CLINICAL TRIALS – SHOULD YOU PARTICIPATE?

by Gwen L. Nichols, MD

Dr. Gwen L. Nichols

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Dr. Nichols trained in internal medicine at the University of Chicago and completed post-doctoral research and a hematology-oncology fellowship at Memorial Sloan-Kettering, where she served as an attending physician on the leukemia service. Prior to joining Hoffmann-La Roche in 2007, Dr. Nichols was the director of the hematologic malignancies program at Columbia University in New York. In this capacity, she managed laboratory research and developed clinical trials focused on hematologic malignancies. While at Columbia, she also maintained an active clinical practice and served as Assistant Dean of Students for Columbia University's College of Physicians and Surgeons. Dr. Nichols was voted "Physician of the Year" at Columbia, as well as being chosen for the Humanism in Medicine Award.

The subject of clinical trials has been featured extensively in the recent press. A 2013 article in the New York Times Sunday Review entitled "Do Clinical Trials Work?" raised questions about the long time that drug development takes, the costs, and the measurable benefit of clinical trials as they are currently performed. A recent announcement of the Blood Cancer Research Partnership (BCRP) between the Leukemia & Lymphoma Society and Dana-Farber Cancer Institute has raised many hopes as well as questions about expanding access to clinical trials in community settings. Few would disagree that newly developed, more effective medicines need to get to the right patients faster and less expensively. The formula for doing this more efficiently, without compromising patient safety, is a work in progress. For individuals deciding whether or not to participate in a clinical trial, there is a host of conflicting information. It is not always clear what the purpose of a given trial may be, what a participant should expect, and who really stands to benefit from the patient's participation. While there are no "one-size fits all" answers to the question "Should you participate?" a clear understanding of the questions and complexities involved can help you obtain the necessary information to make an informed decision.

HOW DOES A DRUG GET DEVELOPED?

The long process of developing a new medicine often begins when a laboratory has either targeted a particular molecular pathway or a disease or is screening compounds. If, in the course of these investigations, an activity is discovered that may be relevant against cancer in vitro (in the test tube), a variety of cancer models can be explored to evaluate the innovation's therapeutic potential. This can be accomplished in an academic lab or within a company. It may take years to understand the mechanism of action in cell lines and in animal tumors before a particular discovery can be turned into a drug. This process often involves extensive chemistry and formulation work so that the agent can be produced as a pill or a liquid that is safe for humans, in quantities suitable for further testing. Typically, toxicology testing is the next step. Very specific safety studies (depending on the type of agent) in animal models are required before a drug can be submitted to regulatory agencies for required approvals to allow studies in humans.

Next, an Investigational New Drug (IND) application is submitted to the health authorities which includes extensive documentation of how the drug will be produced and stored, the clinical plans for development, and how patient safety will be assured.

Phase 1 is generally an "Entry-Into-Human" trial. This is usually the first time any human has received the drug. Critical findings for Phase 1 are to understand the pharmacology of the new agent: how much drug to give, how it is metabolized, and how it should be dosed (both dosage amount and frequency) in patients. All this is accomplished with step-wise increments to learn about harmful side effects, as well as beneficial effects. In Phase 1 the goal is always to err on the side of safety, so the dose that initial study patients receive may not be the amount for the final or effective dose.

The studies start at doses well below the doses where side effects were seen in animals, as animals may not predict what is seen in humans. Dose testing in Phase 1 continues either to a maximum biological dose (where an effect is predicted to be seen) or to a maximum tolerated dose. Phase 1 trials increasingly are looking for effects of the drug in blood or tissues or through scans as the doses are increased. Patients participating in a Phase 1 trial must agree to the testing required for the study by signing an informed consent form. Overall, the amount of testing, the number of days at the clinic, and the requirements for biopsies and scans may be extensive in order to determine the best way to give the drug in the future.

