TITLE:

An analysis of clinical-side barriers to the enrolment of women in clinical trials

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ABSTRACT:

This study reviews the barriers to female participation in clinical trials. A historical understanding gives rise to the conclusion that government policy has not significantly influenced rates of female enrolment in clinical trials. The paper introduces both patient-side and clinical-side barriers that discourage female enrolment, to then focus on the latter group. Detailed analysis of clinical-side barriers, including healthcare and trial level barriers, revealed that lack of access to healthcare, lack of diversity in trial leadership and rigid trial requirements were factors that affected rates of female enrolment. The impact of each factor varies significantly depending on location and socio-economic context. The study includes a quantitative analysis on the role of female leadership in clinical trials in encouraging female enrolment. It also includes a quantitative analysis on whether contraceptive requirements in clinical trials discourage female participation in AMI trials in Europe. The results indicated that the role of female enrolment alone was not statistically significant in Acute Myocardial Infarction (AMI) trials conducted in America. The results showed that there was no significant different in proportion of female participants in trials that required contraceptive use as compared to trials that did no. Based on the findings, the study finds evidence that advocates for decentralization of clinical trials as a short-term solution to address the significant clinical-side barriers to enrolment. The study advocates for strong government and community corporation to achieve these aims.

KEYWORDS:

Women enrolment rate, Clinical Trials, Underrepresentation, Gender bias, Decentralization

INTRODUCTION:

The basis for modern evidence-based medicine is the performance of clinical trials (CTs) to test medicine efficacy and safety. Historically, women have been underrepresented in such research [1], among several reasons, due to policy responses to pharmacological catastrophes in pregnant women in the 1950s and 60s [2], [3]. As a result of the NIH Revitalization Act of 1993 passed by the congress, the National Institution of Health (NIH) revised policy guidelines in 1994, mandating the inclusion of women and minorities as subjects in NIH-funded CTs. Despite these efforts, early investigations of the impact of these federal policies continued to demonstrate the underrepresentation of women in RCTs funded by NIH [1], [4]. This disparity persists today, particularly in the studies regarding cardiovascular diseases, HIV, and chronic kidney diseases [5]. Hence, this proves that policy mandates for inclusion alone are insufficient to increase the recruitment and retention of women in CTs.

It is crucial to address female enrolment in CTs since female under-representation can lead to a poor risk evaluation, that can have severe consequences for an entire population. For instance, 8 out of the 10 drugs withdrawn from the market between 1997 to 2000 posed greater health risks for men than women, according to findings from the FDA Ambien, a “widely prescribed insomnia drug” containing zolpidem, was approved by the FDA in 1992 [6]. In 2011, approximately 9 million patients in the USA received zolpidem products, with 63% of them female [6]. However, it was identified only in 2013 by the FDA as a drug that was significantly more likely to cause adverse drug reactions in women than men[7]. To identify and address such scenarios, the population sample of CTs needs to be balanced in accordance with the demographics in which it will be administered.

Several socio-economic and cultural factors have been identified as barriers to female enrolment [8], [9]. These factors can fall largely into two categories: clinical-side barriers and patient-side. Clinical-side barriers include factors that are independent of any patient but instead determined by clinical settings and systems – such as referrals to CTs, trial requirements, trial leadership. Conversely, patient-side barriers are those that are influenced by a patient's environment– including their risk appetite, social influences, and altruism[10]–[12]

Patient Side Barriers

Several studies corroborate that the rate of female enrolment is influenced by social and interpersonal factors to a greater extent than for men [12]–[14]. Lobato et al shows that women were more likely to report a decision influenced by their social interactions with friends, family or researchers or by general altruistic instincts [12]. While social factors themselves do not explain underrepresentation of females in CTs, when considered within a socio-economic context, the connection is self-evident. Sullivan et al, a study considering women's views about contraception, a significantly greater proportion of Malawi women were concerned about the social perception of a woman using contraceptives compared to American women. Similarly, in 2 similar multicenter studies of hypertension and genetics conducted between 2001 and 2003, showed distinct trends in female participations. While no women in the US trial sought the advice of a partner before participation, whereas 47% of women in the Nigerian trial did [13]. Another supporting example is found In Ghana, where the decision of female volunteers was frequently subject to the approval of a parent or husband [14]. These cross-cultural studies illustrate the nature of some of the patient-side barriers that prevent female enrolment. Nevertheless, this position paper aims to gain a comprehensive understanding of clinical-side barriers. The following section, core of the paper, digests in detail these clinal-side factors. The paper concludes with a discussion on the barriers and proposes some recommendations.

