Women in Clinical Trials Transcript:

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Hello and welcome to another episode of the Yale Journal of Biology and Medicine Podcast. YJBM is a PubMed-indexed, quarterly journal edited by Yale medical, graduate, and professional students and peer reviewed by experts in the fields of biology and medicine.

In celebration of the 50th year of women at Yale College and the 150th year of women at the Yale graduate school of arts and sciences, we're doing a special series of podcasts focusing on women and science.

In this series we wanted to not just highlight some of the amazing women in science here at Yale, but also explore some key issues in the science of women.

Today we wanted to talk about research on and about women, specifically looking at the inclusion of women in clinical trials throughout history and what that has meant for our understanding of women's health.

I. Introduction - current situation (Descovy pre-exposure prophylaxis as a case study)

Let's start by talking a little bit about human immunodeficiency virus or HIV. There are approximately one million people living with human immunodeficiency virus (HIV) in the US and about a quarter of them are women. There are about 40,000 new cases of HIV each year and about one in every five or six of those cases are among heterosexual women and 80% of those new cases are among women of color.

Although still too high, this is a substantial decrease even from about ten years ago, due in part to strong public health efforts to promote HIV prevention including increased awareness, testing and safe sex practices. Another incredible HIV prevention tool is Pre-Exposure Prophylaxis, more colloquially known as 'PrEP.' PrEP is a drug that when taken daily is about 99% effective in preventing HIV infection from sex.

When you visit the Centers for Disease Control and Preventions (CDC'S) website about PrEP there are a lot of great resources there - what is PrEP? Is it effective? Should I take PrEP? But, when you scroll down to that last section there's one statement that pops out (in part because it is both italicized and bolded):

"Descovy® (one of two PrEP drugs) for PrEP is recommended to prevent HIV for people at risk through sex, excluding people at risk through receptive vaginal sex." AKA women.

Why is Descovy not recommended for women? Because women were excluded from the clinical trial.

It's not the first time women have been excluded from important clinical trials and unfortunately probably won't be the last. We'll dive a little bit more into

the story of the Descovy trial a little later in this podcast, but to understand how we got where we are today let's step back through the history of research on women, or at least until recently, the lack thereof.

Before we do that, I do want to make a quick clarifying note - as we talk today about research on women, we are almost exclusively going to focus on research on cisgender women. A lot of what we'll cover today applies, perhaps even more so, to transgender women and men who have not been adequately represented or included in biomedical research. But, this podcast can only be so long, so hopefully we'll be able to come back to that important topic at some point in the future.

II. History of research on women's health

The title of this next section in our outline is the "history of research on women's health" but the truth is that this history is woefully sparse. Most 'advances' (and if you can't tell from my voice, I'm using air quotes) in women's health research were just plain wrong. As a 2017 Bustle article so aptly put it, the history of gynecology, the branch of medicine dedicated to women's health, is "Racist, Sexist and Just Plain Scary."

The Ancient Greeks blamed a number of conditions on what they called the "wandering womb" phenomenon - essentially the idea that the womb moved around your body and caused all sorts of trouble. They would try to lure it back its proper place by wafting sweet aromas up the *you know*

Things didn't really get any better from there for a very, very long time. Up until the 1950's, essentially just being a woman could earn you a diagnosis of "hysteria." Even when people did actually start formally studying women's health, it wasn't necessarily in the best of ways. The so-called father of modern gynecology, J. Marion Sims, made some of his pioneering discoveries by experimenting on his slaves. This is just one example of the numerous occasions in which women, particularly women of color, were exploited in the name of research, even research on women's health.

Not great.

I think we can all agree that things are better for most women today than they have been for, well, millennia. A lot of credit for putting research on women's health in the spotlight, at least in the United States, belongs to the Women's Health Movement, which arose during the second wave of feminism in the 1960s. The main focus of the Women's Health Movement was initially reproductive rights and it was the work of feminist groups, including the Women's Health Movement that achieved legalization of abortion through the decision in Roe vs. Wade. As the movement continued, their fight broadened beyond reproductive rights to achieve one common goal: "improved healthcare for all women and an end to sexism in the health system."

