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Master's Thesis

“How do researchers view sex and gender differences in research?

*An analysis of the strategies for female enrollment and retention in medical
research”*

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Abstract

Background: In recent years, multiple studies have been conducted regarding the necessity of including both sexes in medical research. This dissertation analyses the point of view on the subject from the prospective of 12 researchers active at a University Medical Center in the Netherlands. The Research Questions: *How do researchers view sex and gender differences in research (1), and which are the strategies for female enrollment and retention in medical research (2)?* were answered.

Methods: In-dept semi-structured interviews were performed by asking questions about researchers' perspective on sex and gender differences in medical research, obstacles in different research phases, as well as enrollment and retention strategies. The interviews were audio-recorded and transcribed verbatim. **Results:** Researchers reported being aware of the importance of including sex and gender differences in research. Although, researchers report that less is known about gender and dropout reasons. Researchers noted that obstacles exist and try to tackle them by implementing certain strategies. There were strategies implemented by certain medical departments that were more successful than others. However, some researchers noted no activate strategies to overcome obstacles. Overall, my results matched prior literature. **Conclusions:** this study highlights the knowledge gaps that are still present in research regarding the enrollment and retention of women in medical research. To close the gap and guarantee better outcomes and health to all sexes and genders multiple strategies must be activated. All stakeholders need to collaborate to achieve a common goal: equality in female and male ratio in medical research.

Keywords: Sex and gender differences, women enrollment in medical research, women retention in medical research, enrolling strategies

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1. Introduction

“Not incorporating gender and sex analysis in research can cost lives and money. Researchers have a duty to be as rigorous as possible” [Prof. dr. Schiebinger, Stanford University, Kilden Gender Research, November 2020].

Traditionally and historically, healthcare has been based on men and consequently, women were not considered in the medical debate. The male body was studied and analyzed by scientists and doctors, who were also men. As a result, women's bodies were not investigated, because they were considered just a "variant" of the male body, and therefore not interesting for study (Young et al., 2019). Nowadays, we find ourselves studying both bodies, but there is still a big gap between men and women in medical research. Although women have been involved in drug research more since the 1990s, equality remains a long way off.

What are the consequences on women's health by not conducting research on them? In the EU, although women live longer than men, they spend a considerable portion of their lives unwell (WHO, 2016). It has been estimated that women spend 77% of their life in good health while men spend 81% of their life in good health (Eurostat, 2012). According to the Gender Equality Index of 2019, in 2016, women in the EU spent on average 19 years of their lives in poor health, compared to 15 years for men. In the Netherlands, this difference is greater, with women facing more than 25 years of poor health compared to roughly 20 years for men (Eurostat, 2012).

According to research, one of the reasons women experience poorer health compared to men is due to underrepresentation in clinical trials (Goldstein et al. 2019; Mirin, 2021). Evidence shows that in the last two decades, several drugs have been withdrawn from the market due to adverse drug reactions for women (Coakley et al., 2012). According to research, women are 50% more likely than men to suffer from medication side effects, and 33% more likely to be hospitalized due to medications (Rodenburg et al., 2011). The pharmaceutical industry invests in clinical trials based on the demand

for medicine from the population at large, and thus, men are preferred over women in clinical trials because of difficulties in achieving satisfactory and complete results (Holdcroft, 2007). In addition, in pre-clinical trials, only 9% of rats and mice are female when it comes to analyzing animals (Dekker et al., 2021). The male-oriented medical approach that is still dominant today comes with great consequences for women's health (Holdcroft, 2007; Rodenburg et al., 2011). This inequality within the pharmaceutical industry is also being recognized as increasingly important within our society.

Recently the problem of female participation in research has been addressed in scientific and public debates (Guardian, 2021). Several studies demonstrate that improving women's health is beneficial for society at large (Davidson et al., 2011). Thus, this topic has both scientific and social relevance; society is now realizing how certain medical approaches can harm women. There are differences between the male and the female body, therefore, both should be studied to guarantee the same health opportunities for both sexes. This highlights the need for promoting clinical trials between all sexes in medical research, or, if this is not possible, to clarify why it focuses only on one sex (van Diemen et al., 2021).

1.1 Research questions

My thesis proposes to answer two research questions: *How do researchers view sex and gender differences in research (1), and which are the strategies for female enrollment and retention in medical research (2)?*

To answer these research questions, I interviewed researchers from a Medical Center in the Netherlands regarding their perspectives on the topic of sex and gender differences. Also, I asked if researchers feel the necessity of changes in recruitment, enrollment, and retainment methods to tackle the obstacles women might encounter when enrolling and staying enrolled in medical research. Moreover, I investigated whether there are any strategies that they use to address the lack of resources and knowledge regarding how to increase and retain female participation in clinical trials. This

analysis provided information regarding what is known about the topic, and what strategies are in place in the Netherlands. The strategies that I found in the literature are mainly North American based. Thus, I examine how researchers feel about the availability of enrolling and retention strategies in the Netherlands.

While previous studies looked at sex and gender differences in research mainly from the perspective of research participants, I decided to examine it from the perspective of researchers. Thus, I further investigated the underrepresentation of women in research by identifying the key priorities and barriers researchers may encounter when enrolling women. Targeting researchers added information regarding the problem from the perception of the research designers and conductors. Also, this study further demonstrates strategies that can help to fill this “knowledge gap” and help women to enroll and stay enrolled in medical studies with positive consequences on women’s health.

Regarding the expectation of the study, I expected to find strategies that are already in place to enroll women in medical research, as well as strategies and techniques that are planned to be done soon. Furthermore, I expected to have a higher share of researchers that are aware of the importance of the topic and that try to commit themselves to enrolling more women in research. This study seeks to reinforce the current literature and to further contribute to female enrollment and retention methods in the medical field.

This thesis has an interdisciplinary approach since it focuses on social science aspects and mechanisms, as well as public health and government issues. Furthermore, it investigates medical research, with a focus on clinical trials, which involves the scientific and medical fields.

2. Overview of existing research and Theoretical Approach

In the last few years, governments and institutions have concluded that the lack of sex and gender-specific data in biomedical research has severely limited research as well as the quality of medical care (Reza et al., 2022). As emphasized before, several studies have been conducted about the motifs for which women might or might not be willing to participate in medical research. This section will give a quick overview of the obstacles that have been found to prevent women from enrolling in medical research as well as what makes them drop out more than men. After, I will analyze the strategies and how they affect retention. These strategies are based on (1) communication techniques (awareness, and patients' empowerment), (2) funding and grants allocations, (3) the use of new technologies and web-based interventions, as well as (4) online registry systems.

