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Working Together to Address Women's Health in Research and Drug Development: Summary of the 2017 Women's Health Congress Preconference Symposium

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Abstract

Historically, women have been underrepresented in clinical research, requiring physicians to extrapolate medical recommendations for women from clinical research done in cohorts consisting predominantly of male participants. While government-funded clinical research has achieved gender parity in phase-3 clinical trials across many biomedical disciplines, improvements are still needed in several facets of women's health research, such as the inclusion of women in early-phase clinical trials, the inclusion of pregnant women and women with physical and intellectual disabilities, the consideration of sex as a biological variable in preclinical research, and the analysis and reporting of sex and gender differences across the full biomedical research continuum. The National Institutes of Health (NIH) Office of Research on Women's Health and the Office of Women's Health of the U.S. Food and Drug Administration (FDA) cosponsored a preconference symposium at the 25th Annual Women's Health Congress, held in Arlington, VA in April, 2017, to highlight gains made and remaining needs regarding the representation of women in clinical research, to introduce innovative procedures and technologies, and to outline revised policy for future studies. Six speakers presented information on a range of subjects related to the representation of women in clinical research and federal initiatives to advance precision medicine. Topics included the following: the return on investment from the NIH-funded Women's Health Initiative; progress in including women in clinical trials for FDA-approved drugs and products; the importance of clinical trials in pregnant women; FDA initiatives to report drug safety during pregnancy; the NIH-funded *All of Us* Research Program; and efforts to enhance FDA transparency and communications, including the introduction of Drug Trials Snapshots. This article summarizes the major points of the presentations and the discussions that followed.

Keywords: clinical trial, women, drug development, pregnancy, precision medicine

Introduction

The inclusion of women in clinical research is essential to determining disease symptoms, progression, and treatment response, as well as accurate dosage recommendations, for women. Historically, women were underrepresented in all phases of clinical research, owing to factors such as concerns about the potential reproductive adverse effects of interventions in pregnant women and the assumed confounding effects of women's fluctuating reproductive hormone levels.[1,2] Following recent attention to the underrepresentation of women in clinical research, near parity has

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been achieved between aggregate enrollment of women and men in gender-mixed phase-3 clinical trials.[3–5] Nevertheless, women continue to be underrepresented in late-phase clinical trials for certain disease categories, as well as in early-phase clinical research in general.[2,6,7] Inadequate testing for sex and gender differences in research findings and the underreporting of results disaggregated by sex/gender also remain problematic in clinical research.[2,8]

Not only does improving the health of women rely on clinical research with race/ethnicity, sex/gender, and age representation proportional to disease incidence in the general population but it also depends on the generation and transfer of knowledge across all stages of the biomedical research continuum—from basic science and preclinical research, through translational research, to clinical research, and finally to healthcare delivery.[9] Optimally designing and executing clinical research to maximally inform sex/gender-appropriate healthcare requires the consideration of sex and gender influences on health and disease, as well as sex-specific reporting of results in preclinical research. Unfortunately, many areas of preclinical research continue to be characterized by sex bias in the use of cells and animal models, the underreporting of results by sex, and often, the insufficient consideration of sex as a biological variable (SABV).[10–13]

Important sex and gender influences on health and disease arise across disease categories and organ systems.[1,14] Accordingly, improving women's health in research and drug development requires synergies among researchers working on different topics and different points along the research continuum, as well as clinicians interested in providing optimal healthcare to their female patients in all areas of medicine and across all stages of life. Research discoveries can then be translated and applied by healthcare providers interested in delivering optimal care to their female patients in all areas of medicine and across all life course stages. The delivery of sex/gender-appropriate personalized healthcare depends on such connections. To help facilitate these synergies, the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) sponsored a symposium on April 27, 2017, in partnership with the U.S. Food and Drug Administration (FDA) Office of Women's Health (OWH), as well as the Academy of Women's Health, the *Journal of Women's Health,* and the Virginia Commonwealth University Institute for Women's Health. The symposium, titled ''Working Together to Address Women's Health in Research and Drug Development: Challenges and Opportunities,'' was held as part of the preconference activities of the 25th Anniversary Congress on Women's Health in Arlington, VA. Symposium presentations focused on innovations in women's health research and the advancement of the science of sex influences, such as the development of pregnancy registries for postmarketing monitoring, new drug labeling rules, and the improved reporting of demographic information on drug applications and clinical trials reports.