In order to improve healthcare for all women, we first had to understand women's health and do so separately from the male-dominated medical research

field. And that brings us to our main topic of discussion for today: the inclusion of women in clinical trials.

III. What is a clinical trial

I think it's important before we start talking about the inclusion of women in clinical trials in the US that we're all on the same page about what a clinical trial is and why they're so important in both our broader understanding of medicine but also the specific process of how drugs get approved and recommended for different populations.

The National Institute of Health (or NIH) definition of a clinical trial is "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

That's a lot of jargon so let's break it down a little bit - first, clinical trials are a form of human subjects' research, so we're working with people. Second, the goal of a clinical trial is to understand cause and effect - - if we do A, does it cause B? - which is incredibly tricky to do with humans. In fact, most studies can only estimate associations and not the cause and effect! "A" is what we call the intervention - it can be anything really, counseling, exercise, etc. but for the purposes of our discussion today "A" is usually a drug or a vaccine. "B" is usually a disease, so generally we want to know if drug A cures disease B.

The basic design of clinical trials is pretty straightforward - you get a group of people with an illness and you give some of them "drug A" and some of them nothing and see what happens. If the people who got the drug get better, and the people who did not get the drug don't then we can say that the drug cured the disease!

Of course, it quickly gets a lot more complicated than that so I want to zoom in on just one more aspect of clinical trial design that will be essential to our discussion today - inclusion and exclusion criteria. That is, who do you enroll in a trial and who do you exclude?

There are a myriad of factors that go into this decision - frequently you're only interested in a specific population, so it doesn't make sense to enroll people who aren't in that population. For example, if you want to know if a new drug can cure a specific type of cancer, you don't necessarily need to enroll people who don't have that kind of cancer. Sometimes you'll have specific exclusion criteria for safety reasons - pregnant women are frequently excluded from clinical trials because of the potential risk to the fetus. Other times it comes down to funding or feasibility - sometimes even when a disease is relatively common in a certain population, it may take too much time or money to enroll people from that population in a trial.

We'll touch on examples when women were included or excluded from clinical trials for all of the reasons above in our discussion today. The key thing to know

about inclusion and exclusion criteria is that the population that is included in a clinical trial determines the generalizability of the results of the trial - basically, we can't draw conclusions about how a drug works in a population if it wasn't studied in that population.

That rule applies more broadly to the field medicine but is particularly important in drug approval processes. The Food and Drug Administration is responsible for reviewing all of the evidence about the efficacy and safety of a drug and providing approval before a drug can be sold or prescribed in the US. In order for a drug to be approved by the FDA for use in a population, there has to be evidence from a clinical trial in that population that the drug is safe and effective.

That's how we end up with language like what we ran across earlier when talking about Descovy, the HIV prevention drug. Because women weren't included in the clinical trials, we don't know about safety or effectiveness in women and so the drug is not approved by the FDA or recommended for use in women.

One last little bit of info about clinical trials and FDA approval - even when there isn't evidence from a clinical trial about a drug in a specific population or for a specific disease or condition, sometimes doctor's will still prescribe it to that population. This is what's known as "off-label" use of a drug - the prescription of the drug for something other than its approved use. It's a relatively common practice and it's not necessarily an unsafe or bad practice. Sometimes it is even the recommended practice. Off-label use will come up a couple times as we start talking about the history of women in clinical trials.

IV. History of Women in Clinical Trials

As we discussed earlier, the story of the inclusion of women in clinical trials really doesn't start until the middle of the 20th century because research on and about women was so sparse before then and unfortunately this history starts with tragedy.

