

## **Biologic Variability in Drug Response: Sex Differences in Clinical Trials**

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### **Discussion Guide**

#### **Introduction**

Individuals can have substantially different responses to the same drug, and in some cases may experience unpredictable adverse events that may not have been previously observed during clinical trials. Understanding how and to what extent specific genetic and demographic factors help explain varying responses is increasingly becoming the focus of medical product development. The impact a patient's sex may have on the safety and efficacy of a drug is of particular interest. Differences in rates of metabolism, absorption, and excretion of a given substance, for example, can have a noticeable impact on how members of each sex respond to a drug. However, even when variability between men and women is observed in response to a treatment during pre-approval clinical trials, it is not always clear what these differences mean or when they might be clinically significant. Randomized controlled trials (RCTs) have long been considered the “gold standard” of clinical drug development, but traditional population-mean-based RCTs are not designed to provide insight into the differential responses of every subgroup (or of a given individual). To better ensure the safety and efficacy of drugs and biologics, it will be important to improve our understanding of when and why biologic variability in drug response occurs, when it should be measured, and how best to design clinical trials to capture it.

In light of these ongoing questions, and under a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy is convening this workshop in order to 1) discuss the potential impact of biologic variability—and sex differences in particular—on the safety and efficacy of FDA-approved drugs and biologics, 2) explore the current methods for detecting and determining the significance of sex differences in clinical trials, and 3) identify viable alternatives to traditional RCTs that may be useful in capturing meaningful sex differences or other sources of variability in drug response.

#### **Biologic Variability in Drug Response**

It is well-known that individuals can have very different responses to the same medication; a treatment that has been shown to be safe and effective in a particular population may have no effect—or can cause adverse effects—in certain individuals or subpopulations. The cumulative effect of this variability is significant. Adverse drug reactions alone cost the US health system between \$30 and \$130 billion per year, and result in more than 100,000 deaths.<sup>1</sup>

Biologic variability in drug response can occur as a result of numerous, sometimes overlapping factors, including genetic differences, demographic factors such as race, age, and sex, and environmental and behavioral factors such as tobacco and alcohol use, climate, and diet. Adequately predicting and addressing the effects of that variability during drug development is a source of growing concern for researchers, drug sponsors, and regulators.<sup>2</sup> These challenges include insufficient comprehension of the sources of biologic variability, underrepresentation of certain demographic groups (such as women and minorities) in clinical trials, and the impracticality of designing and conducting clinical trials that are able to capture meaningful data on that variability.<sup>3</sup> Achieving a better understanding of how and when biologic variability happens—as well as when its effect is significant enough to warrant concern—is necessary to ensure patients' health and safety and to improve clinical outcomes.

## Sex as a Source of Biologic Variability

Sex is perhaps the most well-documented demographic factor linked to differences in drug response. The safety and efficacy of a treatment can vary between men and women in a number of ways. Sex differences can occur as a result of pharmacokinetic factors (i.e., the way in which the body processes a drug) including differing rates of absorption, distribution, metabolism, and excretion of a drug by the body. For example, kidneys tend to clear a drug out of a woman's system at a slower rate than a man's, which may necessitate a different dosage for women.<sup>4</sup> Pharmacodynamic factors (i.e., the ways in which a drug affects the body) can also vary between men and women, and women have been shown to be more sensitive to the effects of certain types of drugs, such as opioids, beta blockers, and antipsychotics.<sup>5,6</sup> Certain physiological factors may also play a role, including differences in size and weight or the effects of past pregnancies on the body. Hormonal differences between the sexes may also impact drug response; evidence suggests that opioid painkillers may affect women more strongly, for example, due to higher levels of estrogen in the body.<sup>7</sup>

### Defining Sex v. Gender

*Sex and gender are terms that are often used interchangeably; however, each has a specific definition. **Sex** refers to the classification of a person as either male or female based upon biological factors such as reproductive organs and chromosomal makeup. **Gender** refers to the manner in which a person self-represents as male, female, or other, and is shaped by environment, experience, and society. Both sex and gender are important—but distinct—potential causes of variability.*

Sex-linked variability in drug response is not fully understood, as women have historically been under-represented or excluded altogether from clinical trials. This under-representation was due to a range of issues, including concerns over the safety risks for women who may become pregnant, as well as reluctance by researchers to address the complex interactions of female hormones and drug compounds.<sup>8</sup> During the 1980s, however, members of the medical community began to recognize that there were significant differences in the ways drugs affected men and women, and that preventing or discouraging women from participating in clinical trials was limiting the ability to fully understand those differences, with negative consequences for women's health.<sup>9</sup> For example, the lack of female participation in studies of aspirin to help treat cardiovascular disease caused concern in the medical community, who were left unsure as to whether aspirin was as safe and beneficial for women as it appeared to be for men.<sup>10</sup>