Opening Remarks

The workshop began with a welcome from Dr. Susan Kornstein, Executive Director of the Virginia Commonwealth University Institute for Women's Health, Editor-in-Chief of the *Journal of Women's Health*, and President of the Academy of Women's Health. The next speaker was Dr. Janine Austin Clayton, NIH Associate Director for Research on Women's Health and Director, ORWH. Dr. Clayton noted the importance of bringing together the many health practitioners who specialize in, and care about, the health of women. Another way of working together—forging partnerships with private-sector organizations and other governmental agencies—is a critical element guiding ORWH's mission to advance women's health and women's health research. The work of ORWH includes implementation of a new policy requiring NIH-funded applicants and researchers to factor SABV into research involving humans and other vertebrate animals.[9,15–17] Dr. Clayton also said that many presenters in the Congress on Women's Health, as well as other experts, emphasize how symptoms, disease progression, and responses to treatments differ by sex and gender, and that understanding these differences helps physicians best treat their female patients.[14,18–21] However, there are gaps in knowledge of sex and gender influences on health and disease, which is a barrier to optimal diagnosis and treatment of women.[10,22,23] A more rigorous accounting for SABV, from the earliest stages of research all the way through clinical care, will make the results of biomedical research stronger and more robust, which will advance health for everyone.[24]

Marsha Henderson, FDA Assistant Commissioner for Women's Health and Director, OWH, reflected on the first years of the annual congress a quarter century ago, when many clinicians, researchers, and patients doubted the value of, and need for, sex and gender research. These attitudes compromised medicine's ability to diagnose and treat women. For 25 years, however, the congress has provided an opportunity to showcase research, identify ongoing challenges, and create networks to move women's health research forward in a strategic way. Together, agencies and individuals supporting women's health research have supplied convincing evidence of medically relevant differences between women and men across the lifespan,[25–28] and not just in the context of reproduction. Today, research continues to confirm the profound effects of sex and gender on health and disease.[29–31] OWH actively works to facilitate this research, to raise awareness about the importance of sex and gender, and to promote the recruitment and retention of women in clinical trials.[4,32,33] Although more work remains to be done, it is important to acknowledge that successful change has been brought about by the community of researchers, private organizations, and governmental agencies interested in women's health.

Presentation Summaries

The Women's Health Initiative

Dr. Michael Lauer, Deputy Director of the NIH Office of Extramural Research, spoke on the return on investment (ROI) of clinical research. The importance of a research effort is often advertised in terms of the amount of funding spent or number of grants received for that effort. However, these measures are not very good at capturing the value of the research.[34] One of the best examples of the demonstrated ROI of government-funded research is the Women's Health Initiative (WHI), a set of large, NIH-funded clinical trials initiated in 1991 to address major causes of morbidity and mortality in postmenopausal women.[35–37]

At a cost of $260 million, the WHI estrogen plus progestin clinical trial revised understanding of the risks and benefits

of combined hormone therapy (cHT) in postmenopausal women.[38] Use of cHT as a preventive strategy for cardiovascular disease[39] and osteoporosis[40] dropped sharply in the decade following publication of the WHI results. This change in treatment protocol was accompanied by decreased incidence rates of breast cancer, coronary heart disease, deep venous thrombosis, pulmonary embolism, and stroke; and increases in osteoporotic fractures and colorectal cancer.[41] The overall benefits to women of these changes have far outweighed the costs, leading some to estimate an economic ROI of $37 billion from 2003 to 2012 (a massive 142:1 estimated return).[41]