In the late 1950s a drug called thalidomide hit the markets, first in Germany as an over-the-counter sleeping pill but quickly became recommended as an anti-morning sickness medication for pregnant women. The manufacturer began marketing the drug specifically to pregnant women, making claims about the safety of the drug during pregnancy with little to no evidence from human studies. And by 1961, off-label use of the drug for morning sickness had become a common practice in many parts of the world.

At the same time that use of thalidomide was skyrocketing in Germany, England and other countries around the world, the manufacturers were applying for approval by the US FDA. At the time, clinical trials in the United States did not have to be registered with the FDA nor was there really any sort of regulation or oversight. There was a "clinical trial" for thalidomide ongoing in the United States, which essentially involved giving a whole bunch of thalidomide pills to doctors across the nation to prescribe as they saw fit. Approximately 20,000

individuals were involved in the trial including nearly 4000 women of childbearing age and about 200 pregnant women. There was very little follow-up being done with any participants and safety surveillance was essentially non-existent. The trial was still in progress as the FDA approval was being considered.

In early 1961 an obstetrician in Australia named William McBride delivered a baby with severely malformed limbs and substantial internal damage. Shortly after that, he delivered two more babies with the same deformed limbs and damaged internal organs. The mothers of all three of these infants had taken thalidomide during their pregnancies.

McBride published a letter in The Lancet which prompted a response from doctors worldwide - they were also seeing cases of severe malformation in children born to mothers who took thalidomide during pregnancy. Many of the infants were stillborn or died shortly after birth. Those who survived were most frequently born with phocomelia, or severely shortened, absent or "flipper like' limbs. It's unknown exactly how many infants were affected, but some estimate that nearly 100,000 babies were affected worldwide. Thalidomide was pulled off the market in most countries the same year.

Thankfully, the drug was not approved in the United States at the time and we have FDA inspector Frances Kelsey to thank for that. Even before the realization that thalidomide could cause severe birth defects if taken during pregnancy, she had concerns about the complete lack of safety and efficacy data on the drug and fought against pressure both from within the agency and from the manufacturers to prevent the approval of the drug.

The later revelation of the severe negative effects of thalidomide during pregnancy prompted a number of changes both in the FDA drug approval process and in the conduct and oversight of clinical trials in the US over the next decade and a half. The vast majority of these changes were for the best and made huge improvements in the safety of human subjects' research and drug development in the country. We now have a biomedical research and drug approval process that puts the safety of its participants first and foremost.

But the thalidomide tragedy also prompted the passing of the FDA guideline 'General considerations for the clinical evaluation of drugs' in 1977 that completely banned the participation of women of childbearing potential in clinical trials.

What is a woman of childbearing potential?

It's just a woman. If we want to get technical, it's a post-puberty, premenopausal woman. But basically, it's just any woman. So the 1977 guidance for the FDA essentially completely banned the participation of women in clinical trials.

You might be thinking - why is that such a bad thing? That whole thalidomide story you just told me was terrifying, we definitely don't want that to happen again, so why should we be giving experimental drugs to women who might get

pregnant? In this case, I think we can say that the decision was well-intentioned. But we essentially went from a situation where we didn't know how the drugs affected women because the trials were improperly conducted to a situation where we didn't know how drugs affected women because we weren't testing it at all. This broadly meant that no new drugs could be approved by the FDA for use in women, essentially making any drug prescription in women off-label. It also meant that research on women's health that involved any sort of clinical trial came to a screeching halt for almost a decade. If women can't participate in research, you can't exactly research women's health, now can you?

This is where the Women's Health Movement we talked about earlier comes back into our story. The women's health movement established in the 1960s was still fighting through the 70's and 80's to improve the representation of women in the healthcare system. In the early 1980's the AIDS epidemic in the United States put a huge spotlight on the drug approval process in the United States and clinical research overall. As scientists worked to develop and test treatments for AIDS, the AIDS activist community became frustrated with how the drug development and approval process was being conducted. Activists protested both how long it was taking for drugs to be approved and the lack of inclusion of minorities and women in drug trials.