## Current Regulatory Requirements and Approaches to Addressing Biologic Variability in Drug Response

Although surveys conducted by FDA in 1983 and 1988 revealed that both sexes had substantial representation in clinical trials, and in proportions that usually reflected the prevalence of the disease in the populations included in the trials, analysis was not regularly conducted on the resulting data to assess subgroup differences in drug response.<sup>11</sup> As a result, in 1985 the agency issued regulations requiring all New Drug Applications (NDAs) to break down safety and efficacy data by sex (sometimes referred to as gender), age, and race, as well as other subgroups when deemed appropriate.<sup>12</sup> In 1988, FDA issued guidance recommending subgroup analysis be conducted when the size of the clinical trial allowed for it, and to include information on that analysis as a part of NDAs.<sup>13</sup> A decade later, the agency issued revisions to its regulations for investigational new drug applications (INDs), requiring annual reports on participation in the drug's clinical trials by age, sex, and race.<sup>14</sup> However, although drug

sponsors are clearly obligated to provide safety and efficacy subgroup analysis data from clinical trials on NDAs, there are currently no statutory or regulatory requirements for sponsors to include any particular subgroups as participants in clinical trials.<sup>15</sup>

Over the past two decades, the agency has issued several guidances for industry regarding research on specific populations, including pediatric, elderly, and female patients.<sup>16</sup> With specific regard to sex differences, FDA issued guidance in 1993 entitled “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” which encouraged the collection and analysis of sex-specific data in clinical trials, recommended that women of childbearing age be included in phase I and phase II trials, and provided suggestions for ways to approach the assessment of sex-based pharmacokinetic differences in drug response.<sup>17</sup> The agency also released draft guidance in 2011 regarding the evaluation of sex-specific data in clinical trials for medical devices. These guidelines include recommendations for enrolling the appropriate number of women in device trials, considerations for building analysis of sex differences into trial design, and recommendations for reporting sex-specific information in device applications to the agency as well as in other public documents.<sup>18</sup>

There have also been parallel efforts to ensure adequate subgroup inclusion in NIH-funded research. In 1993, Congress passed the NIH Revitalization Act, which required NIH-funded investigators to include women and minorities in all of its clinical research studies, and stipulated that Phase III clinical trials must include women and minorities in numbers that would allow for valid analyses of differences in intervention effect.<sup>19</sup>

These federal efforts contributed significantly to the emergence of further research illustrating the importance of studying key subgroups, particularly women. A 2010 Institute of Medicine (IOM) report found substantial progress in a variety of disease areas, including breast cancer, cardiovascular disease, and cervical cancer, as well as improvements for women in treating depression, HIV/AIDS and osteoporosis. However, the report also found inadequate enforcement of requirements that clinical trials include representative numbers of women, and inadequate reporting of results on women, which hampered the identification of potentially important sex differences in both disease and treatment.<sup>20</sup>

The following year, the IOM released another report, “Sex Differences and Implications for Translational Neuroscience Research”, which underscored the importance of research on sex-based differences in disease and treatment response and highlighted some of the challenges to better understanding of these issues. Among the barriers highlighted in the report was the paucity of female animal models in basic research and the lack of attention to cellular-level differences in sex. Other barriers include inadequate and inconsistent analysis and reporting of study results by sex, and reluctance of sponsors to conduct clinical trials that allowed analysis by sex.

### **The Food and Drug Administration Safety and Innovation Act of 2012**

The Food and Drug Safety and Innovation Act of 2012 (FDASIA) directed FDA to examine how well demographic subgroups are included in clinical trials, as well as how readily demographic subgroup data are available in applications for drugs, biologics, and medical devices submitted for approval by FDA.<sup>21</sup> In its report detailing findings from this review, the agency reported that in general, demographic profiles of clinical trial participants were included in applications for approval submitted to FDA, and the majority of applications contained subgroup analysis of treatment effects. However, in many cases racial minority subgroups were underrepresented in clinical trials. The report also noted that participation in clinical trials by subgroup populations does not imply that sufficient data were collected in order to

conduct credible subgroup analysis or to adequately detect differences in treatment effect amongst subgroups.<sup>22</sup>

