Sex differences in health research and clinical guideline development
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Chapter 1

General Introduction
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General Introduction

Traditionally, clinical research on conditions that affect both men and women has largely been restricted to male populations. Women were excluded from clinical studies in part because of a desire to protect them during their reproductive phase and in part because it was assumed that men and women would react similarly to treatment. Another reason was that researchers sought homogeneous study populations, particularly in clinical trials for testing medications, and it was assumed that the female hormonal cycle would introduce unnecessary heterogeneity in the study population.

Since 1990, various public and scientific concerns have been raised about this approach, mainly in North America. It was feared that the results of research on homogenous male populations might not be applicable to the clinical population as a whole, thereby preventing women from receiving the best possible care. In response to these concerns, scientists and research funding organizations, particularly in North America, have taken measures to increase the amount of attention paid to sex differences in clinical research.

The awareness that greater attention to sex differences might improve the quality and the applicability of data from clinical studies was not limited to North America. In 1999, the Netherlands Organization for Health Research and Development (ZonMw) took measures to focus the attention of researchers on the study of sex differences. A second, related topic is that evidence on sex differences should be made available to practitioners. In current clinical practice, evidence-based clinical guidelines represent a key instrument for making evidence available to the practitioner.

This thesis presents a series of studies which evaluated the consideration of sex differences in health research and guideline development in the Netherlands. This introduction provides a brief outline of recent evidence on differences between men and women, in terms of health and of health outcomes. A successive overview of clinical practice guideline development in general and in the Netherlands specifically is provided. At the end of the introduction, the aim, research questions, and outline of the thesis are presented. First, an overview of terms used in this thesis and the measures taken to increase attention to sex differences in clinical research will be given.
Differences between men and women

Several terms are used to refer to differences between men and women in the literature, and differences between other specified patient or population groups (i.e. differences based on ethnic origin, socio-economic circumstances, and age). In this thesis some of the following terms are used:

Gender differences are differences which refer to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women. Sex differences refer to the biological and physiological differences that define men and women. In some chapters in this thesis we use the latter term, and the synonyms ‘sex-related factors’ or ‘sex-specific factors’, to refer to both biological differences as well as differences based on socially constructed roles. When these terms only refer to biological sex differences, we note that in the relevant chapter.

In the Netherlands, ZonMw introduced the term diversity (‘diversiteit’). This term refers to the differences between population groups in general on the basis of gender, ethnic origin, age and socio-economic circumstances. In the international literature, two similar terms are often used: health disparities and equity. Health disparities refers to differences in health status that occur among population groups defined by specific characteristics. Equity refers to the equitable access to health care for different population groups or to circumstances leading to equitable degrees of health. It is often used in the context of a population group’s economic circumstances, which may lead to increased or decreased access to health care. Disadvantaged population groups may have poorer access to health care and receive a poorer quality of care which infringes human rights.

In addition to a socio-economic context, equity is also used in a political, ethnic and cultural context. For example, differential life expectancies for men and women are dependent on levels of education.

Below, an overview will be given of the measures taken to enhance sex-specific health research.

Measures taken to address sex differences in health research in North America and elsewhere

In response to the relative absence of attention to sex and gender differences in health research, in several countries measures have been taken by governments or by public research funding organizations to encourage greater attention to sex differences in research.
United States

Since 1985, scientists and several public agencies in the United States (US) have become increasingly concerned about the lack of attention paid to sex differences and ethnicity in clinical research funded by the National Institutes of Health (NIH). In 1993, this led to the adoption of the NIH Revitalization Act by the US Congress. This act required NIH to ensure the equitable inclusion of men, women and ethnic minorities in every clinical study. In 1994, this legislation was implemented by the NIH in a set of guidelines in which they required equitable inclusion, and also required that the research designs of phase III pharmaceutical trials allow valid and meaningful analysis of differences between the sexes. In 2000, the NIH concluded that although the inclusion of women and minorities had been accomplished, analysis needed to be more consistently reported. NIH policy was amended by providing more extensive guidance on the planning, conducting and reporting of analysis of data by sex/gender and/or race/ethnicity differences.