CLINICAL-SIDE BARRIERS TO THE ENROLMENT OF WOMEN IN CLINICAL TRIALS

Clinical-side barriers are structural factors in the medical field that contribute towards discouraging female enrolment, or towards limiting accessibility for women. These barriers are present at each stage of the trial recruitment process: from the primary phase of referral and eligibility screening to the trial requirements expected from selected trial participants.

The clinical-side barriers will be classified into two categories: healthcare and trial barriers. The first section will examine the disparity in access to healthcare and referrals to CTs between genders. The second section will first discuss the inclusion of women in trial leadership, followed by the requirements imposed by CTs on its participants, which affect women disproportionately.

1. Healthcare Barriers

The underrepresentation of women in CTs is partially rooted in the different interactions women experience with the healthcare system. Cook et al assessed the frequency of cardiology consultations stratified by gender. It was found that women were less likely to receive a consultation than men for coronary heart disease and congestive heart failure. Additionally, women had 15% fewer follow-up consultations [15]. This reinforces that women have limited access to specialists in healthcare.

These differences in accessing healthcare manifest most prominently in old age. Statistically, women are more vulnerable to poverty or social exclusion than men at later stages in their lives, a result of the accumulation of financial inequality over the course of their life [16]. This is significant since women are more probable to experience health issues in their senior years. This leads to unmet medical needs. Cameron et al indicates that though health needs were “substantially greater” among older women, they were less likely

to have hospital stays. They also had fewer physician visits as compared to men with similar health profiles and backgrounds (3.07 vs 3.30 median visits in a period of 24 months) [17].

This disparity in access to healthcare treatment consequently means that women do not have access to appropriate diagnosis and referrals to CTs, since these referrals are made by physicians aware of research studies that are recruiting subjects. Therefore, women deprived of this access are not screened for CTs and fail to qualify to participate in certain disease trials, contributing to lower enrolment rates.

2. Trial Barriers

2.1 Role of Leadership Diversity

Recent studies prove that the diversity of the leadership in clinical trials impact the enrolment rates of women [18]–[20]. Reza et al. found that heart failure CTs with women as senior authors demonstrated higher rates of female enrolment ($r = 0.39$, $p < 0.001$) [18]. The same trend was demonstrated for trials with a larger proportion of female authors [18]. These conclusions were reinforced by Gong et al and Khan et al in studies that included coronary artery disease, vascular disease, arrhythmia, and AF trials [19], [20].

To verify these previous works, this paper includes an original study assessing the relationship between proportion of female authors and women enrolment in clinical trials related to Acute Myocardial Infarction (AMI). The data set considered was obtained from ClinicalTrials.gov, a US government database recording a registry of clinical trials [21]. The filtering criteria was similar to the criteria applied by Khan et al [20]. The criteria included only completed trials labelled with ‘AMI’ with over 400 participants. A total of 51 trials met the inclusion criteria. Authors whose genders could not be determine were excluded.

The average representation of female authors was 20%, which was the same one as reported in Reza et al [18]

24% of publications of CTs had women in the position of first author and 10% of publications had no female authors, which shows the lower representation of female professionals in cardiology.

While there was a difference of 9% in the average participation of women in CTs with more than 35% or more of female authors as compared to CTs with less than 35%, this difference was not found to be significant (p=0.2)

2.2 Trial Requirements

The eligibility requirements set by researchers for each trial present a set of barriers for potential volunteers due to socio-economic, cultural, and historic reasons.

Women's role as traditional caretakers influences their autonomy, mobility and availability [22]. Reports from the 18 National Centers of Excellence (COE) in Women's Health in America found that access to the research site is a challenge faced by women at all COEs, since many women depend on family members for transport, fear public transport or are unavailable for the time-consuming commute[9]. A retrospective survey of women that accepted or declined to participate in the TOMBOLA trial revealed that the primary reason women declined to participate in the trial was due to a preference to visit their own general physician. Commonly cited reasons for this were logistical issues, such as inconvenient appointment timings, commuting time or arranging childcare of time off work [23].

Studies demonstrate that women's ability and willingness to enroll in trials is influenced by rigid requirements [9], [24].The most prominent example of such requirements is contraception. A review of 410 protocols submitted to an Institutional Review Board between 1994 to 1997 showed that studies required up to four countersignatures to confirm

contraceptive use for women. In contrast, no signatures were required by men since contraception use was not mandatory [1]. This elucidates the increased administrative burden that women face due to contraception requirements, which can be further discouraging.