Section 907 also directed the agency to produce an action plan based on this review. Released in 2014, the final action plan contained 27 recommendations to 1) improve the completeness and quality of the demographic subgroup data contained within medical product applications; 2) identify barriers to enrolling members of demographic subgroups into clinical trials and utilize strategies to address those barriers; and 3) make demographic subgroup data more readily available to the public.<sup>23</sup>

Since that time, FDA has taken several key steps to implement the action plan. In addition to updating and finalizing relevant guidances on demographic subgroup data, the agency has also developed a plan to support research aimed at increasing understanding of clinical outcomes across different racial subgroups, and has released a roadmap that lays out strategies for conducting research to improve women's health.<sup>24</sup> The agency has also established a working group focused on implementing communication strategies for populations that are under-represented in clinical trials.<sup>25</sup> All three Centers within the agency have made modifications to their clinical review templates to encourage reviewers to give more consideration to subgroup data and analysis.<sup>26</sup>

The Center for Drug Evaluation and Research has also begun releasing Drug Trials Snapshots for every new molecular entity approved since January 2015. These snapshots outline information on who participated in the clinical trials for a particular FDA-approved drug, broken down by sex, race, and age. Any known differences in benefits or side effects of the drug are also broken down by subgroup. Although demographic clinical trial participation information has been publically-available in various formats, it was never gathered in one centralized location that was easy to read. The Snapshots initiative is intended to not only increase transparency, but also catalyze a broader scientific discussion around variability in drug response, including strategies for determining the appropriate balance of particular subgroups in clinical trials and better analytical approaches to identifying and understanding subgroup variability. To date, snapshots have been developed for 58 drugs.<sup>27</sup>

## Leveraging New Drug Development Tools and Trial Design Approaches

Despite growing understanding of how intrinsic and extrinsic factors like sex, race, ethnicity, and environment can influence drug response, drug development still largely follows a population-driven, "one size fits all" approach. Even in the emerging field of precision medicine, which harnesses advancements in biomarker science and pharmacogenomics to develop more targeted therapies, many of the existing efforts focus on disease driven by specific deviations in genetic sequences, rather than the complex, multifactorial processes that influence a person's health.<sup>28</sup> In order for the field of precision medicine to deliver fully on its promise, there is a need to consider new approaches to drug development and regulation. Efforts are already underway to re-think the underlying design and infrastructure of clinical trials so as to better capture information on subgroup variability, and recent scientific and technological advances in the fields of clinical pharmacology and pharmacogenomics offer substantial promise in supporting these new approaches.

### New Tools for Drug Development

Recent advances in the field of clinical pharmacology—the study of drug interaction, safety, and efficacy in humans—have contributed a number of tools and methods that can improve our understanding of drug disposition and response and better inform both trial design and regulatory decision-making.<sup>29,30</sup> These advances include new pharmacokinetic and pharmacodynamic models that can take into account

disease progression, placebo response, and patient factors like sex and age to simulate and predict clinical outcomes in trials. Such approaches are already being used to inform drug development strategies as well as regulatory decision-making. However, clinical pharmacology tools and principles are not always optimally applied across drug development programs.

Pharmacogenomics—the study of how a person’s genes affects their response to drugs—also plays an increasingly important role in the development of new therapies and our understanding of biologic variability.<sup>31</sup> Genetic factors can influence both pharmacokinetic and pharmacodynamic factors in the body, and the ability to identify and study these variations has increased rapidly in recent years due to the sequencing of the human genome and the development of technologies that allow for individual genomic variations to be detected quickly.<sup>32</sup> Pharmacogenomics is already being applied in clinical trials to enhance the ability to conduct subgroup analysis and detect biologic variability amongst subgroups.<sup>33</sup> Though FDA released guidance for industry regarding clinical pharmacogenomics in early-phase drug development studies in 2013, fully leveraging the principles of pharmacogenomics into drug development is an ongoing process that will continue to evolve.<sup>34</sup>

### Clinical Trials and Subgroup Analysis

Randomized controlled trials (RCTs) have long been the most reliable method for determining the true effect of a given treatment.<sup>35</sup> However, the strict parameters that govern the methodology of RCTs also present several drawbacks that may limit such a trial’s usefulness in certain contexts. Although the internal validity (the extent to which the treatment effect is real and not caused by other outside factors) of an RCT is generally quite high, the external validity (the extent to which results are generalizable) of a randomized trial is often low, and therefore the results may not be easily generalizable to broader populations.<sup>36</sup> It can also be difficult to predict how patients in a real-world setting will react to the treatment, as RCTs are conducted under tightly controlled clinical settings in carefully screened patients.<sup>37</sup> The participants in an RCT may not be adequately representative of the patient population who will regularly use the treatment if it is approved.<sup>38</sup>

