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Gender differences and clinical trial design

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"...if we extend our gender-sensitive research beyond the well-regulated trial setting we might identify variables we would have never considered otherwise, and these might benefit all participants, not just women."

When thinking about gender differences and clinical trials, the first idea that generally comes to mind is the inclusion of limited numbers of women in all phases of clinical investigation. While this still holds true for several disciplines, we should realize that the problem is much more complex and will not be solved by the simple achievement of a 50:50 distribution of participants' gender.

Historically, women of childbearing age had been excluded from clinical trials after the thalidomide tragedy. More then 10,000 babies born to mothers who had taken the sedative and antiemetic during pregnancy developed severe malformations, including limb abnormalities and internal organ defects [1]. In the aftermath of this event and in an attempt to protect all unborn life from unknown drug side effects, all fertile women were banned from participation in clinical trials – pregnant or not. While surely protective against potential teratogenicity, the ban appeared less protective of womens' health. When analyzing the drugs withdrawn by the US FDA due to severe and potentially life-threatening side effects in the years 1997–2000, of the ten drugs withdrawn, four cases were due to the increased incidence of torsade de pointes [2]. This represents a typically female side-effect, which roots in the biology of the female heart conduction. Females tend to have physiologically longer QT intervals, which might be further elongated by the influence of sex hormones. Drugs acting on the myocardial conduction will further this physiological mechanism, putting women at increased risk for conduction arrhythmias. Most importantly, the medications leading to this specific adverse event can hardly be predicted by their class; for instance cardiac medications as well as those prescribed for unrelated systems can lead to increased arrhythmia frequency [2].

Women appear to report increased frequencies of adverse events in most studies conducted to date. Reasons for this might be of multiple origins, including missed dosage adjustment, the potential influence of hormonal factors, increased frequency of comedication and possibly a tendency to report more side effects, maybe due to differences in perception of these side effects. The largest meta-analysis looking at this phenomenon was conducted by Martin and colleagues in 1998. The authors analyzed 48 cohort studies, including a total of 513,608 patients (55% women) and identified an age-standardized relative risk of an adverse reaction of 1.6 (1.5–1.7) in females compared with males [3].

These imbalances in side-effect distribution have been brought to the attention of major international regulatory agencies; most importantly the FDA in the USA and EMA in Europe. These agencies have reacted at different moments in time, the FDA guideline being published in 1993 [101] and the EMA guideline in 2005 [102]. While distinct in their formulations, both recommend the inclusion of sufficient numbers of subjects of both sexes in clinical trials, possibly at percentages adequate in representing the prevalence rates within the general population. The agencies have then conducted separate surveys to address the inclusion of both genders in clinical

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trials finding little differences among the included sexes. In addition to the pharmaceutical regulatory agencies, the NIH, by its 1993 'Revitalization Act', has adopted a code for the inclusion of both genders and ethnic minorities within clinical trials, which is now systematically evaluated upon grant submission [103].

Given all this legislative support and the requirements by the funding agencies, why is a clear translation of this phenomenon still not being observed in practice?

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In a recent analysis we conducted on the inclusion of sex and gender-specific analyses in biomedical research in different clinical disciplines, one of the main findings was a lack of information about gender differences in clinical management [4]. The only analyzed specialty, which included adequate numbers of research publications with gender-specific indications, was cardiology. We attributed the finding to the historical origin of the discipline of gender medicine in cardiology. Furthermore, the widely accepted existence of gender differences in myocardial infarction and coronary artery disease might prompt investigators to pay more attention at gender differences in this discipline. All other specialties demonstrated serious gaps in knowledge [4].

We came to identify several reasons for this and some should be corrected over time by the application of the regulatory guidelines.

First, clinical trials have been conducted – in various forms – for many decades offering much information about the efficacy and adverse effects associated with several drugs used in everyday clinical practice. However, once knowledge is generated about a single preparation, it will most likely not be tested over and over again. This means that most drugs used today have been examined in clinical trials that have not included adequate numbers of women and most likely no gender-specific analysis. In the newly designed clinical trials, this will probably change and we will see a more balanced gender distribution. In practice, however, all drugs that are not considered 'gold standard', and are thus not used in current clinical trials as control medications, will never be re-evaluated according to our current standards. This means that many of the drugs we use everyday will never be appropriately re-evaluated and we will hardly obtain sound research data about their gender-specific effects. The only information we can obtain about those drugs is in the form of pharmacovigilance.