The Women's Health Movement built off some of the work being done by the AIDS movement and fought against the relative lack of focus on women's health and women's issues in biomedical research by supporting female political candidates and funding for women's issues. At the same time, more women were enrolling in medical school and becoming involved in scientific research.

The increasing chorus of women's voices in biomedical research prompted the creation of the Task Force on Women's Health Issues in 1983 by the United States Public Health Service. The Task Force published a report in 1985 which acknowledged that:

"The historical lack of research focus on women's health has compromised the quality of health information available to women as well as the health care they receive"

In some ways, this report can be thought of as the first domino in a series of important institutional and legal changes that took place over the next decade or so. In 1986, the NIH established a policy that encouraged biomedical researchers to include women in research studies - going against the still standing FDA guidance. In 1989 the NIH went further to provide a guidance that explicitly stated that if researchers were choosing to exclude women or minorities from research studies, they needed to provide explicit justification for why. In 1990 following a congressional investigation into the inclusion of women in clinical research, the NIH established the Office of Research on Women's Health and in 1991 after the appointment of the first female director of the NIH, Dr. Bernadine Healy, the Women's Health Initiative was launched.

It took a few more years for all of this to be formally acknowledged in the law.

In 1993, congress passed the NIH Revitalization Act which legally encoded the 1989 guidance on the inclusion of women and minorities in clinical research. At the same time, the FDA formally rescinded the 1977 guidance on the exclusion of women in clinical trials.

Things have been steadily improving since the passage of the NIH Revitalization Act - a study published in 2010 looking at trends in the number of women included in clinical trials for cardiovascular disease prevention found that only about 15% of participants in trials from 1980-1984 were women compared to closer to 35% in 2000-2006. A more recent study found that in pivotal drug trials for FDA approval, men and women were equally represented.

Today, any researcher applying for NIH funding has to explicitly justify why they're excluding women from a trial. The Office of Research of Women's Health at the NIH is still going strong and provides resources for investigators on how to include and retain women in their studies.

With all of these policies in place, you may be asking how women are still excluded from clinical trials today.

It generally comes back to the idea of inclusion and exclusion criteria that we talked about earlier. As we mentioned before, there are a few reasons why a population, such as women, might be excluded from a clinical trial.

Sometimes based on the population or disease that you are interested in, it just doesn't make sense to include women in the trials. Like prostate cancer or erectile dysfunction treatments, you just don't need to include women.

Another reason may be that the group or organization running the clinical trial doesn't have the resources or funding to recruit the population into the study. This is essentially what Gilead, the manager of the HIV prevention drug Descovy, claimed as their reasoning for excluding women from the clinical trials for Descovy.

HIV transmission is more common among men who have sex with men than heterosexual women. Additionally, PrEP use is more common among men who have sex with men. So you can, to a degree, follow their reasoning that it was easier to just focus their study on those who were more likely to be interested in the study and those at higher risk of the disease. Adherence is also a major factor that impacts the effectiveness of PrEP - if not taken daily the effectiveness starts to drop dramatically - so follow-up for the clinical trial involved tracking adherence among all participants which would have been very time consuming and expensive.

In their pitch to the FDA for approval, Gilead did try to explicitly argue that Descovy would be safe and effective in women by showing data from Truvada, the other PrEP drug, and arguing that the biological mechanism of Descovy was independent from sex. The FDA didn't buy it.

Even though not mal-intentioned, the exclusion of women from this trial could

have significant effects on uptake of PrEP and potentially the spread of HIV in women. Part of the reason that PrEP use is lower among cisgender women to begin with is because of much lower awareness in that population. Having one of two PrEP drugs not be approved for use in cisgender women is only likely to perpetuate lack of awareness and lack of knowledge about PrEP for the prevention of HIV in this population.