In addition to this, the US Food and Drug Administration (FDA) took its own measures. In 1993, the FDA recommended in its Gender Guideline that sex differences should be assessed when analysing the data from clinical trials. The FDA is an agency that approves the use of new medications and therapies. Since 1993 the FDA has approved medications only if they have been tested on both men and women.

Canada

In 1997, following the adoption of a general policy to improve women’s health, Health Canada introduced a guideline for drug research and registration. The aim was to encourage the inclusion of women in tests at all stages of drug development, and to facilitate the detection of significant sex-related differences in drug response.

European Union

Since 1993, the EU has taken measures to provide equal opportunities for women in science in a broader sense by means of a financing programme known as the 5th Framework Programme. In 2000, the European Parliament made a clear commitment to promote gender equality in EU-funded research. The aim was to achieve gender balance among participating researchers, while ensuring that studies focus on sex and gender-related factors. Researchers applying for the EU’s 6th Framework Programme (2002-2007) were asked to describe and justify the composition of their study populations according to sex. They were also required to indicate how they planned to integrate a focus on sex and gender issues, where appropriate, into the objectives and methodology of their research proposals.
The Netherlands

In the Netherlands, the Netherlands Organization for Health Research and Development (ZonMw) is the main source of government funding for health research. It funds a broad range of health research and has many different grant programmes, each with its own research focus and set of priorities. In 1999 ZonMw adopted the general policy that its financial support would be subject to the provision that studies must give sufficient emphasis to diversity factors, such as sex, age and ethnicity. ZonMw also developed a specific research programme to make additional efforts to integrate sex-specific health care into mainstream health care. This programme was initiated by the Dutch Ministry of Health, Welfare and Sport in 1999, based on work by the Task Force for Sex-specific Health Care.

Monitoring the Effect of the Measures to Address Sex Differences in Health Research

The NIH and FDA policy has been evaluated by studies carried out both by the United States General Accounting Office (GAO) and by independent researchers. Overall these studies suggest that, while progress has indeed been made in the recruitment of women for NIH-funded and FDA-approved research, research reports often fail to include an analysis of data by sex. The government, by means of the Office of Research on Women’s Health, is currently underlining the necessity for sex-specific research by providing training and expertise for researchers and reviewers on ways to implement the provisions, and by constantly monitoring the effect of the policy.

Marrocco et al. evaluated the efforts of Canadian clinical investigators to recruit individuals of both sexes and to analyse data by sex. This involved an examination of research ethics applications at a Canadian health sciences centre over a five-year period (1995-2000). Their study revealed that 98% of researchers working on non-sex-specific conditions intended to recruit both men and women, while only 20% planned to perform analyses of data by sex.

In Europe the EU-funded 5th Framework was evaluated on gender integration by the Gender Impact Assessments. The evaluation helped to formulate recommendations for the 6th Framework concerning priorities in gender-sensitive research in the different programme areas.

In the Netherlands the measures taken by ZonMw have been evaluated in terms of the consideration of several aspects of diversity by examining the research proposals. The conclusions were that some researchers tended to prefer a consideration of ethnic variations to the consideration of sex or gender differences. No specific research has been performed on the impact of measures taken by ZonMw to enhance the consideration of ‘diversity’ factors in these proposals compared to proposals where measures were enhanced to a lesser extent.
The overall intention of these national and international measures has been to generate more knowledge about the differences between men and women in health and health outcomes. However, although progress has been made, the effects of these incentives still seem to be limited.

Some of the knowledge generated on sex differences is described below.

**Recent evidence on sex differences in health**

Differential health outcomes for men and women are reflected in the data for several diseases. Men and women differ in their reasons for presenting to a general practitioner. Table 1 displays the top 10 presented conditions in general practice for men and women aged 50-55.