Performing subgroup analysis as part of an RCT is a fairly common practice, with some studies finding that anywhere between 40-70% of RCTs involve some kind of subgroup analysis.<sup>39</sup> Such analyses are helpful in assessing the consistency of any treatment effect found in the broader trial population. However, RCTs are often not sufficiently powered to establish true treatment differences between subgroups.<sup>40</sup> As a result, the validity of demonstrated subgroup effects in RCTs is often questionable.<sup>41</sup> A number of criteria have been developed in recent years to aid researchers in conducting subgroup analysis and determining when results are interpretable and dependable.<sup>42</sup> However, evidence suggests that adherence to these subgroup analysis criteria in clinical trials has been mixed, and claims of subgroup analysis often do not measure up to the standards set out in these criteria. As a result, the credibility of subgroup analysis results from clinical trials is sometimes low.<sup>43</sup>

### The Role of Alternative Trial Strategies

Given the limitations of RCTs with regards to identifying and measuring subgroup differences in drug response, it may be necessary to consider alternative trial strategies that may be better suited to capturing biologic variability in a manner that can better support both regulatory and clinical decision-making.

The use of Bayesian statistical methods, either in RCTs or other alternative models, has been suggested as a way to overcome some of the limitations of RCTs with regards to subgroup analysis. Bayesian

statistics provides a quantitative method for combining both prior evidence and current data, and allows for conclusions to change and be influenced over time by new information.<sup>44</sup> N-of-1 trials (also known as single-patient trials) have also been suggested as a potential approach for determining treatment effects in individual members of a particular subgroup.<sup>45</sup> N-of-1 trials are multiple crossover trials in which one patient is switched a number of times from either a treatment to a placebo or between two different treatments. Participants are often actual patients being treated in a real-world setting by their clinicians.<sup>46</sup> This method of trial design helps clinical research more closely resemble clinical practice, which in turn makes trial results more easily generalizable.<sup>47</sup>

Another alternative approach involves supplementing RCTs with additional data from other sources. This additional evidence could come from observational studies, which, although patients are not randomly assigned to the treatment or control groups, have been shown to elicit results similar to those of RCTs.<sup>48</sup> Researchers can also use previous, nonrandomized trial data to establish a rough baseline for the safety and efficacy of a treatment; then succeeding trials can be run to see how a new treatment for a particular disease compares to those historical results.<sup>49</sup>

## Workshop Objectives and Questions for Discussion

Improving our understanding of how and why biologic variability occurs will be critical to improving the safety and efficacy of FDA-approved drugs and biologics. Careful consideration will also need to be given to alternative trial models that could help increase our ability to capture variability and assess its significance. This workshop will bring together representatives from across academia, industry, government, and other stakeholder groups to engage with these issues and identify potential solutions to the barriers that have hindered our ability to understand and address biologic variability in drug response.

### Opening remarks: Understanding the Known Causes of Variability in Response to Drugs

*Objective:* Provide a broad overview of the current understanding of different sources of biologic variability in response to drugs

#### *Questions to address:*

- What are the major known causes of variability?
- Are there lesser known causes of variability?

### Session I: Determining Which Subgroups Matter

*Objective:* Explore the current understanding of when subgroup analysis should be undertaken as part of a clinical trial, discuss the potential of including sex as a secondary endpoint in clinical trials, and identify methods for determining the correct balance of men and women in a given clinical trial.

#### *Questions to address:*

- Given the fact that randomized clinical trials are not designed to test every subgroup, how do we know what subgroups matter?
- How much confidence do we have in our finding? How much uncertainty are we comfortable with?
- What protocols does FDA have in their Review Template to identify variability in response to drugs?
- How do the three P's (power, prevalence, and population) impact the design of the study?