The following question naturally arises: is this a fair estimate of ROI for the WHI? Moreover, what can this initiative teach us about investment strategies for government-funded research? Although the ROI of the WHI may be disputed, the WHI certainly stands out as an extraordinarily valuable funding initiative by NIH. Nevertheless, computing an exact ROI for any given research effort is not a straightforward matter and involves numerous assumptions. Some impactful scientific discoveries come as unanticipated surprises,[42] such as the high-payoff results of the WHI. Indeed, the trials of this initiative could have turned out very differently, so it may be more valid to evaluate the ROI of NIH's total clinical trial investment (including the more successful *and* less successful projects) in a defined research area, over a longer period of time.[43]

Hugely consequential events, such as the WHI, do happen in science from time to time, but it is often difficult to predict which events will have huge outcomes.[44] This places importance on funding a wide range of different studies (*e.g.*, clinical trials) to maximize the probability of including those with massive pay-offs, which make the combined research effort more valuable to society. At the same time, it is important to think about ways of making each funding effort as efficient as possible, to leverage the greatest value from the resulting data. In some cases, for example, researchers may be able to use databases of health insurers, or of integrated healthcare systems, to quantify clinical events in trial participants, as a valuable complement to the more expensive follow-up measures that are rigorously scheduled during randomized clinical trials.[45]

Progress in the inclusion of women in clinical trials for FDA-approved products

Dr. Pamela Scott, Deputy Director of Research and Development at the FDA OWH, detailed how OWH uses science, policy, and outreach to advance women's health, including efforts to improve women's participation in clinical trials, clinical trial design, and the conduct of sex-based analyses. Through guidance to industry, FDA defines what information is necessary to understand how drugs and other products will work in different populations and what expectations companies need to meet when they collect and evaluate sex-specific data. FDA also addresses sex differences by providing regulations and guidance.[46,47] FDA expects sex differences to be considered in both preclinical and clinical studies. In 1987, FDA issued guidance on including both sexes in preclinical research.[48] Since the mid-1980s, regulations for new drug applications (NDAs) have required subset analyses to support modifications of dosage for specific populations (*e.g.*, pediatric populations, geriatric populations, patients with renal failure).[49] In the 1990s, specific requirements were added for the presentation of safety and efficacy data by demographic subgroup (*e.g.*, based on age, gender, and race/ethnicity) and the identification of dose modifications for these subgroups.

FDA's efforts have led to better information on clinically meaningful sex differences. As appropriate, this information is reported in drug labeling, such as recommendations that women and men be prescribed different doses of certain medication for insomnia. One example of a sex difference in drug labeling is the case of flurazepam hydrochloride, an anxiolytic sedative and skeletal muscle relaxant used for the treatment of insomnia. Results showed that this drug had lower clearance in women; therefore, a lower initial dose is recommended for women (15 mg) than men (15 or 30 mg).

One major way that FDA addresses sex differences is through the implementation of the Food and Drug Administration Safety and Innovation Act (FDASIA) 907 Action Plan.[50] Section 907 of FDASIA required FDA to assess to what extent clinical trial participation and safety and effectiveness data by various demographic groups (*e.g.*, according to sex, race/ethnicity, and age) are included in applications to FDA. In an ideal world, representation should reflect the population with the disease or condition, but trial participation may be affected by factors such as insurance coverage, access to healthcare, physician referral rates, willingness to take part in research, comorbidities, and enrollment eligibility.

There is a myth that women are generally not included or are underrepresented in clinical trials. Although this may have been true at one time, women are now not only included, but make up a large proportion of participants. For the past 10 years, participation of women has hovered around 50% in late-phase drug and biological clinical trials.[3,4,32,51] Participation of women has been lower in early-phase clinical trials, at around 31%.[3,52,53]

Another myth supposes that sex-based analysis is not included in the FDA's decision-making process. However, the fact is that sex-based analysis is now generally included in product applications to the FDA. As indicated by the FDASIA Section 907 Report,[54] analyses for sex differences are now routinely done in drug applications.