Another big reason that women are excluded from clinical trials comes from concerns about reproductive? safety - more specifically concerns about the impact that the drug or therapeutic under study could have negative effects on a fetus.

The thalidomide tragedy of the 1960s has continued to echo through discussions and regulations around the inclusion of women of reproductive potential (aka women of childbearing age, as the FDA put it in the 1970's). But more broadly, the paternalistic attitude that the medical establishment has had towards women's health research since its inception (if you can even call the beginnings of women's health research that) still persists today, even with the advances that have been made.

One way this manifests is through birth control or contraception requirements for women participating in clinical trials. While there is no central guidance from the FDA on contraception requirements for women of reproductive potential enrolling in clinical trials, it is relatively common practice for pharmaceutical companies or other organizations conducting clinical trials to have some form of contraceptive use as an inclusion criteria for any women wishing to enroll. Like the 1977 FDA decision, I think we can say that this is probably well-intentioned? In a survey of US women about contraception requirements for clinical trial enrollment, a majority of women supported contraception requirements, frequently citing prevention of fetal harm as the main reason for their support. But unfortunately, these requirements also perpetuate inequities in representation in clinical trials. Contraceptive access is not universal and may present as a barrier to a woman who could benefit directly from enrollment in a clinical trial. Particularly in early stage clinical trials where the potential side effects of a drug may not be known, contraception requirements can be so strict as to essentially exclude all women, even those who have access to and regularly use contraception. There is also the ethical question of autonomy - women are more than just future baby carriers and should be able to make their own decisions about the risks they take with their own body.

Another way that the thalidomide tragedy manifests today is in the inclusion and exclusion of pregnant women in clinical trials. In order to know that drugs are safe and effective during pregnancy, you need to conduct clinical trials among pregnant women. But how? Researchers and regulators are still grappling with this question today. Largely, it has resulted in a dearth of trials among pregnant women.

Many drugs and therapeutics recommended during pregnancy don't have clini-

cal trial results to back up the recommendation. One example of this is maternal vaccines - there are currently two vaccines recommended during pregnancy by the Advisory Committee on Immunization Practices (the body that makes vaccine recommendations in the United States), the American College of Obstetricians and Gynecologists, the March of Dimes and numerous other organizations. There is ample evidence from numerous studies on the safety and efficacy of these vaccines for both mother and fetus. However, because clinical trials were not conducted specifically among pregnant women if you were to look at the FDA-produced labels for these vaccines you would not find pregnant women under the groups that use of these products is approved for.

These are just some of the examples of how while gender representation in clinical trials has become more equal and gains have been made in the field of women's health, we still have progress to make. In 2016, the FDA published a roadmap for the future of women's health research, which includes, among other things, efforts to improve clinical trial design, conduct and analysis to better support and understand women's health research.

We also need to recognize that the strides in representation in research that have been made for women are not universal. Non-white women, and men, are still vastly underrepresented in clinical trials. In a study of pivotal drug trials between 2011 and 2013, nearly 80% of participants were white, while only approximately 7% of participants were Black or Asian. This is reflective of years of systemic racism in the medical establishment. Enrollment in clinical trials is about more than just eliciting any biological differences in responses between participants - it can be a way to receive lifesaving treatment and it is a way to have your voice heard in the medical research process. There is no mention of racial or ethnic disparities in the 2016 FDA roadmap for women's health research and, at least as of June 2020, the link to the 2016 report on strategies to improve representation of minority women in clinical research does not work.

Women are not just 'differently shaped men' or 'men with hormones that make everything more complicated.' Our bodies are unique, and our health issues are unique. We are also the experts on our bodies and our health. It is more than just more clinical trials conducted among women - we need more women involved in every part of the process. Research on women needs to have women's voices present at every level - participants, researchers and regulators.

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We'd love your feedback and questions, so feel free to tell us your thoughts by emailing us at yjbm@yale.edu! If you enjoyed our podcast, please share our

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