2.1 Obstacles perceived by female participants when enrolling in medical research

Some reported mechanisms behind women's higher share of underrepresentation in clinical trials are rooted in behavioral aspects. These include women's greater perception of harm from medical trials compared to men. Women report feeling more responsibility for their role in the family and thus feel they do not have the time to participate in clinical trials. They also are more likely to consult with external sources before which may affect their choice as well as the timeliness of their decision to enroll (Scott et al., 2018). There are also logistical reasons which include women struggling more than men to reach the venues where the clinical trials are conducted, as well as finding places where to leave their children during the experiments (van Diemen et al., 2021). Because of these reasons, women have been found to be time-consuming and are considered costlier to engage than men (Coakley et al., 2012), thus further dividing the enrollment of men and women.

2.2 Strategies for enrollment and retention of women in medical research

To tackle “behavioral and gender-based obstacles”

Since perceptions of harm differ significantly between men and women, there are specific strategies that have been found effective to deal with the problem of underrepresentation in medical research (Ding et al., 2007; van Diemen et al., 2021). First, the sex of the recruiter does matter. It appears that women are more inclined to be recruited in research if their recruiters are of the same sex (Coakley et al., 2012). As I previously mentioned, women perceive participating in medical trials as riskier than men. According to a conducted study, researchers should train doctors to spread awareness to their patients through the provision of transparent, complete, and quality information regarding medical research (Coakley et al., 2012). This process might help to convince women to feel safer when it comes to enrolling in clinical trials and will also inform them about the vital role they play in medical research (Cheung et al., 2008).

To tackle “logistical obstacles”

Several strategies have been developed to address transportation-related issues (Coakley et al., 2012). Targeting where to conduct the studies can be a crucial way to reduce costs, and time, and tackle the transportation problem women might have when trying to reach research venues. Another solution has been identified through the implementation of innovative strategies, such as the use of web-based research (Chung et al., 2008; Coakley et al., 2012). The use of new technologies would reduce costs, geographical barriers, and scheduling difficulties by allowing the participants to remain at home without the need to travel to a research site (Coakley et al., 2012).

Some countries, such as the United States, have developed recruitment systems to help make recruitment of women easier for them. The University of Michigan has developed a tool known as the “Women’s Health Registry”, which is a database consisting of women who are at least 18 years

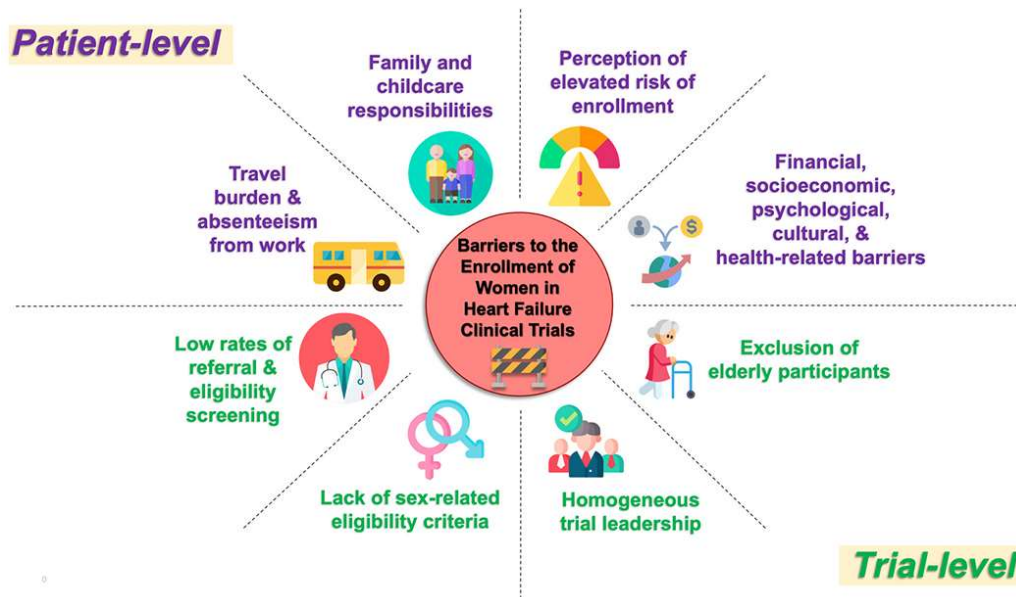
old and are interested to participate in research (Rogers et al., 2007). The researchers who were contacted during the study reported that thanks to the Registry, they were able to recruit out of it more than 36% of the women in their studies (Rogers et al., 2007).

2.3 Theoretical Approach

I used a combination of concepts and models. Two approaches were needed to answer both my research questions. With the aim of answering the first research question (“How do researchers view sex and gender differences in research?”), I used the “Framework to analyze gender bias in research” which has been shown to have both social and clinical relevance (Ruiz-Cantero et al., 2007). According to this framework, gender biases are carried out during the research and affect the way in which researchers analyze and view results. Furthermore, the framework focuses on the necessity of eliminating gender bias when it comes to developing and testing hypothesis and substituting them by applying a gender perspective. As a result of assuming that there is sex equality, gender-based disparities have emerged in healthcare, health promotion, and preventative services, of which clinical trials are a part of (Ruiz-Cantero et al., 2007; Chilet-Rosell, 2014). Through this framework, I asked questions to researchers about whether they view gender bias as a current issue. If researchers identify that there is a bias, I was also interested to know how they address it (Appendix 3).

To answer my second research question (“Which are the strategies for female enrollment and retention in medical research?”), as a theoretical approach, I followed a figure by Reza et al. (2022), which I will refer to as a model. The model is focused on the patient-level and the trial-level on the barriers that women encounter when enrolling in cardiovascular diseases and heart failure clinical trials (Figure 1), and it is highly based on the US Food and Drug Administration (FDA) Research, Policy, and Workshops on Women in Clinical Trials.