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Nervous system</td>
<td>Nervous system</td>
</tr>
<tr>
<td>260</td>
<td>159</td>
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<tr>
<td>Screening</td>
<td>Common cold</td>
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<tr>
<td>247</td>
<td>100</td>
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<tr>
<td>Common cold</td>
<td>Overweight</td>
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<tr>
<td>136</td>
<td>99</td>
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<tr>
<td>Overweight</td>
<td>Hypertension</td>
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<tr>
<td>129</td>
<td>81</td>
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<tr>
<td>Varicose veins</td>
<td>Neck pain</td>
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<tr>
<td>117</td>
<td>59</td>
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<tr>
<td>Menopause complaints</td>
<td>Back pain</td>
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<tr>
<td>107</td>
<td>59</td>
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<tr>
<td>Hypertension</td>
<td>Obesity BMI&gt;30</td>
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<td>98</td>
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<tr>
<td>Obesity BMI&gt;30</td>
<td>Cerumen</td>
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<td>91</td>
<td>51</td>
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<tr>
<td>Neck pain</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>89</td>
<td>46</td>
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<tr>
<td>Oral contraception</td>
<td>Dermatitis</td>
</tr>
<tr>
<td>85</td>
<td>43</td>
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</tbody>
</table>

Also in studies that are relevant to the prevention, diagnosis and treatment of diseases, sex differences have been found. For example in the use of aspirin for the primary prevention of stroke and myocardial infarction (MI). A sex-specific meta-analysis has shown that aspirin compared to placebo leads to a 19% reduction in stroke in women (RR, 0.81; 95% CI, 0.69–0.96; p=0.01) and no reduction in MI (RR, 0.99; 95% CI, 0.83–1.19; p=0.95). In men, aspirin leads to 32% reduction of MI (RR, 0.68; 95% CI, 0.54–0.86; p=0.001), and no significant reduction in stroke (RR, 1.13; 95% CI, 0.96–1.33; p=0.15) 30. The authors of this article were not able to find plausible explanations for the null finding for the risk of MI in women, and confirm their data outcomes only by referring to other studies 30.

In the screening for diseases or risk factors, sex differences also occur; for instance, when using the AUDIT screening instrument for alcohol problems. Scores can range from 0 to 40 and the standard cut-off point for an alcohol problem is 8 31. The
instrument is less sensitive (66 vs 91 p<0.05) and more specific (97 vs 80 p<0.05) for women than it is for men, indicating different cut-off points (for men the standard cut-off point is 8 and for women, 5 or 6) 31.

In diagnosing patients, the sex of the patient matters since men and women may suffer from different complaints or symptoms. In patients with Chronic Obstructive Pulmonary Disease (COPD), women are more likely than men (OR 1.30, 95% CI 1.10–1.54) to experience severe dyspnoea, one of the symptoms of COPD, but are less likely than men to undergo spirometry to establish a diagnosis (OR 0.84, 95% CI 0.72–0.98) 33. Also, in the research population of COPD patients in this study, the women were younger than men (mean age 61.2 (SD 10.5) vs. 64.4 (SD 11.0)) and women had significantly fewer pack-years of smoking than men (36.9 (SD 29.6) vs. 46.6 (SD 35.1) p<0.05). As a possible reason why women receive less spirometry testing, the authors state that COPD might still be considered to be a male disease 33.

Another example of sex differences influencing a diagnosis was reported in a study that found that general practitioners, when referring patients with rheumatoid arthritis (RA), appear to take longer to refer female patients with symptoms of RA for specialized care than they do male patients with the same level of disease activity (median of 93 days vs. 58 days, p = 0.008) 34. Similar findings were published in another study 35. Early treatment of RA is beneficial for patients to suppress the progression of the disease 36.

Observational studies have revealed different treatment strategies for men and women. An example of such a difference can be seen in patients with asthma. For children who reported wheezing at least once, boys are more likely than girls to have asthma medication prescribed at some time in the first 18 years of life (69.4% vs. 57.7%, p<0.005) 37. The explanation offered by the study authors is that under-treatment of girls might be due to the earlier onset of symptoms for boys 37. The time lag between the first episodes of frequent wheezing and the first use of medicine is longer for girls compared to boys (2.8 ± 3.8 years for girls vs. 1.6 ± 2.5 years for boys, p < 0.005) 37. Hospitalization for boys with frequent wheezing is significantly more likely than for girls (29.3% vs 13.6%, p<0.02) 37. These differences in strategies might be explained by a different symptom presentation for boys and girls 37.