Although progress has been made in the representation of women in clinical trials overall, the FDASIA Section 907 report indicated that there are still some specific areas of lower participation of women and racial groups. Capitalizing on the success of an increase in the overall participation of women in clinical trials, FDA's OWH has launched new efforts that focus on increasing diversity in clinical trials to include women of diverse ages, races, ethnicities, and sexual orientation, as well as women with disabilities and comorbid conditions. To improve transparency, quality, and participation—the three areas outlined in FDA's 2014 Action Plan for Enhancing the Collection and Availability of Subgroup Data—FDA has launched initiatives including the following:

- Transparency—Drug Trials Snapshots (DTS).[55] Cataloged online since January, 2015, DTS make data about the demographic makeup of clinical trial cohorts more transparent to the public.
- Quality—Inclusion of Women in Cardiovascular Trials. FDA researchers are taking a closer look at the data on women's participation in cardiovascular clinical trials For example, in 2015, FDA researchers ana-

lyzed DTS data for drugs approved for cardiovascular disease,[56] finding that participation rates for women averaged 35% (ranging from 22% to 80%).

- Participation—Diverse Women in Clinical Trials Initiative. This effort aims to promote diverse clinical trials participation by reaching out to investigators as well as the general public. Launched in 2016, the initiative includes an awareness campaign and webinar series for professionals on clinical trials design and recruitment. The campaign incorporates the NIH toolkit, ''How to Engage, Recruit, and Retain Women in Clinical Research.''

Plans for other FDA initiatives are also underway. OWH is analyzing NDAs in the areas of cardiovascular disease and opioid painkillers to assess women's participation in clinical research, especially compared with disease prevalence among women, and to look for the source of any discrepancies. For example, the screening process could drive disparities in how many women participate in clinical research. Published results are expected soon.

In addition, the Center for Devices and Radiological Health has created a new position—Assistant Director for the Health of Women, held by Terri L. Cornelison, MD, PhD, FACOG—as part of an initiative to improve sex and gender reporting and analysis for medical devices. Furthermore, the 21st Century Cures Act, which provides more than $500 million to FDA over 9 years for patient-focused drug development, advancing new drug therapies, and modernizing clinical trial design, also established a task force for research on pregnant and lactating women. OWH's Marjorie Jenkins, MD, MEdHP, FACP, is the FDA lead for the task force.

OWH encourages researchers to use its resources to enroll more diverse groups of participants in future studies and continue working to increase transparency in data reporting and decision-making. FDA will continue to encourage diversity in clinical trials, because when diverse populations are involved in clinical research, all benefit from greater knowledge about the safety and effectiveness of medical products.

Clinical trials in pregnant women: illuminating, path-breaking, and humbling

Dr. Tonse N.K. Raju, Chief, Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), spoke on general issues related to research studies[57] on pregnant women. Despite the importance of pregnancy as a window into the future health of a woman[58] and her offspring,[59] pregnant women's participation in clinical trials remains limited.[60]

The 1993 NIH Revitalization Act, which required researchers to justify excluding women and minorities for reasons other than cost, led to the greater participation of women in clinical research. However, the Act did not specify pregnant women as a group that should not be excluded, and the number of pregnant women participating in clinical trials did not increase. Researchers have numerous concerns about including pregnant women in studies, including physiological differences complicating study design; questions about whether consent from the mother, father, or both is required; regulatory roadblocks; fetal side effects; and the possibility of the woman carrying more than one fetus. Research participation by pregnant women is governed by federal regulations, which define the conditions for their inclusion in clinical research.[60,61] The regulations also define the criteria for Institutional Review Board approval of research with vulnerable populations, such as pregnant women, children, and prisoners.