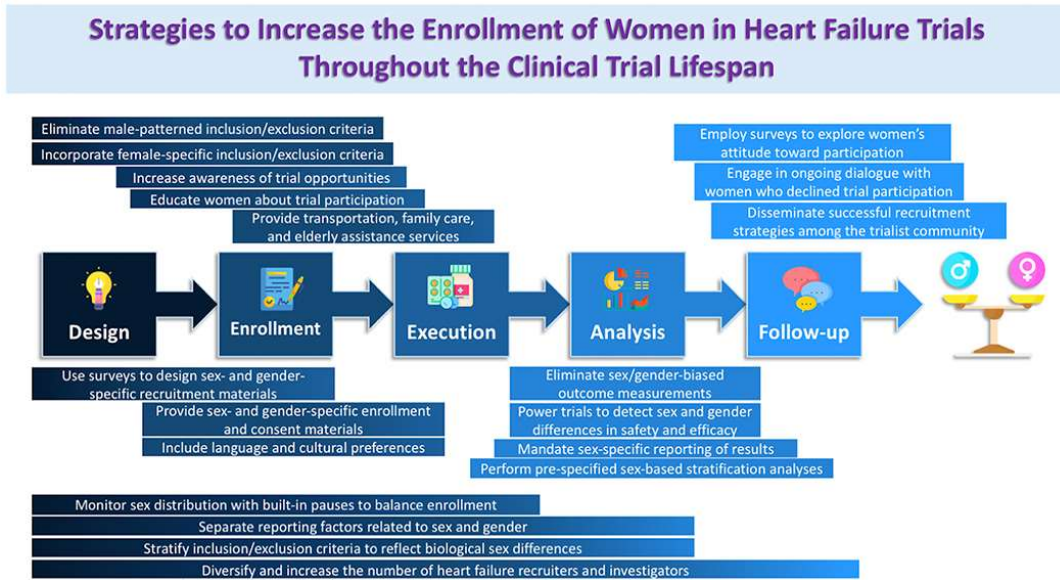
Figure 1. Source: Fig. 1. Patient- and trial-level barriers to the enrollment of women in heart failure clinical trials (Reza et al., 2022)



I adapted the model by asking how researchers view these obstacles and how they overcome them when enrolling and retaining women in clinical trials. Further, this model was only used in a North American setting, which I adapted to focus on the Netherlands. Currently, the model has been only applied to the representation of women in heart failure trials (Parwani et al., 2022). I expanded the application to the broader medical field, to highlight the differences and similarities between different medical specialties and departments.

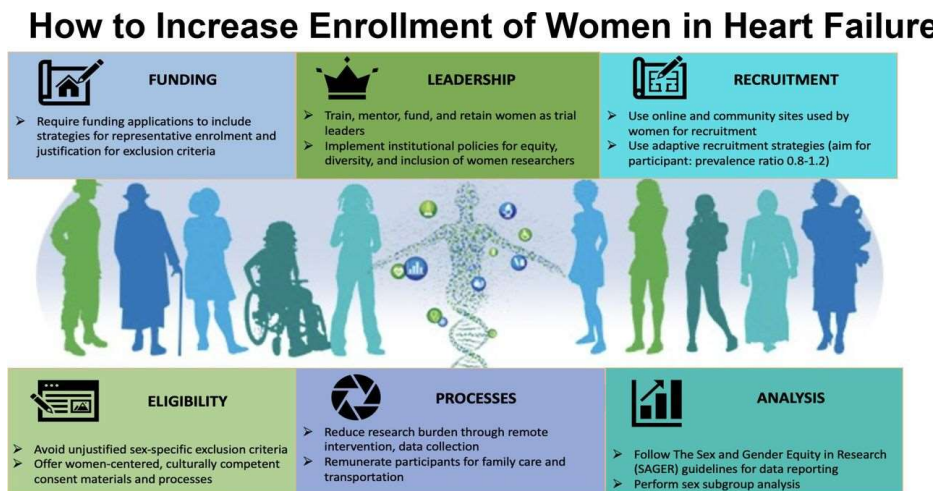
Reza et. al (2022), in the same study, produced another model that illustrates strategies on how to tackle obstacles regarding women's enrollment throughout the lifespan of a heart failure study (Figure 2). Once again, I adapted this model to the broader range of medical research specialties. Figure 2 illustrates how this model suggests ways to overcome female participants barriers at each stage of a clinical trial. Based on this diagram, I formatted my interview questions regarding how researchers conduct their research and how they perceive enrollment obstacles at various stages of a clinical trial.

Figure 2. Source: Fig. 2. Strategies to increase the enrollment of women in the heart failure trials throughout the clinical trial lifespan (Reza et al., 2022).



Parwani et al. (2022), create a model to overcome the barriers to enrollment discussed by Reza et al. (2022). From the Parwani et al. (2022) model (Figure 3) I chose to concentrate on two factors that were not mentioned in the previous model (Figure 2). These two factors were “Funding” and “Leadership”. In my model, I included these two specific factors and asked questions to researchers regarding their opinions about the necessity/importance of funding and leadership in women's enrollment.

Figure 3. Source: Fig. 1 The central illustration highlighting various strategies to increase enrolment of women in heart failure trials during the course of research study (Parwani et al. (2022))



Overall, my theoretical approach consisted of few different frameworks. First, I used the “Framework to analyze gender bias in research” to investigate whether researchers perceived the presence of gender bias in the medical research field. As well as how they handled this bias when designing and conducting their research. Second, I focused my questions by relating them to Reza et al. 's study (2022) on the barriers that women encounter when enrolling in research. Third, I used Reza et al. (2022) strategies model to emphasize the stages within a clinical trial in which these barriers occur. As well as strategies to overcome the obstacles that are specific to these stages. Lastly, I used the paper by Parwani et al. (2022) to incorporate two more crucial factors (funding and leadership) that might influence women's enrollment and retention in clinical trials.

3. Research methods

3.1 Study design

This research is based on a collection of qualitative data through in-depth semi-structured interviews with researchers who are currently active at a University Medical Center in the Netherlands. I decided to use interviews instead of another data collection technique since open questions were necessary to have complete answers. Using a quantitative approach, such as a close question survey, would not have produced such complete and in-depth results, nor would it be feasible within the scope of the study.