Second, many investigators do not conduct separate analysis of distinct patient groups. Most relevantly in this case, they do not perform adequate gender-specific analysis. The example of the DIG study, a large study to investigate the impact of digitalis on mortality, is frequently mentioned in this context [5]. While the initial investigation demonstrated a marked reduction in mortality in the mixed group taking the drug [5], a subsequent *post hoc* analysis revealed how mortality trends in women and men differed strikingly, to the advantage of men and the disadvantage of women [6]. Women represented only 22% of the study population and without being separately analyzed the information about the female participants was simply diluted within the whole group. The study is also a relevant example of the need of dosage adaptation, which would not have been recognized without the *post hoc* analysis. Current guidelines, which indicate desired plasma concentrations at lower levels then previously envisioned, would probably not have been developed if these results had not been published.

Unfortunately, many authors still fail to perform group and subgroup analyses and limit themselves to the enumeration of, for example the female and male, young and old, Caucasian and African–American participants in the study, which obviously provides little information about mechanisms and side effects.

Third, the need for adequate (sub)group analysis leads to another controversial question. How much is enough and how much is too much? Clinical trials are lengthy, complicated and very expensive endeavors, which might lead to unexpected results. Considering the cost factor especially, the question about the statistical power of the numbers always arises – and generally scares the ones who are financing the trials. Adding subgroups, such as women, elderly subjects and ethnic minorities to the trial design leads to an increase in variability, which has to be controlled for and which has to be adequately planned when defining the statistics to be performed [7]. This eventually means larger numbers of subjects and more money to be spent. However, as being recognized by most of the funding agencies, these specificities cannot be ignored anymore in today's medicine. In most cases, funding agencies will accept the inclusion of larger numbers of subjects, if clinical and therapeutic differences are to be expected. Furthermore, one should always consider the costs – economic but also indirect and intangible – of withdrawing a drug from the market in comparison to the costs of a well-powered clinical trial.

Fourth, preclinical studies should also be taken into account. It is well-known that for several reasons, such as susceptibility to disease, aggressive behavior and longevity, experimental animals of one or the other sex are

generally used for preclinical studies. To minimize variability and to optimize sample sizes, groups of female or male animals are employed rather than a mix of both [8]. Today, it is well known that animals display sex differences in their pharmacokinetics too and that frequently these differences might even predict some of the effects that might incur in humans. Furthermore, in a time where alternatives to animal testing are more and more encouraged, we will probably come to see much more *in vitro* drug testing, performed on native or modified human or animal cells. These cells might harbor striking differences as well, such as hormonal receptor expression or X chromosome-linked gene expression differences.

Last is a question about the generalizability of clinical trials. Much has been said about the lack of representation of our patient population by the healthy, middle-aged, 70 kg Caucasian male. This is not up for question and represents a limitation to all clinical trials, which nonetheless remain, if well-executed, the best instrument of premarket testing that we currently have. One thought should, however, be given to the striking discrepancy between pharmacovigilance reports, which always find increased numbers of women affected, and the claim for only slight differences identified in the aforementioned agencies' reports and by many critics.

The question is whether women do not differ more from the ideal test subject than men, and not just due to the fact that they are, indeed, women and not men. Problems arising in the real world, after the trial has been conducted, might explain some of these differences. In fact, patients might not display the desired adherence; they might take many more medications in combination with our newly approved product than previously imagined; they might display comorbidities that interfere with the molecule's pharmacokinetics; they might not be able to afford our newly marketed product. This is where unexpected gender differences, which possibly no trial can control for, come into play. Women generally experience more side effects than men, which impacts adherence [3]. Women frequently fill more prescriptions than men, especially with advancing age [9]. Women frequently suffer from comorbidities, which tend to increase with age, and frequently display worse control of these comorbidities, such as diabetes, hypertension and hypercholesterolemia [10,11], just to name a few. Women generally display lower incomes than men, especially at older age, which might make them ineligible or unable to afford some of the medication they might need [12].

All these factors can impact the eventual performance and acceptance of the novel drug, which might behave unexpectedly in the real world due to factors that not even the most perfect clinical trial could have controlled for. These are some of the aspects that gender medicine investigates, frequently with the aid of other disciplines, and which go beyond the simple question of how to design the perfect trial, which includes all relevant subjects in the most representative way and analyzes all information appropriately.

There are no guidelines for the design of the perfect trial, however, due to regulations, interest and respect from the organizers of clinical trials, we will probably see more and exciting new results, which will also dramatically improve our gender-specific knowledge. Nonetheless, we cannot terminate our research after the trial has been performed. Real life will point out unexpected issues, but if we extend our gender-sensitive research beyond the well-regulated trial setting we might identify variables we would have never considered otherwise, and these might benefit all participants, not just women.

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