A significant number of pregnant women are affected by conditions unrelated to pregnancy itself, including hypertension, diabetes, malaria, and psychiatric illness. Between 1976 and 2008, the proportion of women taking four or more medications at any time during pregnancy increased from 23.3% to 50.1%; considering just the first trimester, the respective proportions increased from 9.9% to 27.6%.[62] Over-the-counter drugs and off-label prescriptions commonly used by pregnant women are largely untested in pregnancy and are not monitored by federal agencies. Establishing effective treatments for maternal conditions and diseases is critical for the health of the mother and fetus, and for improved pregnancy outcomes. Use of unstudied drugs and therapies may be more dangerous than investigating drugs under planned and controlled conditions.[63] Outbreaks of infectious diseases are also an important consideration, as with the 2009 H1N1 pandemic, which disproportionately affected pregnant women, many of whom were not immunized or treated.[64]

Indifference to including pregnant women in research has a significant impact. Although concerns about fetal safety have been used as a rationale for excluding pregnant women from research, the risk of undertreatment of conditions such as depression, gestational diabetes, and malaria may outweigh that of using medication. Pregnant women often take medication, and unplanned pregnancy is common, yet, the risks of birth defects from about 90% of drugs approved since 1980 are unknown.[62] The National Institute of Child Health and Human Development funds investigator-initiated research with pregnant women, and NICHD also promotes the inclusion of pregnant women in clinical trials through research networks, such as the Maternal-Fetal Medicine Units Network. Studies enrolling pregnant women have included the Prenatal, Alcohol, SIDS (Sudden Infant Death Syndrome), and Stillbirth (PASS) Network studies[65]; the Sleep-Disordered Breathing study[66]; the Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy[67]; and the Management of Myelomeningocele Study (MOMS).[68] The MOMS findings changed clinical practice by demonstrating benefits to performing prenatal surgery to repair the most severe spina bifida defect. Other clinical trials with pregnant women have stopped ineffective, costly, and potential harmful therapies,[69–74] and prevented poor pregnancy outcomes.[75–77]

The knowledge gaps that result from excluding pregnant women from research often lead to harm to these women or their babies. However, a recent revision to federal policy removed pregnant women from the list of populations that are potentially vulnerable to coercion or undue influence.[78] Common Rule Policy revisions have been published, and implementation of the revised policy is expected to occur early in 2019.

In addition to continuing its support of trials, in which pregnant women participate, NICHD established the Global Network for Women's and Children's Health Research in 2001 to address the alarming rates of morbidity and mortality in women and children, and the lack of research expertise and infrastructure in the developing world. The network hosts seven sites in the United States, partnering with seven clinical sites in low- and middle-income countries. Research

underway includes studying whether low-dose aspirin prevents preterm birth, if preconception maternal nutrition support improves fetal growth, and whether maternal ultrasound performed in low-resource settings by trained nonexperts will improve pregnancy outcomes.

FDA pregnancy updates: drug labeling, registries, and clinical trials

Dr. Tamara Johnson, Team Leader, Maternal Health Team, Division of Pediatric and Maternal Health, Center for Drug Evaluation and Research, FDA, reviewed the steps FDA is taking to include available human data about the safe use of drugs during pregnancy in product labeling. When drug and biological products are reviewed for initial marketing approval, data evaluating safety and dosing in pregnancy are often lacking because pregnant women are often excluded from premarketing clinical trials. There are over 6 million pregnancies in the United States per year,[79] and half of pregnant women report using at least one medication during pregnancy.[62] Almost all information about medication use in pregnancy comes from the postmarketing experience with the products.

The FDA's Pregnancy and Lactation Labeling Rule[80] took effect on June 30, 2015. The rule requires the gradual removal of pregnancy letter categories from all prescription products by June, 2020. Products approved after June 30, 2001 have additional formatting and content requirements. The rule is intended to do the following: provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women, facilitate a more complete statement of the known risks based on the available data, include the considerations of medical/disease factors, put animal data in the context of human exposure, add human data when available, and explicitly state when no human data are available.