Though more than half of women are supportive of the practice for requiring contraception at CTs, this can potentially be a burden to many, discouraging participation [8]. Sullivan et al revealed that women's primary concerns include side-effects and influence on fertility, as well as suspicion of infidelity from their partners. Notably, geography and culture play a significant role in such deciding factors. This is proven by the key distinction that American women tended to have an increased focus on bio-medical risks whereas Malawian women primarily paid attention to social aspects. [8]

This paper includes a study analyzing trial requirements and proportion of female enrolment. The dataset was obtained using EudraCT, a government database for all European CTs

Using EudraCT, the clinical trial registry for the EU [25]. Trials that did not publish data about participation rates by gender were excluded. A total of 101 trials met the inclusion criteria for this.

The average proportion of female participants was 36%. Contraception was not found to be a barrier to female participation in AMI CTs in Europe ($p = 0.006$). This reinforces the hypothesis that contraception is not as significant a barrier in developed countries as compared to developing countries [11].

However, excluding women of child-bearing potential was a significant factor that reduced female participation ($p=0.001$). This is expected since such restrictions limit the pool of women that are eligible for the trial: 62 out of the 101 trials studied excluded women of child-

bearing potential. This reflecting the persistent underrepresentation of women in CTs, even in developed countries.

DISCUSSION:

Based on the reviewed studies, several types of clinical-side barriers play a significant role in the representation of women. However, trial barriers, including contraceptive requirements and female leadership, were shown to have statistically less significant impacts on female representation. Hence, it can be deduced that healthcare barriers, including diagnosis and referrals, have a stronger influence on female enrolment. However, these cases are more difficult to detect. Thus, addressing healthcare barriers will require long-term changes.

The recommendations given will focus on trial-side barriers, reviewing short-term solutions that are proven to work. The socio-economic context of the gender-specific barriers for women participation in clinical trials is complex. Nevertheless, there are pragmatic recruitment and retention strategies that have proven to be successful in enabling women to enroll in CTs. To ease women's ability to overcome autonomy, mobility and availability barriers, it is recommended that patient follow-ups are performed by home visits on occasion and that transportation, meals and support of dependents is provided on a need-basis. Though these actions are labor and cost intensive, they outperform the efficacy of guidelines and federal mandates in promoting accessibility to CTs [1], [4]. As an example of its success, the ENRICHD study had a female participation rate of 44% as a result of the above efforts and incentives [26]

In 2011, Pfizer conducted the first direct-to-patient (DTP) study, REMOTE, managing the recruitment and trial of participants online [27]. By leveraging tools for mobile engagement

and multichannel intervention, DTP CTs emerge as a feasible model to practice at scale [28]. In fact, decentralized drug CTs with DTP models have become increasingly common due to the pandemic, reducing mobility challenges or convenience issues of the patient. This method can enhance medical research, giving researchers access to a broader variety of patients. Simultaneously, it optimizes time and fund allocation by reducing costs associated with frequent physical visits.

In order to implement the DTP mode, trial designs require a fundamental framework for this model which will encompass coordinated communication among sponsors, investigators, and participants, as well as DTP supply shipment, checkpoints in clinical centers of General Practitioners or Hospitals, and e-counselling. This is implementable, as proven by the increasing number of DTP CTs today. However, the greatest limitation in implementing DTP CTs is the lack of regulatory guidance. In July 2020, regulatory acceptance was cited as the largest barrier in conducting such CTs. Only in 2016 did the US FDA establish guidelines for the acceptance of eConsent. In Europe, no centralized guidance for eConsent exists today [29]. Hence, regulations must be established not only to provide uniform guidelines for this practice, but to ensure that remote data-collection is conducted ethically and securely [30].

Additionally, the promotion of female enrolment can be reinforced through editorial policies. The journal European Association of Science Editors, a pioneer of inclusion in medical research, has formulated recommendations for reporting sex and gender in study design and results. Similarly, the Committee of Medical Journal Editors urges researchers to be “inclusive” of all genders, ages and races [3]. Such actions have been undertaken by an increasing number of scientific journals [31]. To extend the impact these journals have, similar recommendations should be applied to the inclusion of female leadership in conducting CTs. Findings show that the proportion of female Principal Investigators has not significantly increased in the last decade [32], proving that progress is stagnant and must be

propelled forward by action. Hence, along with peer-review journals, sponsors must insist on leadership diversity.

CONCLUSION:

This work reviews the clinical-side barriers to the enrolment of women in clinical trials and concludes that decentralization of trials is one of the most effective immediate measure to address women underrepresentation. To promote this shift towards the decentralization, strong and collective government action and community support are required.

ACKNOWLEDGEMENTS:

Lumiere Writing Program is acknowledged for the support to finish the manuscript.
Dr. Jorge Corral Acero is acknowledge for the guidance and supervision towards the completion of this work.

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