RECRUITING WOMEN FOR FIRST-IN-HUMAN TRIALS

Tips for Success

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Introduction

Sponsors interested in recruiting women—particularly those of childbearing potential—into First-in-Human (FIH) clinical trials, often find that doing so presents some unique challenges above and beyond those encountered when recruiting men. The challenges range from overcoming concerns about risks, to appreciating what attracts female participants, to simple logistics. Consequently, women tend to be under-represented in FIH studies. Indeed, in Frontage Lab’s experience, men outnumber women in these early trials three to one.

Yet, there are compelling reasons for including women in FIH trials to the greatest extent possible. Data generated from these studies, theoretically, can identify potential sex-related differences in product safety and efficacy; such differences could have a bearing on dose ranging, safety concerns, and other aspects of future protocol designs involving key pivotal studies.

Programs that need to include women in their FIH studies will find that successful enrollment of women is achievable; however, it requires a concerted effort, with the correct strategies and proper support. In the following pages, we explore the challenges in recruiting women for FIH studies and present a set of practices that have proven successful towards improving the recruitment rates of women for these studies.

Policies Toward Women in Early-Phase Clinical Trials: Times Have Changed

In 1975, the US enacted regulations to provide extra protection to vulnerable subjects involved in clinical research—specifically fetuses—on the basis that investigative drugs may have a teratogenic effect on those fetuses. From this followed the rationale that the most appropriate and foolproof means to protect fetuses was to exclude all women of childbearing age from research. In 1977, the US Food and Drug Administration (FDA) specified that premenopausal women capable of becoming pregnant be excluded from early-phase trials.

Beginning in 1993, the FDA recommended that clinical studies (although not necessarily FIH studies) include sufficient members of each sex to detect clinically significant differences in the drug’s efficacy and safety and that those differences should be reported in marketing applications.

Today, due to the acceptability and ready availability of long acting and reversible contraceptive methods (LARC) (including injections, hormonal implants and several IUDs) that are at least 99 percent effective in preventing pregnancy, we can confidently minimize the risk of pregnancy and thereby potential threats to a fetus during ongoing trials. Therefore, provided that proper precautions against pregnancy are taken it is now appropriate and acceptable (and sometimes required) to include women of childbearing potential (WOCBP) in carefully monitored early-phase research.

Currently, the FDA and Institutional Review Boards (IRBs) sanction the inclusion of women in clinical research with certain provisions. For example, an FDA guidance specifically states that risks associated with the “unintentional exposure of an embryo or fetus before information is available concerning the potential benefits versus potential risks” can be minimized in several ways:

- Studies can include women not of childbearing potential (those who are postmenopausal or who have been permanently sterilized);
- The inherent risks of a drug can be studied and cautiously extrapolated to humans through animal reproduction and toxicity studies; and
- The potential risks can be minimized by instituting precautions within trials to prevent pregnancy with the use of highly effective methods of birth control and pregnancy testing upon trial entry and exit.

Leading the effort to enhanced inclusion of WOCBP in clinical trials, the National Institutes of Health (NIH) actually mandates the
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inclusion of women for all NIH-funded studies that are not gender specific. The Institutes’ policy states:

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research... Women of childbearing potential should not be routinely excluded from participation in clinical research.7

Women in Early-Phase Research: The Scientific Rationale

There are several sound scientific reasons for ensuring that the effects of pharmaceuticals are tested in women during Phase I studies, which are specially designed to gather preliminary safety and tolerance data and to determine the drug’s pharmacokinetics and dynamics in humans.

• ADME differences. With many drug treatments, there are observed differences between men and women in the way that drugs are absorbed, distributed, metabolized and excreted (ADME).6 These differences are thought to be caused by the effect of hormones and women’s generally smaller body weight.9 What’s more, because the biology of pre- and postmenopausal women is different, drugs intended for the general female population should be tested in both populations. Ultimately, after a drug is marketed and subject to ongoing pharmacovigilance reporting, any differences subsequently discovered in the way that women respond will be used to further modify treatment decisions.

• Greater risk of adverse reactions. Women have a 1.5 to 1.7 fold greater risk of adverse reactions than men, and these sex-based reactions have caused some drugs to be pulled from the market.10

• Possible drug-drug interactions. There is a need to establish whether the investigational drug has an impact on the pharmacokinetics and/or pharmacodynamics of other medications, including oral contraceptives, or if these medications (including oral contraceptives) have an effect on the investigational drug’s behavior.11

Additionally, US regulations enacted in 1998 require that sponsors analyze trial results for men and women separately to measure differences in response rates and adverse events and report the findings in new drug applications (NDAs).12

Recruiting Women for FIH Studies: A Practical Challenge for Sponsors

The Center for Information & Study on Clinical Research Participation (CISCRP) reports that 62 percent of people who participate in clinical trials choose to do so to advance medicine and to improve the lives of others. Another 15 percent do so to improve their own condition, 5 percent to earn extra money, and 3 percent to receive free medical care.13 Thus, most people—at least in what they are willing to admit—are motivated to participate for altruistic reasons.

However, when it comes to FIH studies, this is a “tough sell” for women with conflicting priorities and concerns about their reproductive health. Through our experience in recruiting women, we have identified several factors that appear to play a role in their reluctance to participate in FIH studies: (Note that the list below is not comprehensive, but does represent barriers to participation that we have frequently encountered.)

• Logistics. Many women between 18 and 44 years of age have family responsibilities that make it logistically very difficult for them to stay in a clinic for the required time, which can run up to 72 hours.

• Perceived Risk of FIH Studies. A general lack of knowledge about the rigor of pre-clinical testing that has already been completed prior to FIH studies and of the regulations protecting participants tends to inhibit participation.