The rule revises labeling format and content for reporting information about drug use in pregnant women (Subsection 8.1 of the new drug labeling), lactating women (Subsection 8.2), and females and males of reproductive potential (Subsection 8.3). For drugs that are systemically absorbed, the *Pregnancy* subsection must include an integrated summary of fetal risks known from available human data, animal data, and (if applicable) pharmacology. Any contraindication for use in pregnant woman must be stated at the beginning of the subsection. In addition, labeling should include background information on the rate of birth defects and miscarriages in the U.S. general population, to be used as context for explaining risks to the patient.

Clinical considerations are described under a separate heading in the *Pregnancy* subsection. This subsection should include any known adverse reactions in the fetus/neonate, pregnant women, or during labor/delivery. In addition, this subsection includes any information available regarding dose adjustments for pregnant women and about known risks of the underlying disease to the mother and fetus/neonate. For example, now included in the labeling of drugs that treat diabetes mellitus is a statement about how poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, and delivery complications, as well as the fetal risk for major birth defects, still birth, and macrosomia-related morbidity.[81,82]

Data in support of the information in the integrated summary of fetal risk and in clinical considerations are reflected in the drug labeling. As mentioned above, these data are usually obtained after approval. Postmarketing safety data may be collected from pregnancy exposure registries, cohort studies, case–control studies, the enhanced pregnancy surveillance program, and case reports or case series.

Pregnancy exposure registries, studies that collect data on exposure to drug and biological products during pregnancy, are the most common postmarketing studies in pregnant women that FDA has required. In 2014, FDA convened a public workshop to assess such registries and identify successes and challenges. Key messages from this workshop include the following: multiproduct or disease-based registries have generally been more successful than single-product registries; recruitment is crucial for overcoming low enrollment and improving the registries' success; personal connections between patients and healthcare providers are effective for recruitment and the reduction of loss-to-follow-up; the use of electronic medical records is changing the landscape for approaches to data collection; standardization of outcome definitions is needed; use of internal comparator groups improves interpretability of results; and complementary study designs may help overcome the limitations of individual study designs. As a result, FDA is planning to revise the 2002 *Guidance for Industry on Establishing Pregnancy Exposure Registries* based on the recommendations from this public workshop. FDA seeks to explore opportunities for collaboration through private–public partnerships with the goal of improving safety data collection and improving health outcomes for pregnant women.

All of Us*: The Precision Medicine Initiative*

Stephanie Devaney, PhD, Deputy Director, *All of Us* Research Program, discussed efforts to launch the *All of Us* cohort, part of the Precision Medicine Initiative. President Obama introduced the initiative in 2015, which involves up to a dozen government agencies. The *All of Us* Research Program began enrolling participants in late 2017, with the ultimate goal of enrolling 1 million or more people who reflect the diversity of the United States. Participants will contribute health and lifestyle clinical data, ideally over many years, creating a rich resource for scientists to advance understanding of how individual variability affects health.

The research program is guided by core values such as transparency, treating participants as partners, giving participants access to their own data, and making data widely accessible for research. It aims to incorporate people from communities that have not previously been well represented in research cohorts, such as people who are sexual and gender minorities, have disadvantaged backgrounds or disabilities, are from racial or ethnic minority groups, or live in geographically or culturally isolated environments.

Investigators hope to use the program to advance novel approaches to research, such as expanding data access to researchers who do not belong to NIH-affiliated institutions. Participants will be able to contribute to building the program and having input into guidelines for data access. Consent will be updated over the life of the program, giving participants the option of withdrawing at any time. The data will reside in an enclave, not available for download, and access will be stratified. Program infrastructure will include a data and research support center, biobank, participant centers, and healthcare provider organizations (HPOs).

Participants will be able to enroll in one of two ways: either through HPOs, such as academic medical centers, Veterans Affairs centers, or other federally qualified health centers, or, for those who do not live near an HPO, as direct volunteers (DVs). DVs will be able to enroll online and will contribute samples and have their physical measurements taken through a national network of partner organizations, such as Walgreen Company stores. The enrollment process will include filling out consent forms and demographic questionnaires, as well as providing baseline health information and urine and blood samples.