## Sex-Specific Questions

- What are the current theories of sex differences in response to drugs?
- What is the standard for “biologic sex” as a variable to consider in drug development?
- Are there clinical trials that could be viewed as a model for achieving appropriate balance of sex and generalizable results for women?
- When should sex be a primary consideration in clinical trial design?
  - How do we design *a priori* future clinical trials to incorporate sex as a secondary hypothesis?
  - Does there need to be shift in a new working definition on presentation of how men and women differ in presentation of cardiovascular disease?
- To what extent can the following considerations be used to inform the number of men and women in a clinical trial:
  - sex-specific prevalence of the disease;
  - sex-specific diagnosis and treatment patterns;
  - expected overall trial size;
  - clinical endpoints;
  - proportion of women included in past studies for the target indication; and
  - identifying known clinically meaningful sex differences in outcomes related to either safety or effectiveness

## Session II: Incorporating Variability in Drug Development

*Objective:* Discuss current methods of understanding variability in drug response as a result of sex, and identify possible alternatives to randomized controlled trials (RCTs) that may be better suited to capture sex differences or other kinds of variability.

### Questions to address:

- If we believe there is a biologic plausibility that a certain subgroup will respond differently to taking the same drug, how do we design a trial to capture that difference?
- How do we develop a framework for systematically advancing the science of variability to drug response?
- How can we as a scientific community, incorporating all our stakeholders, improve the nature of the “learn-confirm” clinical trial process to better understand variability in drug response?
- Are there viable alternatives to RCTs that may be more useful in identifying meaningful differences in drug response?
- “N of 1” trials: when can we use them to understand variability in response to drugs?
- At what point do we make a *post-hoc* subgroup analysis the secondary endpoint of a clinical trial?

## Sex-Specific Questions

- Do clinical trials have enough of each sex to detect a difference, and should that subset analysis always be a planned secondary analysis?
- What is the current framework for analyzing and interpreting subgroup analyses to determine sex differences?
- Can we be doing anything better than the RCT to look for sex differences?

- What would be the benefits and risks of adopting a new framework of testing drug safety and efficacy beyond the gold standard RCT?
- What is the value of subgroup analyses for sex differences?

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<sup>3</sup>Public Comment on FDA Drug Trials Snapshots to the Honorable Margaret Hamburg, M.D. dated January 23, 2015 for docket number FDA--2014-N-1818. Retrieved from <http://swahr.org/wp-content/uploads/2014/06/01-23-FDA-Drug-Trials-Snapshots.pdf>.; Ferdinand, K.C. (2015) Clinical trials: assessing safety and efficacy for a diverse population. FDA conference slides. Retrieved from [http://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/slides-diversity-workshop/0\\_2\\_Slides\\_Ferdinand.pdf](http://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/slides-diversity-workshop/0_2_Slides_Ferdinand.pdf).

<sup>4</sup> Whitley, H.P., Lindsey, W. (2009) Sex-based differences in drug activity. *American Family Physician*, 80(11):1254-1258.

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<sup>7</sup> Jacobson, R. (2014) Psychotropic drugs affect men and women differently. *Scientific American Mind*. Retrieved from <http://www.scientificamerican.com/article/psychotropic-drugs-affect-men-and-women-differently/>.

<sup>8</sup> Raz, L., Miller, V.M. (2012). Considerations of sex and gender differences in preclinical and clinical trials. In Raz, L. Miller, V.M., *Sex and Gender Differences in Pharmacology*, 14(1):127-147. *Handbook of Experimental Pharmacology*. New York, NY: Springer.

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<sup>10</sup> See Part IV of Federal Register as of July 22, 1993: Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. Retrieved from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126835.pdf>.

<sup>11</sup> Merkatz, R.B., et. Al. (1993) Women in clinical trials of new drugs—a change in food and drug administration policy. *New England Journal of Medicine*, 329(1):292-296. Doi: 10.1056/NEJM199307223290429.

<sup>12</sup> See CFR - Code of Federal Regulations Title 21, Volume 5, Chapter 1, Part 314.5 as of April 1, 2015. Retrieved from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.50>.

<sup>13</sup> See FDA Guideline issued July 1988: Center for Drug Evaluation and Research guideline for the format and content of the clinical and statistical sections of an application. Retrieved from <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM071665.pdf>.

<sup>14</sup> See CFR - Code of Federal Regulations Title 21, Volume 5, Chapter 1, Part 312.33 as of April 1, 2015. Retrieved from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.33>.

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<sup>15</sup> See FDA Report: Collection, analysis, and availability of demographic subgroup data for FDA-approved medical products. (2013) Retrieved from <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAAct/FDASIA/UCM365544.pdf>.



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See *supra*, 10.
- <sup>17</sup> See *supra*, 10.
- <sup>18</sup> See *supra*, 9.
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- <sup>23</sup> See *supra*, 21.
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- <sup>26</sup> Ibid.
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