When considering therapies, a different approach may be needed for men and women because of a different response to pharmaceuticals. For instance in response to antidepressant treatment, men show a more favourable response to imipramine (a tricyclic) than to sertraline (an SSRI) (62% versus 45%; p=0.04) whilst for women this is the opposite (46% versus 57%; p= 0.02) 38. Explanations for the underlying mechanisms leading to this sex difference, according to the authors, are sought in differences in pharmacokinetics, the differential presentation of depressive symptoms (i.e. more likely typical for men vs. more likely atypical for women) and the role of hormones in the male or female body 38.
In the treatment of patients there is also a difference in the advice given to adapt personal behaviour. In the previously described observational study of COPD patients, men were significantly less likely to receive anti-smoking advice than women (28% vs. 37% (p<0.05)) 33.

In treatment strategies to reduce alcohol consumption (in a primary care setting), a sub-group analysis of a Cochrane review showed the benefit of brief interventions in men (mean difference: -57 grams/week, 95% CI -89 to -25), but not in women (mean difference: -10 grams/week, 95% CI -48 to 29). Although the authors of this review suggest the difference might be due to low statistical power (outcome of 499 female participants), they stated that brief interventions for lowering alcohol consumption in women are not yet justified 39.

In the prognosis of diseases, sex differences are also apparent. For example, men suffering a malignant melanoma have a poorer life expectancy as compared to women (HR 1.4, 95% CI 1.05-1.61) 40, even when the melanoma is less thick 40. There may be a biological explanation for this.

If the quality of care for both women and men is at stake, it is essential that the evidence concerning sex differences be taken into consideration in daily practice. Therefore, it needs to be integrated into regular health care. The translation of sex-specific evidence into health care has shown to be problematic 41. A common form for disseminating evidence into health care practice is by integrating the evidence into clinical practice guidelines 42, 43.

**Clinical practice guidelines**

Clinical practice guidelines provide evidence and recommendations concerning optimal strategies for the prevention, diagnosis, and treatment of specific clinical conditions 44, 45. Clinical guidelines have been developed for several decades 46, but in the last two decades the number of guidelines has grown 46, 47. An often used definition for clinical guidelines from the Institute of Medicine, developed by Field and Lohr in the early 1990s 44, states: guidelines are ‘systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances’.

In the Netherlands this definition was adjusted in 2004 by the editors of the Dutch handbook on Evidence Based Guideline Development. They state that a guideline is: ‘a document containing recommendations, advice and treatment instructions intended to support the decision-making process of health care professionals and patients, derived from the results of scientific research and upon the discussion and medical opinion evolving from it, with the aim of establishing effective and efficient medical treatment’ 47.
As described in both definitions, guidelines consist of recommendations, which describe what practitioners need to do in specific circumstances; as described in the latter definition, guidelines are based on conclusions derived from evidence.

Earlier, guidelines were mainly based on consensus among the opinions of experts. Because of the growing interest in evidence based medicine, the method of developing these guidelines evolved towards an internationally standardized evidence based method for which the scientific literature is used as a primary source of knowledge. This method includes the following stages: the formulation of key questions; the formulation of a search strategy for locating relevant literature; the critical appraisal of selected literature; and the writing of the guideline document.

Although guideline development evolved towards a standardized procedure, a guideline is not based purely on evidence. The evidence is interpreted and weighed on its clinical relevance and cost-effectiveness by representatives of a guideline's end users. The interpretation of the evidence by guideline developers has been an important part of the process of guideline development. This group of representatives and one or more staff members of the relevant guideline organization are called the guideline working group or guideline development committee. Staff members of the guideline organizations support group members in the standardized process of guideline development.

