BRIDGING THE GENDER GAP IN CLINICAL RESEARCH:

ADDRESSING INEQUALITIES TO IMPROVE WOMEN'S HEALTH OUTCOMES

WHAT CONTRIBUTES TO DIFFERENT HEALTH OUTCOMES IN WOMEN VS. MEN?

Factors that contribute to different health outcomes in women are widespread, ranging from how the social norms, expectations and responsibilities placed on women can impact their access to healthcare services and research settings, through to molecular and cellular differences between men and women [1]. Physiological variations may translate into differences in pharmacokinetics and/or pharmacodynamics for specific drugs, meaning that medications can work or be processed differently in people of different sexes [2].

Given my background in pharmacovigilance, I'm acutely aware that too many medications have been developed and approved which have later proven to be sub-optimal or even unsafe for women. For example, the medication Dofetilide was approved in 1999 to help control irregular or fast heart rhythms (atrial fibrillation). Despite this, it was only in 2018 that a study found that the recommended twice daily dose was too high in over half of female participants, as they developed other abnormal heart rhythms which could carry a risk of cardiac arrest [3]. In the original phase III DIAMOND study, there were only 61 women compared to 188 men in the treatment arm, with females constituting less than a quarter of all trial participants [4]. Sadly, this gender divide in clinical trials is often seen. Only in the last decade has this been highlighted as a cause of significant concern.

THE SEX AND GENDER GAP IN SCIENTIFIC RESEARCH

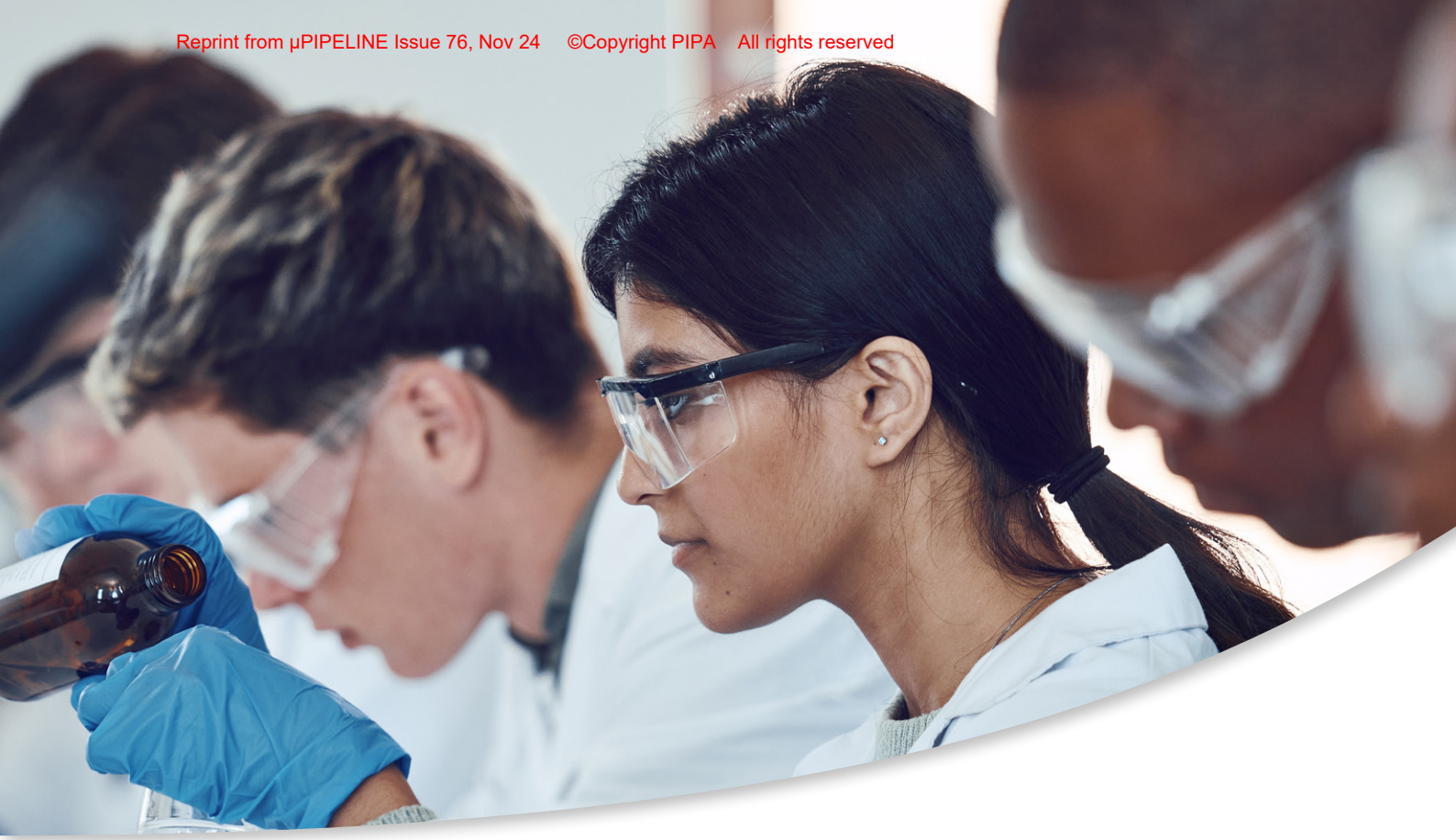
An unequal gender divide isn't just present in late-stage human trials, but also in early-stage cell and animal testing. It was recently found that fewer than half of in vitro studies report the sex of their cells, and where they do, they are more likely to use cells which are male [5]. In another study across ten fields of biology, it was found that 80% of the animals used in early-stage research were male [6]. Given these findings, it is perhaps unsurprising that women are 50-75% more likely to experience adverse drug reactions than men [7].