As the *All of Us* Research Program takes shape, stakeholders in the scientific community will help define the types of data that are collected, including developing questions for future surveys. The program will look for researchers' input on the types of data that will help answer questions about women's health, as well as questions in other scientific priority areas, that cannot be addressed with smaller studies.

The initial set of data collection tools will include six surveys, and more will be developed over time. Surveys are also seen as a tool to keep participants engaged; testing what works best will be part of the implementation. ORWH took part in the planning efforts for a March 2018 workshop that generated use cases and had representatives from the office give input to help develop ideas for future survey modules at the meeting.

The research program has also established a partnership among leading electronic health record vendors to standardize data reporting for facilitating research, primarily to support participation from DVs. Because concerns remain about policy and ethical issues regarding electronic consent, Health Insurance Portability and Accountability Act (HIPAA) regulations, special populations (*e.g.*, children, incarcerated persons, and pregnant women), and data privacy and security,[83] the research program is planning a slow and careful rollout. The research program will continue to seek input from all stakeholders to define and set priorities for its scientific agenda. The *All of Us* Research Program recently entered the beta phase, which includes developing the enrollment website, building the biobank capacity, funding opportunities for community groups, and finalizing the protocol.

Expanding FDA transparency and communications: what every provider should know

Dr. Milena Lolic, MD, MS, Lead Medical Officer, Professional Affairs and Stakeholder Engagement, Center for Drug Evaluation and Research, FDA, discussed the drug approval process, introduced the DTS, and compared the style and comprehensiveness of the demographic data of DTS to that in FDA reviews and FDA-approved labeling.

The process of approving new drugs takes 8–12 months and requires a detailed overview of data from chemistry and toxicology studies, clinical trials, and other research. Typically, more than 15 scientists are part of this review process. The team of scientists holds numerous review meetings, both with its members and with the applicant. The review can end with three possible outcomes: a complete response (denial), extension (request for more data), or approval. Approval covers not just the drug's efficacy and safety but also naming, labeling, packaging, promotional materials, and other elements. FDA's approval may also include a postmarketing research requirement.[84] FDA has several initiatives and methods to increase the transparency of the data that informed the approval process, including making all the reviews public.

Owing to the mandates of FDASIA, FDA introduced the DTS initiative in 2015. FDASIA requires FDA to report demographic information about the participants in clinical trials that lead to the approval of new drugs, biologics, and devices. This information, published within 30 days of a drug's approval, also helps explain differences in a product's efficacy and safety by age, sex, and race/ethnicity. DTS is presented in question and answer format in two layers:

(1) Information intended for consumers is presented first and in consumer-friendly language.
(2) Each consumer section is followed by a ''*More Info*'' section, where expanded information is presented using technical language and more data. This section is directed toward professionals who want to explore further the statements from the consumer section.

Users can search the DTS database by brand name, date of approval, or active ingredient.[85] Providers and patients can also use this tool to discuss specific treatments. One example of DTS is the KENGREAL (cangrelor) snapshot. Regarding sex differences, it states that KENGREAL was similarly effective in men and women, and that considering drug safety, more bleeding was seen in women taking KENGREAL compared with men taking KENGREAL. Both statements are followed by respective analyses under *More Info*.

When interpreting subgroup differences, FDA uses the different levels of subgroup analyses. Inferential analysis is preferred, as it is the most credible. At times, FDA will accept supportive evidence—for example, analysis of consistency of the treatment effect across different variables. If only results from exploratory analyses are available, FDA will consider them, but such data are regarded the least credible and must be used with caution. The potential for error with exploratory data is higher, mostly because of the subpopulation sample size and lack of prespecification.[86]

FDA has published over 90 DTS, providing data showing efficacy and safety by sex, race/ethnicity, and age. In comparison to the FDA reviews and prescriber information, DTS do not include FDA's rationale for approving a drug or the demographics from the drug development program, nor do they provide reasons for the over- or underrepresentation of certain groups of clinical trial participants. However, DTS information is accessible, concise, and easy to share with patients and may help an individual determine whether a drug is right for him or her.