Group-based guideline development will never be a completely unbiased procedure and this may influence the quality of guidelines. Several studies have been performed to find the most formalized method of group decision making for guideline development, yet all methods of guideline development still include consensus as well as evidence. The decision making process in guideline development groups is the object of ongoing studies. Findings show that members seem to favour treatments they use themselves. Social interaction between the different group members also influences group judgements. In multidisciplinary groups there appears to be a hierarchy of contributors to discussions by the different group members. It is unclear what the effect this hierarchical contribution has on the content of the guideline document, i.e. the inclusion of evidence and specifically, evidence on sex differences.

The next paragraph focuses on guideline development in the Netherlands, describing the specifics of the two main guideline development organizations.

Guideline development in the Netherlands

In the Netherlands, two organizations have longstanding experience with guideline development: the Dutch Institute for Healthcare Improvement (CBO) and the Dutch College of General Practitioners (NHG). Both organizations work according to the standard methodology of guideline development.
CBO

CBO began developing guidelines in 198152. The CBO works with multidisciplinary groups of experts representing the end users of a particular guideline. Staff members of the CBO (known as consultants on guideline development) support guideline development groups in the evidence based methodology of guideline development. CBO guidelines focus on the medical (and paramedical) professions involved in the care of patients with a specific disorder. CBO has developed guidelines on about 130 different clinical topics 52.

NHG

NHG began developing guidelines for general practitioners in 198966. The NHG works with mainly mono-disciplinary groups of experts representing the end users of the guideline: general practitioners. NHG staff members (known as scientific staff members) are the principal authors of the guideline, and they use the group members as a sounding board. Guidelines from NHG focus on general practice. The NHG has developed guidelines on about 90 different clinical topics 66. The guideline documents of the NHG are less extensive than the documents of CBO as a result of the fact that they have a more limited scope of end users.

Internationally, the consideration of matters of equity and differences between men and women in the development of clinical guidelines is of growing interest 7, 41, 67, 68 and in some countries it is already a legal obligation to take these equity issues into account in guideline development 69. Also, international quality criteria for the development of guidelines, formulated in the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument 70,71 prescribe a detailed description of the guideline’s target population. The AGREE instrument names gender as one of the factors that may be considered in such descriptions. Taking the above into account, strategies need to be developed to implement the consideration of matters of equity in guideline development. The focus of this thesis will be on sex-specific issues.

Objectives of the study presented in this thesis

The findings presented in this thesis are based on the data derived from two research projects financed by ZonMw as part of their specific programme to integrate sex-specific health care into mainstream health care. The project ‘Gender bias in scientific research and guideline development in Dutch health care’ was designed to evaluate the consideration of sex differences in health research and guideline development, and the follow-up study, ‘Diversity consultation for guideline developers: implementation project with the aim of enhancing the systematic consideration of differences between
In Guideline Development: Sex Differences in Men and Women

Aim: To develop a framework for integrating sex differences in guideline development and to evaluate the current practice.

Methodology: A stepwise approach was followed, addressing incentives for promoting sex-specific health research, the integration of sex-specific health research in guideline development, and the development of an educational intervention.

1. How do formal measures taken by the financiers of health research encourage applicants to pay attention to sex differences in research proposals?

   To answer this question, the extent to which applicants submitting health research proposals to ZonMw considered sex differences in their proposals and the impact of formal measures by ZonMw to encourage attention to sex differences in research were examined.

2. In what way do guideline developers address evidence on sex factors in their guideline development methodologies? Could attention to these factors be improved, and if so, how could this be achieved?

   The process of clinical guideline development by NHG and CBO was determined and evaluated in terms of the consideration of sex differences. Potential barriers to and facilitators of the consideration of differences between men and women in guideline development were identified. Recommendations for enhancing the consideration of sex differences in guideline development were formulated.

3. How can an educational intervention to encourage the consideration of sex factors in guideline development be developed?

   A training course was developed to enhance the consideration of differences between men and women in guideline development. It was aimed at both the formal process of guideline development and at the barriers and facilitators that were determined to be a factor in considering differences between men and women in guideline development.

4. What is the effect of an educational and feedback intervention to enhance the consideration of sex differences in clinical guideline development?