3.2 Study sample

Case description

The Dutch institution in which the study has been conducted is a University Medical Center, an academic hospital. The Medical Center conducts a lot of research, and its research output has increased significantly, with the highest number of publications in 2021. I choose to conduct my research at this specific medical center since there are many initiatives to achieve gender balance as

described in their Gender Equality Plan and Research Code. The enrolled sample was collected within the networking of the Medical Center. First, I recruited participants by using a list of researchers who subscribed to a series of seminars regarding Diversity and Inclusion. Then, following a database that contained the names of all the researchers employed at the Medical Center, I selected and contacted those that work with human or animal subjects. Both lists contained names of researchers who had a broad range of medical research specializations. I contacted them via email with an informational letter (Appendix 1) that explained the topic and the aim of the study to recruit those who were interested in the project and willing to share their experience.

The interviews were conducted as expert interviews, as the interviewees have extensive knowledge about the research topic. The number of researchers I interviewed is 12 (Table 1). This number was sufficient since qualitative saturation (Saunders et al., 2018; Friedman et al., 2015) was achieved. Both male (3) and female (9) researchers were interviewed, to have a more complete perspective and to explore whether researchers of different sexes use different tactics to recruit and retain women in their research. Furthermore, the target group included researchers at different levels, and from different departments, but that have sufficient knowledge of recruitment and retention of research participants, as well as about research policies and strategies. Some (5) of them are classified as Senior researchers, while others are Ph.D. candidates (6), and one is a Postdoctoral researcher.

By following this process, I had different points of view about how women's recruitment is conducted by researchers who occupy diverse positions, as well as differences between medical departments and specializations. The choice of including researchers at different levels was dictated by the decision of testing if they all had the same opinions about female enrollment in research, as well as the different involvement that they might have in the recruitment strategies and in the implementation in the medical research practice. Almost all the interviewed researchers work with human subjects, but 2 researchers work in the early clinical trial phases (pre-clinical) with animals (mice) as research subjects.

Table 1. Characteristics of interviewed researchers

	<i>Job position</i>	<i>Department</i>	<i>Subjects</i>
Researcher n.1	PhD Candidate	Cardiology	Humans
Researcher n.2	PhD Candidate	Epidemiology	Humans
Researcher n.3	Senior Researcher	Cardiology	Humans
Researcher n.4	Senior Researcher	Psychiatry	Humans
Researcher n.5	Senior Researcher	Pharmacology	Animals
Researcher n.6	Academic Teacher, observations of when they were PhD candidate	Medical Biology	Animals
Researcher n.7	PhD Candidate	Cardiology	Humans
Researcher n.8	Senior Researcher	Epidemiology	Humans
Researcher n.9	Senior Researcher	Geriatrics and Gerontology	Humans
Researcher n.10	PhD Candidate	Cardiology	Humans
Researcher n.11	PhD Candidate	Health Sciences	Humans
Researcher n.12	Postdoctoral Researcher	Epidemiology	Humans

The average interview lasted for about 25 minutes and all the planned questions were answered in all the 12 interviews. The interviews were audio-recorded where out of 12 interviews, 9 were done via MS Teams and recorded through the software. While 3 interviews were conducted in person at the Medical Center and recorded with my personal phone. All the audio records were transferred from the personal devices to the secure U-Drive immediately after the interviews and deleted from the personal devices.

Regarding the ethical aspects, my research was conducted in line with Utrecht University policies, as well as the Medical Center ones. It does not include sensitive, real personal information, or the violation of the physical and/or psychological integrity of the participants, since the study was conducted with experts. The study received ethical approval (number 22-0912) by the Ethical Review Board of the Faculty of Social and Behavioral Sciences of Utrecht University on March 21st, 2022. Before starting the interviews, research participants were provided and signed an informed consent form (Appendix 2) to participate in the study. The form guarantees their privacy and that their data

would not be shared outside the study, and that they would all be anonymous. Regarding the anonymization, the interviews were anonymized by not referring to any other strictly personal information to not compromise the respondents' identities (Kaiser, 2009).

3.3 Data and measurements

During the interviews, a list of open-ended questions was asked to the interviewed researchers (Appendix 3). The interviews did not follow a predetermined order, as I preferred to have answers come up more naturally, allowing for more realistic responses. Although, I considered that all the questions were answered (Gill et al., 2008).

3.4 Data analysis

The in-dept interviews were transcribed by using the “transcribe” option on Microsoft Word Online. After, the transcriptions were manually reviewed to correct dictation mistakes. The analysis had the goal of finding patterns and analyzing in-depth what is known and what has been done so far in terms of strategies to enroll and retain women in medical research.

Coding strategy

For analyzing the interviews, I used the software QSR NVivo by adding the transcriptions to the software, which I have then coded. I used an inductive approach for my coding process. I created my codes based on the qualitative data I collected during the interviews. I began my coding process by identifying big concepts that my interviewees' answers intersected with. I associated codes and concepts with sentences and answers I found important and that had a practical application for the study. I repeated this process until all the data had been coded (Medelyan, 2021). Lastly, I created a coding tree which is a graphic illustration of the analysis. This allows to physically identify the most relevant concepts and themes that arose from the interviews (Appendix 4).

4. Analysis and Results

To answer the question “*How do researchers view sex and gender differences in research?*”, during the interview study, participants were asked questions regarding their perspectives on the topic of gender and sex differences. While, to answer to the research question “*Which are the strategies for female enrollment and retention in medical research?*”, the interviewed researchers were invited to share their experiences connected to the research they have conducted, starting with questions regarding the research design and expectations about female enrollment, followed by others about the implementation stage to see if their expectations were met and if women were enrolled and retained into their studies.

I will now quickly illustrate again the obstacles that women encounter when enrolling in medical research. Then, I will show in which phases of research these obstacles arise. After, I will analyze how these obstacles relate to the researchers’ obstacles. Lastly, I will explore the strategies that the researchers at the Medical Center are aware of, those they successfully apply during their research, as well as those they do not apply.

4.1 Obstacles to women enrollment in medical research

In the research overview section, I have illustrated which are the barriers women report as crucial to their enrollment and retention in clinical trials. I have illustrated them in two categories, one related to behavioral and gender-related obstacles, the other related to logistical obstacles. A researcher added something interesting about gender-related obstacles. Women have been found to decline more than men when it comes to new therapies and medications: “*There is a new type of medication for anticoagulation that have been around for more than 10 years and when we see registry data, we see that men are more into these new therapies than women. What happens is that the guidelines suggest the new treatment, but then women are more reluctant to move to a new treatment, even though it is recommended. Maybe they are just not willing to make that change if they aren’t really comfortable*”

with it, or they might not feel safe” [Research n.1]. In the future, these findings may pose a problem, as it means that if new therapies are not tested on enough women, they might not be applied to them.