In conclusion, snapshots enhance the trial transparency and promote the importance of encouraging diversity in clinical trials to meet the health needs of patients across the demographic spectrum.

Discussions and Closing

The symposium included discussions with the audience after each pair of presentations. The first discussion concerned results from WHI that supported different interpretations and advised against generalizing the WHI's findings to populations to whom the findings do not apply. For example, results from a population of older women have limited applicability to the use of estrogen or cHT in younger women, who might benefit from these therapies.

Responding to a question about how NIH can determine the next large-scale clinical trial program with a huge ROI

such as WHI, Dr. Lauer pointed out that the WHI continues to be active, with ongoing dietary and physical activity trials that are using novel methods to conduct large-scale trials at a reasonable cost. One important lesson from the WHI is that when a large-scale cohort is needed, efficient and low-cost approaches to conducting experiments are necessary to maximize results and ROI. This is particularly true when conducting large-scale clinical trials in times of fiscal austerity.

Another discussion concerned WHI investigators and their plans for effective communications to engage women, especially women of color. Women who were consulted responded well to messages that emphasized how a study would benefit women like them, especially their own family members or members of their community. Results from those focus groups would be a rich source of information for OWH's Diverse Women in Clinical Trials campaign.

One inquiry fostered a discussion around obtaining informed consent when enrolling pregnant women in drug trials. Dr. Raju said that rules governing consent vary by state, and that there are also differences depending on whether the treatment under investigation is directed toward the mother or fetus, or pregnant adolescents.

Another question concerned whether NIH was considering giving industry incentives to conduct research on pregnant women, as was done for children through the 2002 Best Pharmaceuticals for Children Act. Dr. Johnson replied that FDA is still in an information-gathering stage regarding pregnancy. She was optimistic that some type of incentive would be possible, but it was too early to say.

A series of questions around the *All of Us* Research Program concerned training, participant withdrawal, compensation, and the approach to engaging partners. Dr. Devaney replied that staff would receive rigorous training, and strict guidelines would be laid out for all clinical sites. Trial runs for the training model have been undertaken at participating HPOs since late in 2016. Biosample collection is likely to start at a few sites and to expand gradually. Dr. Devaney further explained that participants can withdraw at any time by submitting a written request, accessing their online account, or contacting the Research Program's call center. Any samples that were collected from the withdrawing participant would be destroyed, with the caveat that any samples or data already released for further study could not be withdrawn. Participants can receive $25 for participating, but are not offered compensation for any discoveries researchers make.

Regarding the engagement of *All of Us* participants as partners, Dr. Devaney said that although no participants have enrolled yet, the cohort is being designed with participant representatives. Two participant representatives have joined the program's steering committee, and others have reviewed the protocol. The process of planning and establishing the *All of Us* program is an iterative process that will build on what is learned at each stage. Participants will be invited to join the program's governance as they enroll. In addition, the research program's digital platform will allow for extensive user testing. The program also plans to hold workshops to engage participants and learn about their needs and desires, so that the program can develop meaningful policies regarding the return of information. This approach will contribute to the dynamic nature of the *All of Us* Research Program.

Closing remarks

Marjorie Jenkins, MD, MEdHP, FACP, Director of Medical Initiatives and Scientific Engagement, OWH, FDA, thanked the presenters and organizers and reviewed the presentations, while reflecting on the importance of evidence, data, and policy in advancing women's healthcare. She noted that the presentations highlighted the significant advances brought about by the requirement to explicitly address sex and gender in the conduct of research and the resulting data. Dr. Jenkins also commented on the ongoing challenges and limitations in women's health research and drug development. This year marks the 25th anniversary of the Women's Health Congress, which has ''grown into the signature clinical women's health event in the United States,'' according to Dr. Jenkins. She added that the great successes and progress of the past 25 years create greater opportunities and expectations for the future. Dr. Jenkins concluded by inviting clinicians to use the resources introduced by the presenters, and to encourage their patients to participate in clinical trials.

Author Disclosure Statement

No competing financial interests exist.

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