   To answer this question, the educational course and expert feedback for guideline development were tested in a quasi-experimental design in three CBO and three NHG guideline working groups. A before-after measurement of the attitudes towards the relevance of considering sex differences in guideline development compared with a control group was performed and analysed. Also, a qualitative document analysis was performed and analysed for the evaluation of attention to gender differences in guideline documents compared with a control group.
5. What are the characteristics and conclusions of discussion episodes on sex-specific, data-based research issues (subject matter, initiator, group approach towards the topic and themes) during the process of clinical guideline development?

To answer this question, observations of the meetings of the six intervention guideline groups were performed and data were analysed by means of a qualitative method.

The justification of the chosen intervention strategies applied for research questions 3, 4 and 5 is provided below.

**Framework of strategies for enhancing the consideration of sex differences in guideline development**

For our study, we needed a theoretical framework to develop an intervention to change the behaviour of guideline developers. Since information on changing the behaviour of guideline developers was lacking we framed our actions with the evidence based implementation strategies which were already described in the literature. Barriers and facilitators to incorporating a consideration of sex-specific evidence in guideline development needed to be identified and the target groups needed to be motivated and provided with knowledge and tools based on the identified barriers and facilitators.

Studies have 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). The latter approaches are likely to be effective if they are used to challenge negative attitudes of professionals or to teach new skills. Expert feedback is also proven to be a useful method to improve practice. Although this knowledge is mainly obtained from studies on the implementation of guidelines and, a bit more broadly, studies on health promotion, the knowledge also applies to the group processes of guideline development and the understanding, willingness and actual inclusion of sex-specific notions in guideline development. Therefore we developed interventions based on both interactive educational approaches and expert feedback. The interventions were developed together with CBO and NHG and were focussed on their staff members. Our assumption was that they were the most constant factor in guideline development and that they play a prominent role during the process with their methodological support.

Since we performed our interventions in a setting where the circumstances could not be controlled we decided on a quasi-experimental study design.
Question 1 is addressed in Chapter 2. In this chapter the consideration of sex differences in grant applications is explored. The hypothesis we tested was whether proposals submitted to two programmes conducted by ZonMw considered sex differences. For this, 213 proposals were analysed and categorized according to the expressed intention to take sex differences into consideration. Furthermore, those proposals in which such an intention was absent were appraised by researchers to determine whether an intention of this kind would have been relevant.

In Chapter 3, in which question 2 is addressed, we described the development of clinical guidelines and tested the hypothesis of whether guidelines consider sex differences. For the latter, seven recent guidelines compiled by CBO and NHG on four conditions were selected. The contents of the guideline documents were analysed according to their consideration of sex differences. Also, information was obtained from interviews with key persons on the guideline committees. Findings were discussed at a meeting of experts. As an outcome, recommendations to enhance the consideration of sex differences in guideline development are presented.

Chapter 4 addresses question 3 and deals with a method for integrating the consideration of sex differences in the development of clinical practice guidelines. The chapter describes the development of a training course which was used as an intervention to implement a more systematic approach towards considering sex differences in guideline development. For the development of the training course, strategies were used for changing provider behaviour and adult learning styles. In addition, some initial results of an evaluation of this course are presented.

Question 4 is addressed in Chapter 5. This chapter shows the description of the design of the quasi-experimental study, of which the training course and feedback by a gender expert are the two interventions under study. This chapter also describes the outcomes of the evaluation by means of two methods: statistical analysis of the answers on a questionnaire for guideline developers on the consideration of sex differences in guideline development, and the screening of six intervention guidelines on their consideration of sex differences.

Chapter 6 addresses question 5 and describes the exploration of characteristics of guideline committee discussions on sex-specific data and which of those characteristics facilitated or inhibited the uptake of this data into guidelines. For this, six guideline working group meetings were observed. Isolated transcriptions of discussions on sex differences were matched with the content of the guidelines concerned and analysed.

The overall findings and reflection to the research methods of Chapters 2 to 6 is provided in the last chapter, the general discussion. Implications for future guideline development and research are also described.
Reference List


21. General Accounting Office.Women’s Health. NIH has increased its efforts to include women in research. 2000.