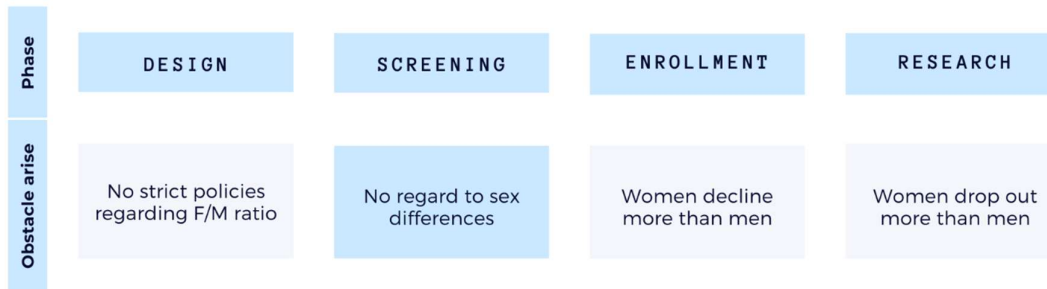
Most of the researchers I have interviewed have confirmed the literature findings regarding women’s obstacles to enrollment. Although, some researchers reported that the decision of not enrolling in research is not always explained by women. They also add that it could be difficult for them to activate strategies if they are not sure on which obstacles they should concentrate on.

4.2 Stages when the obstacles to women’s enrollment in medical research arise

“When we start finding them [contacting potential research participants], we notice that there's more males that are willing to come over than females. That's where the issue starts. Then, at the third step, to eventually sign the informed consent there's another selection, so more and more females drop out, instead of males. So, the imbalance is getting greater. You start with maybe 60-40, 60% male, 40% women. Then, it's 70%-30%, and then 80%-20%. So, that's where the difference starts” [Researcher n.3].

Findings from the interviews, show that there are four crucial stages during a clinical trial study in which sex differences emerge (Figure 4): Research Design (1), Screening (2), Research Enrollment (3), Research Analysis (4). The Research Design (1) is the phase in which the researcher and their team design how the study will be conducted and defines the study sample. The Screening phase (2) refers to the moment in which participants are selected based on the inclusion criteria established during the research design. At this stage, before starting the research, patients are enrolled and screened regardless of their sex. The Research Enrollment (3) is the phase in which the participants sample is approached to enroll in the clinical trial. After signing the informed consent, the participants are officially enrolled in the research. Lastly, Research and Analysis (4) is the phase in which the study is conducted, that ends with the analysis of the results and their publication.

Figure 4. Crucial phases when obstacles arise. Author’s elaboration based on Reza et al. (2022). For simplicity and to make clearer the phases, I condensed the 5 phases illustrated in Figure 2 to the 4 shown below.



Design. During the interviews, researchers reported that policies for female and male ratio in research are not always activated. Furthermore, some of the policies in place are still only recommendations and researchers report that even if they design their study considering the sex and gender dimension, sometimes it not always applicable during the other phases of the research.

Screening phase. Regarding the screening phase, all the researchers sustained that this stage needs to be done without regard to sex and gender differences. This is because it is a phase in which people are screened only regarding their pathologies. Although, not having policies that oblige to screen both sexes from the very beginning of the study leads to screen more men than women before the enrollment would even start. In this sense, women “drop out” before even being able to take part into the study.

Enrollment. When it comes to enrollment, patients are approached and informed regarding the research. At this stage, women are found to decline participation more than man.

Research. Lastly, when the research is conducted, women are reported to drop out of the research more than men.

Drop out

There is a lot of speculation regarding women's motifs for dropping out from medical research. In the interviews, researchers reported that when participants dropout from a study, they are not required to tell the reasons of their drop out. *"We really don't try to do the other questions much. We feel that the patient maybe is already uncomfortable saying no, and we don't want to let them feel more uncomfortable, so we know we don't go further"* [Research n.1]. Also, if patients decide to express their reasons for dropping out, some researchers reported the impossibility of collecting data about it, because of privacy reasons. Therefore, I did not collect enough data about drop out and this showed that there is still very little evidence about women's motifs for dropping out of clinical trials, as well as regarding retention strategies. Closing this gap and focusing on this stage, might be more difficult than concentrating on the enrollment stage.

4.3 Factors that influence the researchers' perspective in the enrollment and retention of women in medical research

I have illustrated the obstacles and the stages in which researchers find the most difficult to include women as participants in medical research. I will show now which are the common motifs for activating or not activating strategies for female enrollment. As well as which are the successful or unsuccessful attempts to employ these strategies. The patterns that emerge include 6 different factors: Awareness (1), Time (2), Policies (3), Research grants and funds (4), Leadership (5), and Approach (6). To better understand these factors, I have categorized them as "external to the researchers' intervention" (coded as "External factors") and as "internal to the researchers' intervention" (coded as "Internal factors").

4.3.1 Factors external to researchers' intervention

I grouped all the factors that actors perceive as being outside their control under the code "External factors". These factors include the categories of "Research grants and funds", as well as "Policies" and "Leadership".

Research grants and funds

"The grants really dictate what the researchers will do, but they are also the ones who need to finance it, because it [including both genders] will probably mean doubling your sample size, so they also need to pay for it" [Researcher n. 4]. The funder of the research project is often the one who "dictates" how the study must be conducted. During the interviews, several participants mentioned that the grants are given by organizations which set the guidelines that researchers must follow when designing and conducting their studies. For example, pharmaceutical companies, put great emphases on reaching the biggest number of people, regardless of their sex. A researcher says: *"What we see is that the companies, and I would act the same if I were the company, want to get their drug delivered to as many patients as they would like. So, the design of the studies is extremely broad. Not only males and females, but as bigger population as you can get. If you get registration for big population, you can earn more money because it's applicable to more patients"* [Researcher n. 3]. By prioritizing the quantity of patients over their diversity, the grant funders and agencies contribute to causing sex and gender inequalities in medical research. With this approach, they discourage researchers from focusing on strategies that directly target the inclusion of women and other different genders. Most of the researchers expressed the necessity of allocating specific grants and funds for proposals that pay attention to sex and gender differences in all phases of research.

