for the patient or care that the patient provides to others)?

**Communication**

- Does the sex of the patient and the doctor affect the way in which they communicate about symptoms?

To practice formulating sex-specific key questions and using the tool, the participants are given two assignments, which are subsequently discussed.

Assignment one (in subgroups): Please think of a guideline on which you have recently worked. Try to formulate sex-specific key questions for this guideline, using the formats provided in the tool as an example.

Assignment two (in subgroups): Imagine that you are member of a guideline working group on the topic of osteoporosis. The working group has formulated the following key questions as a point of departure for the guideline.

1. What is the prevalence of osteoporosis in the Netherlands?
2. What are the most clinically relevant risk factors for developing osteoporosis?
3. What is the value of diagnostic research?
4. What are meaningful prevention measurements for osteoporosis and what are the different treatments?
5. When is treatment cost-effective?

Please explore the following questions:
- Should the key question be rephrased into a sex-specific key question?
- If so, what would the sex-specific question be?

You may use the tool in your exploration.
Module 3: Locating literature on sex differences in health

**Topic:** Which literature-search strategies may allow the identification of potentially relevant literature on sex differences?

Introduction to this module: In order to answer the key questions for a specific guideline, guideline developers usually perform a systematic search in electronic databases that include biomedical literature. For this task, they use search terms. In this part of the training course, we provide websites and sex-specific search terms for locating sex-specific evidence. The tool for this specific module provides information about general databases that provide information on sex or gender-related factors in health. The tool also provides information on gender-specific search terms that may be useful for locating research publications on sex differences for the electronic databases that are most commonly used in biomedicine: Medline, Embase and PsycInfo.

A plenary discussion is held, in which participants are asked about any experience they may have in searching for sex-specific information.

The trainer introduces the tool for this module.

**Tool: Examples of websites**
- Medlineplus is a service of the National Library of Medicine. This website provides information on women’s health and men’s health.
  - [http://medlineplus.gov/](http://medlineplus.gov/)
- World Health Organization (WHO): The WHO actively promotes attention to sex/gender health research and policy. The website provides information on women’s health and gender.
  - [http://www.who.int/topics/womens_health/en/](http://www.who.int/topics/womens_health/en/)
  - [http://www.who.int/topics/gender/en/](http://www.who.int/topics/gender/en/)

**Tool: Examples of specific search terms**
- Medline (PubMed): Sex factors [MeSH], sex characteristics [MeSH], sex differentiation [MeSH], sex [MeSH], gender differences [text word], sex differences [text word], gender [text word]
- Embase (Ovid): Sex difference [subject heading], sex ratio [subject heading], gender [subject heading], sex factor [text word], gender bias [text word], gender difference [text word]
The tools are discussed in a plenary session.

Assignment: No assignment has been provided for this module. However, if computers and an internet connection are available, the participants can work with the search terms.

**Module 4: Critical appraisal of sex-specific information**

**Topic: How can we assess whether the retrieved studies provide relevant information about sex differences?**

Introduction of this module: Once research articles have been located through a systematic literature search, they must be screened for scientific and clinical relevance.

The trainer introduces the tool for this module.

**Tool: Sex-specific questions for assessing evidence**

The first screening involves the titles and abstracts of articles. The following can be used as an initial screening question for selecting articles on sex differences:

Do the title and abstract contain information about gender, men/women, both sexes or a comparison between the two?

If so, the article can be assessed further by using the following questions:

- Does the research question apply to both men and women?
- What is the sex composition of the study population?
- Are both sexes sufficiently represented in the study population?
- Are differences between men and women analysed?

If the answer to the last question is ‘no’:

- Are the conclusions as valid for men as they are for women?

If the answer to the last question is ‘yes’:

- Was the subgroup analysis performed correctly?
- Could a sex difference be of clinical relevance?
If the article contains a subgroup analysis between men and women, the following steps can be taken to obtain relevant sex-specific information:

• How was the subgroup analysis performed? Was it performed well? The participants learn how a subgroup analysis is performed statistically and how to know whether it was performed well.
• If it was not performed well, correct it.
• If it was performed well, are there any significant differences between the two sexes? (see Altman 7).

Assignment one (in subgroups): Please use the abstract to assess the following article, which was found with help of a sex-specific search strategy, using the tool for this module:


Abstract:

**Background**

 Coronary heart disease is a major problem in both men and women, but several studies have shown sex differences in symptoms of acute coronary syndromes (ACS). Some findings, however, have been disparate and inadequate, and thus a comprehensive overview of this literature would be of value.

**Method**

 Fifteen studies that identified symptoms of ACS for both women and men were examined through a review of the literature from 1989 to 2002. Terms used for the search included “myocardial infarction,” “symptoms,” “gender differences,” and “acute coronary syndromes.”

**Results**

 Although chest pain was the most common symptom in both men and women, several differences were also noted. In all types of ACS, women had significantly more back and jaw pain, nausea and/or vomiting, dyspnea, indigestion,
and palpitations. In a number of studies, which solely sampled patients with acute myocardial infarction, women demonstrated more back, jaw, and neck pain and nausea and/or vomiting, dyspnea, palpitations, indigestion, dizziness, fatigue, loss of appetite, and syncope. Men reported more chest pain and diaphoresis in the myocardial infarction sample. The designs and methodologies of the studies varied considerably.

**Conclusion**

In addition to the typical symptom of chest pain in ACS, women experience other atypical symptoms more frequently than men. Thus, there may be sex differences in the symptoms of ACS, differences that have a bearing not only on clinical practice, but also on the interpretation of available clinical studies and the design of future investigations.

Assignment two (in subgroups): Please use the following fragment of an article to assess whether the subgroup analysis was performed correctly (ten assignments and answers are available from the authors). Please use the tool for this module.

**Fragment**

**Methods (randomized trial)**

Subgroup analyses were performed for the primary efficacy variable. Subgroups were stratified by race (non-black or black), age (<65 years or ≥65 years), and sex.

**Results**

Overall, each subgroup experienced clinically meaningful reductions in blood pressure with both treatment regimens. The results for the subgroups comprising the largest percentage of the sample (non-blacks and those younger than 65 years of age) were similar to those for the overall population. Within treatment arms, numerical differences were seen across sex (reductions of 10.2 and 7.8 mmHg for women and men, respectively) for losartan.

The results of the assignments are discussed in a plenary session.
Module 5: Integration of sex-specific information into the guideline document

**Topic: How can information on sex differences be integrated into the final guideline document?**

Introduction to this module: Once the relevant evidence has been collected, it should be written in the guideline.

While writing the guideline, there are several ways in which to pay attention to sex-specific information. In this module, several of the options that are available for presenting information on sex differences are discussed.

The trainer introduces the tool for this module.

**Tool: Options for paying attention to sex differences in the composition of guideline documents**

Option one: Where can information about sex differences be placed in the document?
- in the recommendations
- in the running text
- in the footnotes
- in a separate paragraph
- in separate boxes

Example (for a recommendation): ‘Women with an osteoporotic fracture of the spine or the hip under the age of 50 or men with an osteoporotic fracture of the spine or the hip under the age of 65 must be referred to a specialized care provider for further evaluation of the underlying cause’⁸.

Option two: What kind of information will be included if there is no sex-specific evidence?
- Write about sex differences only if there is evidence.
- Mention a lack of evidence.

Example (for missing information): ‘Because of lack of evidence on male subjects, it is almost impossible to make any pronouncements about the preventive value of physical exercise in men. The opinion of the working group is that the outcomes of research on women subjects can be extrapolated to men’⁸.

This tool is discussed in a plenary session.
Reference List