One reason why this gender imbalance has been historically overlooked is because of the so-called 'bikini medicine' approach, a worrying misconception that women's health only differs from men's in the parts of the body that a bikini would cover. Sadly, this perception is still evident in scientific research today. Analysing the health content of around 1,500 articles from major medical journals, a study found that the proportion of women's health content focused on reproductive health had increased between 2010-2020, whereas areas such as cardiovascular disease, infectious diseases, and musculoskeletal disorders – which pose a greater burden to women worldwide – were under-represented [8,9].

This dominant focus on reproductive health, combined with overwhelmingly male-centric preclinical and clinical datasets, has contributed to worse health outcomes in women across a range of areas. For example, women are more likely to suffer with chronic pain and experience a higher chance of diagnosis later than men across hundreds of diseases, including some types of cancer [10,11].

WHY DOES THIS GAP EXIST?

The current underrepresentation of women in research stems from several historical failings and has been perpetuated by societal factors. In 1977, due to the thalidomide tragedy and concerns about potential risks to foetal health, the Food and Drug Administration (FDA) recommended excluding women of



childbearing potential, including those using contraception or with vasectomised partners, from early-stage drug trials.

While this blanket FDA exclusion rule was lifted almost three decades ago, low participation amongst women persists for several reasons. One significant concern is the potential ethical, financial and legal risks that sponsors may face if a female participant becomes pregnant during a trial. This concern stems from the need to ensure the safety of both the mother and foetus, which adds complexity to study protocols and increases liability for sponsors. However, rather than protecting women, evidence has shown their exclusion from trials has led to an unrepresentative assessment of drug efficacy and side effects, potentially leaving them at risk of serious harm [12].

The differences between the male and female responses to medicines are not simply related to average body size, but fundamental metabolic and hormonal differences. For example, female hormones allow women to convert food into fat more easily, causing increased deposition of fat, which has an impact on drug metabolism. [12]

Moreover, women may experience a greater risk of adverse reactions to medications and interventions compared to men, which may also lead to added burdens such as the disruption of daily activities, decreased quality of life, and increased financial costs [7,12]. These adverse reactions may deter some women from participating in clinical trials.

Many studies lack sex-specific analysis, despite clear evidence that men and women respond differently to treatments and disease progression. Excluding sex analysis from clinical trials limits the generalisability of the research findings, as biological factors can have a significant impact on disease manifestation, pathophysiology, and response to treatment. It's striking to note that only an estimated 5-14% of studies examine outcomes by sex [13] highlighting how critical it is to address this significant gap in the data.

It appears there are both methodological and political barriers to advancing the knowledge of sex differences in clinical trials, with this additional complexity and cost unfortunately leading to sex specific analysis being underperformed.

Another important factor leading to underrepresentation is that women face practical barriers to taking part in clinical trials because they are often the primary caregivers, which leaves them with limited time and flexibility to take part in clinical research.

Furthermore, study design can be complicated due to age-related changes, such as the menopause which may introduce additional variables and considerations that need to be accounted for in the design and methodology of the trial.