Policies

As mentioned by a researcher, some institutions and grant providers are moving in the direction of establishing policies for the inclusion of a ratio of women in medical research. First, at the European level, after the Horizon Europe 2020 project, rules regarding the inclusion of both sexes in research have been reinforced. While at the Dutch level, the attention towards sex and gender in research is increasing, predominantly thanks to the “Gender and Health Research Program” from ZonMw. Although, a researcher (Researcher n.2) has described this approach as “*minimal*” compared to what other countries have done. Some researchers reported that in many cases policies are not very strict and can easily be followed more as recommendations than as actual mandatory policies. This mechanism of proposing policies, but then not really activating them, could be connected to what prof. Sara Ahmed refers to as “non – performative policies”. The author describes how some policies could be considered policies only on paper, because they are not actually implemented. She also explains that bringing up a policy does not automatically bring it into effect (Ahmed, 2016).

Leadership

According to some researchers, the Medical Center internal structure might also influence the enrollment of research participants. Having gender diverse teams is proven to facilitate scientific progress and innovation, and to promote the creation of better research and policies (van der Lee & Ellemers, 2015). “*I think if you diversify in staff, also the research will become more diverse. I mean that’s how groups work. In that sense, I think how a University Medical Center does with regards to this issue, the consequences will be felt at all different levels, including medical Research and Preclinical Research*” [Researcher n.5]. This finding aligns with the literature that sustains that the sex of the researcher might influence the decision of women to enroll or not enroll in research. In fact, according to three researchers, the underrepresentation of women in research is a direct result of the lack of women working in research, especially in senior and leadership positions.

4.3.2 Factors internal to researcher's intervention

Under the code “internal factors” I grouped the factors that are closely connected to researchers’ “awareness”, to researcher’s time management (coded as “time”), and to researcher’s “approach” (3).

Awareness and semi-awareness

All the interviewed researchers are aware of the necessity of including both women and men while conducting medical research. Four researchers highlight that they are aware of the problem, but they do not activate any strategies to enroll women and keep them enrolled. This leads to a subcategory of awareness, that I will call “semi-awareness” here. Although, the motifs for which two researchers do not activate strategies (Researcher n.9 and Researcher n.11) might be connected to fact that they do not experience too many obstacles in enrolling women in research. While for the other two (Researcher n.8 and Researcher n.12) might be because they are not directly involved into the recruitment of participants in research.

Furthermore, the following quote clearly shows that, especially for young female researchers, there is still another big unsolved problem regarding awareness. The way in which different sexes are approached in research. *“Whenever I try to advocate sex differences or make people aware of it. Yeah, there are some mixed reactions. I think 80% of people are very receptive to it and 20% of people are like: ah yeah, it's a girl talking, so why should we take her seriously?”* [Researcher n.2]. Even if the number of female researchers has increased and keeps increasing every year, this shows that some women still do not feel fully accepted.

Time

“It's amazing. It's incredible how slow this is going” [Researcher n.3]

Researchers have expressed that including both sexes in equal portion takes more time and it must be expected that research would take longer to be completed. Although, as a researcher reported, “*active*

time” needs to be applied. If the obstacles to women’s enrollment are investigated with further attention, the process of enrolling and researching might become faster. This reflection suggests a change in the approach. Researchers could change the way in which they administer their time and how they design their study. Reza et al. (2022) suggested to conduct surveys before starting research to collect data about the possible obstacles research participants might encounter and tackle from the very first phases of the study.

Approach

“Often, we provide people who have participated in a study with a small monetary reward to compensate them for the time, and perhaps that is just less attractive for women. It's also something that you really see in the brain” [Researcher n. 4]. Researchers explained that in their experience the same strategies do not work the same way with people of different sexes. This finding matched the literature. Arguably, women have different ideas and perceptions about clinical trials and medical research than men do (Liu & Mager, 2016). Furthermore, several researchers explained to me that the obstacles that women encounter when enrolling in research vary largely from one study to the other. As a researcher mentioned *“I think we need to take one step back first before we go into the solutions we need to define. I mean, we define the problem. The problem is obvious. The problem is there's too little women in trials, period. We all agree, everybody agree. Second is, what are the causes? This is what we really need to find out first, the causes and only. When we know the causes, we can try to intervene and do something about it”* [Researcher n.3]. This researcher’s perspective made me reflect about how the problem of women’s enrollment and dropout from medical trials has been approached and what are the directions in which it should develop. Trying to activate strategies without investigating further the obstacle might not be the best solution. This approach is one of the internal motifs for which researchers believe it is hard to implement successful strategies. According to researchers, it is necessary to take a step back and looking at the bigger picture. First, focus on deeply understanding the reasons for female underrepresentation in medical research. Then, successfully

implement the strategies. Some researchers have proven that this mechanism works, I will analyze it further, in the strategies section.

Medical specialties and departments differences

During the interviews, I have found that there are variations between different studies, which make it more difficult to find a common ground of rules and policies. Each medical department faces different challenges when it comes to enrolling women in research. For example, Cardiology has more difficulties than Psychiatry. Another factor to consider is the type of study. Researchers reported that lab studies are less likely to attract women due to the difficulty of reaching the trial sites. For Cardiology studies, to screen patients that have been selected, it is necessary for them to be physically present in the hospital or the study's site to undergo the research since they require the use of instruments and tools that cannot be taken into patients' homes. As showed in previous sections, reaching the research venues is at times harder for women than men.

4.4 Strategies employed to tackle the underrepresentation of women in medical research

In this section, I will first analyze the strategies that researchers have reported employing to tackle the behavioral and gender-related obstacles that women encounter when enrolling in medical research. I will then move to the logistical obstacles. Later, I will illustrate the emerging strategies that have only recently started to be implemented, but that researchers consider to be important for future developments in enrollment and retention in medical research. Lastly, I will show the strategies that are known, but have not been implemented yet by researchers.