• Birth Control Requirements. The protocols for most FIH studies require that WOCBP be on an adequate method of birth control for three months prior to participation and for 30 days after participation. Adequate methods include either a double barrier method or an IUD, or hormonal implant or injection. As many otherwise eligible women rely only on condoms for pregnancy prevention, they are excluded from participation.

• Other Exclusion Criteria. Most FIH protocols require that

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9“Exploring the Biological Contributions to Human Health: Does Sex Matter?,” Institute of Medicine, National Academy Press, Washington, DC: 2001
12https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm133181.htm
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Women have a body mass index (BMI) between 18 and 30 and that they weigh over 110 pounds, criteria that exclude many possible participants. According to the National Institutes of Health, 36 percent of US women over 20 years of age are obese.\(^\text{14}\) WOCBO also experience a high incidence of anemia, another disqualifying factor. According to the Centers for Disease Control 12 percent of women between the ages of 12 and 49 are anemic.\(^\text{15}\)

Recruitment Solutions: Address the Physical and Attitudinal Impediments

Some sponsors attempt to recruit women who are surgically sterilized, thus limiting themselves to 25 percent of contraceptive users.\(^\text{16}\) Others focus on recruiting postmenopausal women, but that poses additional problems. First, the drug is being tested only in older women who, depending on their health and age, may be biologically different than younger women. Second, as participants’ age increases, so do their co-morbidities which are typically exclusion criteria.

It is possible though, to improve recruitment rates of WOCBP via proactive efforts such as those listed below:

- **Get the word out.** As a first step, sponsors need to spark women’s interest. Women cannot participate in trials that they know nothing about. Successful strategies include using a multi-channel advertising approach that incorporates social media and launching a grass roots effort to reach women where they congregate such as at women’s health clinics, college campuses, health fairs, gyms, book clubs, women’s groups, etc.
- **Cast a wide net.** Canvas—and stay in touch with—community health clinics and other referral sources.
- **Stay in touch with prospects.** Maintain an active database of possible participants that can be sorted by relevant screening criteria, such as BMI. Maintain communications with women in the database to sustain their interest and keep the information fresh.
- **Offer inducements.** There is an opportunity to emphasize

the benefits to be gained from a thorough and free health screening. Trial participants are given a comprehensive physical examination, blood testing, and close medical monitoring.

SELECTING A RESEARCH PARTNER:

**KEY QUESTIONS TO ASK**

A sponsor’s choice of Contract Research Organization (CRO) is an important one in ensuring successful recruitment of women for FIH studies. To ensure that they select a partner capable of recruiting sufficient numbers of women, sponsors should ask prospects:

- **What percentage of past FIH studies have met their recruitment goals for women?**
- **What novel approaches has the organization employed to reach women subjects?**
- **Does the organization maintain relationships with community physicians and clinics?**
- **How many prospects are captured in the organization’s database? Is the database kept up to date?**
- **What portion of your clinical staff is female?**
- **What evidence can you provide that your clinical staff are trained in and attuned to the special needs of WOCBP?**
- **Has the clinic staff been trained in cultural sensitivity?**
- **Is the clinic staff able to communicate in the local language(s)?**
- **Does the clinic have an Ob/GYN on staff?**
- **What is the condition of the clinic facilities?**

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\(^\text{14}\)https://www.niddk.nih.gov/health-information/health-statistics/Pages/overweight-obesity-statistics.aspx

\(^\text{15}\)https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.htm#tab1

\(^\text{16}\)https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states
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• Provide education. The R&D pharmaceutical industry as a whole would derive value from leading a national campaign to educate women on the benefits and risks of participating in clinical research, for example via the GoBoldly web site. Such a campaign could build on the initiative launched by the FDA's Office of Women’s Health, in conjunction with the National Institutes of Health Office of Research on Women’s Health. The Diverse Women in Clinical Trials Initiative includes a consumer awareness campaign and educational resources.17

• Make participation easier. Sponsors can address some of the logistical impediments that women face in taking part in early phase research. For instance, a sponsor might want to offer women free transportation to and from the clinic.

• Make participation more pleasant. To be competitive, many hospitals have patterned their culture, service, and environment after that of the hospitality industry. FIH trial clinics can do the same, making a stay more inviting and enjoyable for women. This could encompass the décor and cleanliness of the facility, the amenities provided (everything from toiletries to the quality of the sheets and towels), the staff’s ability to anticipate subjects’ needs, and the staff’s language and cultural sensitivity.

Conclusion

Women—and especially those of childbearing potential—remain under-represented in FIH clinical trials. To the extent that a protocol requires it, sponsors can hope to increase the recruitment rate of women by considering the characteristics of that population. Successful tactics range from launching outreach campaigns and educational programs to catering to women’s needs in making participation both easier and more pleasant.

17http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118508.htm

Founded in 2001, Frontage is a full service CRO with over 500 employees globally. Headquartered in Exton, PA, Frontage has additional laboratories and clinical centers in Somerset and Secaucus, NJ, and Shanghai and Suzhou, China.

Our integrated core services include: DMPK, Bioanalysis, CMC (Chemistry, Manufacturing & Control), Early Phase Clinical (Phase I-II), Biostatistics & Data Management

What sets us apart is our ability to collaborate closely with our clients to ensure a thorough understanding of their drug development goals and our ability to provide flexible solutions that are customized to each client’s needs. At Frontage, we are committed to providing rigorous scientific expertise assuring the highest quality and compliance for each project. Frontage proudly serves innovator, generic and consumer health companies from IND enabling through late stage clinical projects. Frontage successfully assists clients to advance hundreds of molecules through development to commercial launch in global markets. This partnership with our clients is how we turn services into real solutions that get our clients ahead.