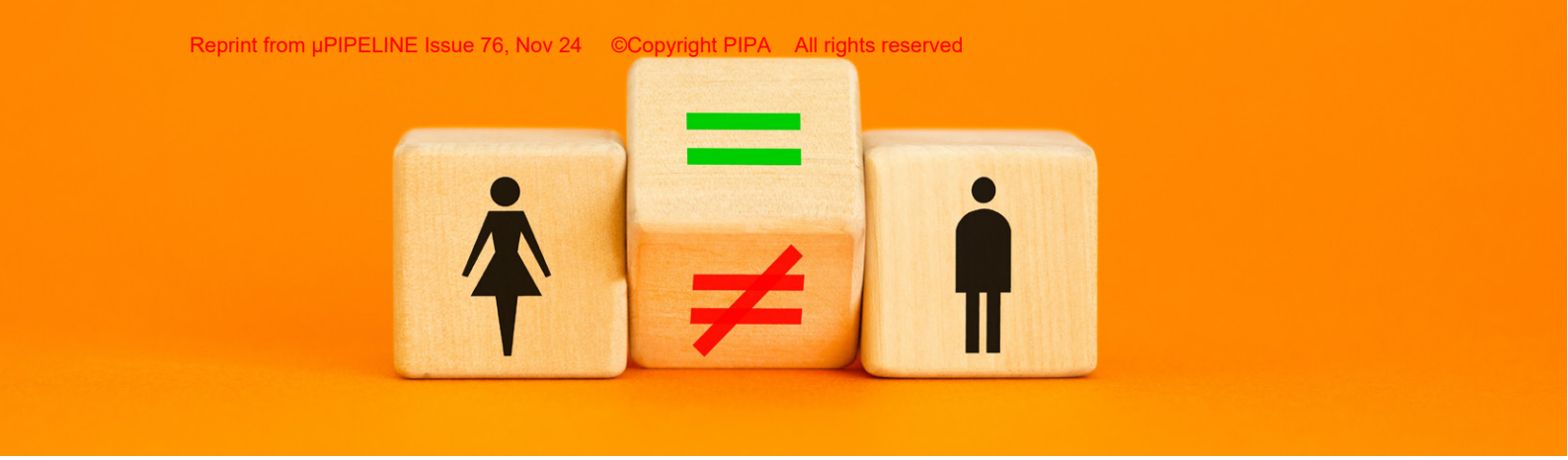
Engaging with women directly and effectively to encourage participation in clinical trials remains a challenge, and while many women health experts openly acknowledge these barriers, there remains a surprising lack of proposed solutions.

WHAT IS CURRENTLY BEING DONE TO COMBAT THIS ISSUE?

It is essential that scientific research, from a cellular level, through animal testing and into clinical trials, particularly early phase trials, include more female representation to ensure better health outcomes and safety of healthcare interventions for women. This is not only for ethical and moral reasons, but to ensure more rigour and richness in the pursuit of understanding human biology, which could pave the way for future breakthroughs.

Gender equality in scientific research could bring with it significant economic impact at the individual and national level. According to recent projections, tackling the 25% disparity in the time spent by women in "poor health" compared to men could lead to an annual economic boost of at least $1 trillion globally by 2040 [14].

Encouragingly, steps are being developed to try to address gender inequalities in clinical trials. For example, the UK Health Research Authority (HRA) and Medicines and Healthcare products Regulatory



Agency (MHRA) have an initiative aimed at increasing diversity in research participation. This regulatory workstream is focused on developing guidance that encourages researchers to consider representation of underserved populations, including women, at the application stage.

However, while this is an important step, guidelines alone are not enough. There needs to be more innovation in trial design, utilising technological advancements and tapping into real world data sources to support a decentralised approach, to help encourage more female recruitment and alleviate the inequality burden further.

WHAT STEPS CAN WE TAKE TO ADDRESS THIS ISSUE?

As researchers, one of our core priorities needs to be ensuring inclusivity and diversity in clinical trials, including women and those hard-to-reach populations. A comprehensive strategy that focuses on collaboration and innovation is essential to tackle this issue. Having strong partnerships across different sectors, including healthcare providers, industry stakeholders, regulators and community advocates is critical to achieving gender equality. Enhancing the representation of women in clinical trials calls for trial design to be flexible, convenient, and decentralised in design, to minimise barriers whilst leveraging innovative technology and real-world data.

A data-driven approach is essential for uncovering and addressing healthcare disparities. Analysing and re-assessing historical data with a focus on gender can highlight key gaps in women's health outcomes, enabling targeted intervention strategies.

It's important we establish trust and transparency through open communication and sharing of study results with participants to create a sense of value and encourage ongoing engagement. Advocacy and education are also crucial in raising awareness about these issues, empowering women to take charge of their involvement in research, and actively contribute to shaping inclusive and equitable scientific progress.

Instead of waiting for regulatory requirements to drive change, it is our ambition to make it possible for women to take an active step in increasing their inclusion in scientific research.

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