Strategies to tackle behavioral and gender-related obstacles

According to a researcher, women's brain is proven to be different from men's, which also effects their behaviors and emphasizes behavioral differences (Goldman, 2017). Four researchers reported that women spend more time reading the informed consent than man do. Also, they ask more questions about the research and generally tend to pay more attention to understanding what the

benefits of the research are. This shows that the researchers' experience aligns with literature findings. Researchers who activate strategies to reassure women, tend to spend more time listening to the questions and answer to them. Thus, this suggest that certain communication strategies and approaches might work well.

A researcher reported, *"I think it's really good for women to emphasize that their participation is very important for future diagnosis and treatment of other patients because I think they are quite willing to do something good for society and especially for people who may have the same disorder as they do so. That would be a different reinforcement than just giving them a monetary reward"* [Researcher n. 4]. Contrary to what one might think, even if women are reported to perceive higher risk of harm when it comes to medical research, financial incentives are proven to not motivate their participation to research (Zutlevics, 2016). Men seem to be more "money-driven", while women are more willing to enroll in medical research if they know that it might contribute to society, and even more to find solution to a disease or issue they are experiencing.

Strategies to tackle logistical obstacles

"I noticed two differences in the willingness to participate. If you perform online research more women than men are willing to participate, and again, quite a large difference. So, for example, we did a very large Internet based investigation and 70-something percent of the participants were female and I see that often in the online surveys. If you want face to face research, for example observational studies, maybe newer imaging, or participation in a randomized control trial, then it's quite the opposite, men are much more willing than women to participate" [Researcher n.4]. In line with the literature, researchers reported that women are more likely to enroll and remain enrolled in medical studies if the interviews are conducted online or by telephone. While, according to a researcher's experience (Researcher n.4) men are more willing to participate in medical research if it is performed in person. Furthermore, when the option of performing online research might not be possible, such as in the Cardiology case, a researcher reported that *"Sometimes they [women] don't*

even drive themselves and then we can order them a cab [to reach the research site from home and back]" [Researcher n.7]. Therefore, implementing strategies that align to women's lifestyles can make them more willing to participate in clinical trials.

4.5 Emerging strategies

Personalized Medicine

All interviewed researchers believe that a good approach, that has only recently been developed, is personalized medicine. It differs from the "one size fits all" approach that has largely been used in medicine and drug trials. According to the National Institute of Health (NIH), personalized medicine is "*an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease*". As a researcher explained to me during the interview, personalized medicine means having a more targeted sample that can be analyzed in more detail and creating specific and ad hoc programs and therapies. Because of these reasons, this approach takes more time and finances to be applied. As has been previously discussed, the institutions that carry out the research grants play a crucial role in redefining the rules for enrolling participants in medical research so that both sexes can be included. "*Grant suppliers and journals will hold the key to change, and we, researchers, always follow what our grant institutions want us to do*" [Researcher n. 4]. All researchers agree that this approach could be a win for a more accurate sampling system that considers the inclusion of different sexes and genders, with positive consequences in therapies and treatments. Four researchers (Researcher n.1, Researcher n.3, Researcher n.4, Researcher n.7) reported trying to already move into the use of personalized medicine as a main approach in drug guidelines and dosages. However, they all reported being aware of the necessity of the allocation of more funds to drive to this innovative method. Eventually, all researchers agreed that this approach might be the future of medical research (Vicente et al., 2020).

Ratio

“Every trial should have at least a certain percentage of women, or at least a bandwidth within the women is represented. So, what I mean here is that a disease that has 60% women and 40% male, should be at least 50% women in a trial. If there is a bandwidth of 20% women, you can say at least 50%, but it should be according to the prevalence of the disease” [Researcher n.3].

Even if some policies are already in place regarding the inclusion of both sexes in research, a ratio between female and male’s enrollment in research is still not defined yet. Although, a researcher (Researcher n.7) reported that the Dutch Heart Foundation has recently introduced a guideline that makes researchers sign a contract in which they agree that at least 40% of participants in trials must be female. If the agreement is not met at the end of the trial, researchers are supposed to limit the inclusion of men, to keep the balance between sexes. Even if most of the researchers (10 out of 12) sustain that implementing this aspect could be a winning move, 2 researchers also reported that it might not be feasible for all studies and might take too long to be able to reach equality in the study sample.

4.6 Strategies known by researchers but not employed

Registry systems

The interviews showed that in the Netherlands several different databases are used by researchers to screen patients and enroll them in medical research. However, compared to the registry system created by the University of Michigan, these databases do not make difference between sexes and do not always show patients consent to be contacted for participating in research. Furthermore, the Netherlands, for now, does not seem to present a registry system which contains specifically women who are willing to participate in clinical trials.

4.7 Researchers who do not implement any strategies

As have already mentioned, not all researchers activate strategies. Two researchers (Researcher n. 9 and Researcher n. 11) reported they do not experience difficulties in enrolling women in research. On the contrary, they experienced more difficulties in enrolling men. Although, this phenomenon might happen because of the differences that are present in the specific research conducted by those two researchers and their topic. In fact, as explained by a researcher, men are reported to enroll less and decline more than women in mental health programs and studies (Ellis et al., 2014).

5. Discussion and Conclusions

The aim of this study was to investigate the researchers' perspective regarding sex and gender differences in medical research (1), as well as exploring the strategies known and activated by researchers to enroll and retain women in medical research (2).

One of my main findings is that all interviewed researchers are aware of the necessity of including sex and gender differences in research (van Diemen et al., 2021). Additionally, researchers reported that they perceive there are “external factors” that need attention from grant agencies and funders (Parwani et al., 2022), as well as organizations and research hosting institutions. According to researchers, these actors own the power (through grants and funds, leadership, and policies) to help transition to a more inclusive and equal research. Moreover, researchers discussed “internal factors” that affect female enrollment as well as retention. These factors (awareness, time management, and approach) need direct attention from researchers, and could help them successfully activate strategies for female enrollment. Also, some departments are more successful than others in enrolling and retaining women. The department of Psychiatry and Health Sciences enroll and retain female participants with less obstacles since they largely use online instruments (Chung et al., 2008; Coakley et al., 2012). This shows that certain strategies could work better than others with female participants (Liu & Mager, 2016; Zutlevics, 2016) and should serve as models for other departments. Furthermore,

the way of communicating with female patients could also be a strategy to tackle women's higher perception of risk with participating in clinical trials (Chung et al., 2008; Coakley et al., 2012). Lastly, I confirm that even though the Netherlands is investigating female enrollment in medical research, the United States of America present more advanced strategies that researchers should apply.

Limitations of my study

One of the limitations of my study is that the knowledge and studies on gender differences are still limited and in development. For this the reason, I was not able to fully answer my first research question, due to a lack of gender specific information. A large portion of the researchers does not record gender or does not have a large enough gender diverse sample. Second, all the researchers were asked about retention strategies but very few had employed any strategies. Because of this, too little is known about women's reasons for clinical trials dropouts. Mainly privacy policies protect from knowing the reasons behind dropouts but knowing these reasons could be crucial to understand the motifs for dropouts.

Contribution and recommendations

This study, compared to prior studies (Parwani et al., 2022; Reza et al., 2022), targeted researchers and their point of view on the topic of sex and gender differences in research. It became clear throughout the interviews that there is a necessity for future studies in areas in which gaps are still present. First, more studies need to be conducted regarding the inclusion of gender in medical research. Second, retention strategies must be expanded. Furthermore, difference between medical specialties and departments need to be investigated. Following a model that focuses on the different phases of a study where obstacles might occur (Figure 4), similar to Reza et al. (2022), could help researchers tackle these obstacles in an easier and faster way. This could lead to positive consequences both from a time management and financial point of view. Lastly, to improve future medical development, it is necessary that stricter policies about the consideration of sex and gender dimension

in medical research are established and achieved, both by the Agencies and by the University Medical Center through internal policies.

In conclusion, what emerges from this study is that it is difficult to find a solution that will somehow “fix” the problem of underrepresentation of women in medical research. Investing resources towards researching obstacles and strategies to tackle this underrepresentation should be in the policy-makers agenda. Policymakers need all the actors to collaborate in order to target sex and gender specific obstacles and successfully activate strategies. Thus, a multisector collaboration among researchers, research participants, grant funders and agencies should be attempted to close the gaps and optimize care and health for all sexes and genders.

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7. Appendix

Appendix 1: Information E-mail

Dear Researcher,

I am a master's student of Social Policy and Public Health at Utrecht University, and I am conducting a research internship.

By means of this letter, we would like to invite you to participate in the research project "*How do researchers view gender differences in research? An analysis of the strategies for female enrollment and female retention in medical research*".

The purpose of this study is to analyze the underrepresentation of data from women in research by identifying the key priorities and barriers researchers may encounter. The aim is to answer to the research question "*How do researchers view sex and gender differences in research?*", and to determine which are the strategies that researchers use to address the lack of resources and knowledge regarding how to increase female data and participation in clinical trials and medical research.

You are being invited to take part in this research because we feel that your experience as a research expert can contribute much to our understanding and knowledge of the research topic.

Data will be collected manually through one-time individual interviews that would take up to 30 minutes. The entire interviews will be tape-recorded throughout the use of a recording device. We would not mention your name in the interview. If you do not wish to answer any of the questions during the interview, you may say so and the interviewer will move on to the next question.

Questions will regard only research and research strategies. Questions regarding sensible information and patients will not be asked, as they are not the focus and scope of this research.

The collected data will remain confidential and will be anonymized before being stored. Only researchers directly involved in the study can access to the data. The data will be stored until the end of the study and will be kept in accordance with Utrecht University and University Medical Center privacy policies.

The results will be published. Before publication you will have the right to request access to your personal data and to change these if they are not right or to erase your data.

To enroll into the research or for questions about the study, you can answer to this email.

Appendix 2: Informed Consent Form

I have read the Informed Consent Form and I understand what the purpose of the research is, and that data will be collected from me. The research has been explained to me clearly and I have been able to ask questions.

By signing this Form, I

1. Consent to participate in this research.
2. Confirm that I am at least 18 years old.
3. Understand that participating in this research is completely voluntary; and
4. Understand that my data will be anonymised for publication, educational purposes and further research, unless I give my consent to the Quotes, and/or Education and further research options below.

Consent Special categories of personal data

I give my consent to the collection, processing, use and storage of my personal data for the purposes of this research.

Audio/Video

I hereby consent to having audio and/or video recordings made during the research and to have my answers transcribed.

Quotes

I hereby consent to having my answers quoted in research publications. When quotes are used, your (real) name and other direct identifiers will not be mentioned.

Education and further Research

I hereby consent to having the anonymized data stored and used for educational purposes and for future research, also in other areas of research than this research.

Name of the participant:

Signature of the participant:

Date:

You will be given a copy of the full Informed Consent Form.

Appendix 3: Interview guide, questions outline

1. Sex and gender dimension in medical research (gender bias in research)

1.1 Design phase

- 1.1.1 Do you include sex and gender dimension in your research/study design?
 - 1.1.1.1 If you do not include the gender dimension, why? (E.g., data not available, complexity)
- 1.1.2 When you design your research, do you make sure to have a certain percentage of data or samples from females (animals/humans)? Do you follow a M/F ratio?

1.2 Screening and Enrollment phase

- 1.2.1 Does your research involve the enrollment of women?
 - 1.2.1.1 If, yes, what do you think are the best techniques and strategies to activate to enroll women in research?

2. Obstacles to the enrollment and retention of women in medical research

- 2.1 From your perspective, what are the obstacles women might encounter while enrolling in research?

3. Strategies to the enrollment and retention of women in medical research

3.2 Behavioral and gender-related obstacles

- 3.1.1. Studies have highlighted women's high-risk perception when it comes to enrolling in research. Which communicational mechanism might be used to explain the overall safety of the research?

3.2 Logistical obstacles

- 3.2.1 Women experience more transportation obstacles than men in reaching research venues (van Diemen et al., 2021), how do you improve access to the research sites?
- 3.2.2 The time in which research is conducted is an important element to consider. Do you pay attention to the schedule while designing and conducting research?
- 3.2.3 Do you make use of a “registry system” to access data of women who have already been involved into research project or are willing to participate?
 - 3.2.3.1 Yes, can you name it?
 - 3.2.3.2 No, do you think it would be useful to have a similar database?

3.3 Policies and Grant Funders

- 3.3.1 What is your opinion regarding the policies in place about the inclusion of both sexes in research?

4. Future developments for enrollment and retention in medical research

- 4.1 According to you, what do you think is the best direction to catch for future developments in the enrollment and retention of women in medical research?

Appendix 4: Coding Tree