Phase 2 trials often involve more patients. At this stage researchers analyze the drug's efficacy and safety in patients selected by disease characteristics. These trials may be performed in combination with or in comparison to a standard of care treatment. Phase 2 trials have specific eligibility criteria for selecting patients. Factors may include particular stages of a given disease, the number of prior treatments, general health characteristics, tumor biopsy, or pathologic characteristics. The number of patients and the studies being performed are based on the required level of statistical assurance to support reproducible findings that would demonstrate benefits superior to available treatments.

Questions to ask your physician about participation in a clinical trial:

What is the phase of the study and what is the goal or endpoint?

How frequently will I need to be in the hospital/in the clinic for testing and what type of testing is required?

If I fail to respond to the drug, does getting this treatment prevent me from getting other treatments?

Does the science make sense?

What is the likelihood that I will be helped by participation?

Are there approved or standard therapies which make sense to use first?

Questions to ask yourself before participation in a clinical trial:

Am I willing to have a biopsy or other studies (x-rays, blood work) required for participation?

Am I ready to participate in order to help others in the future if this has only a small chance to work for me?

Am I a person who believes in the scientific process?

Am I willing to follow all of the elements of the research study, even if they are inconvenient?

To participate in a Phase 2 trial, patients need to meet all the entry criteria to ensure that the study data is reliable. This can be frustrating, particularly if one's disease characteristics differ from the norm. For researchers there may also be a valid concern that highly selected populations may not adequately reflect the more general population of patients with a given condition. Novel ways to expand where Phase 2 trials can be performed may improve the success rate of Phase 2 studies and help in predicting success in Phase 3.

Phase 3 trials are based on Phase 2 data. They are chiefly designed to statistically demonstrate clinical benefit versus a standard treatment. Phase 3 trials involve more patients and an increased number of locations. Most Phase 3 trials are done in order for the drug to seek approval for marketing. Phase 3 trials are generally randomized and are often double-blinded. Randomization means that patients are assigned to a particular treatment by chance (the test treatment may or may not contain the new drug being tested). Double-blinded means that neither the patient nor the treating physician knows which treatment the patient is getting. Placebos are rare in oncology trials, but participants in a Phase 3 trial may get a standard of care drug that is also available for those with the same disease who are not participating in the trial.

Results of Phase 3 studies are presented to health authorities as part of a new drug application (NDA). Phase 3 trials often take years to perform. One reason is the large number of patients who need to participate. Another is that the endpoints of the study in oncology are frequently progression free survival or overall survival over a significant period of time. Thankfully, as treatments improve, median overall survival for many diseases is longer than in the past. But this poses a difficult question for drug development. Do we have to wait years to answer the question of benefit for patients based on survival or are there "surrogate" endpoints that will adequately predict what will happen years down the road? Researchers and regulatory authorities are carefully examining these questions for future drug development. It may seem obvious that shrinking of a tumor or lymph node would predict improvement in progression free survival or overall survival, but this is not always the case. Each particular disease must be examined for adequate markers of efficacy that can serve as reliable "surrogates" for helping patients live longer.

Lastly, you may hear about studies that fall outside of the typical Phases. These may involve pharmacology or new formulations of a drug, different dosing and schedules, or testing of biomarkers which predict activity; still others are simply conducted to learn more about the disease. These trials may provide patients access to drugs when the patient doesn't fit the particular entry criteria for a randomized study.

SOME FREQUENTLY ASKED QUESTIONS

Why does drug development take so long?

The development process has a lot of safeguards to protect participants. Some complain that drug development isn't safe enough, that drug companies rush drugs through to approval, and that too many drugs get withdrawn from the market after they have been approved. It is a delicate balance between getting new medicines to patients, making sure the business of research and development is financially sound, and discovering rare (1/1,000 or 1 /100,000) but important side effects. This can take years. Companies often agree to post-marketing or Phase 4 evaluations for safety and efficacy precisely to learn about these rare but important side effects.

Why are many of the trials only in large research centers?

Determining a drug side effect compared to the effects due to underlying disease, other medical conditions, or other medicines can be a challenge, particularly in oncology patients. If an investigator is too conservative, the drug testing may be stopped before an effective dose is reached. If an investigator is too liberal with criteria, safety may be compromised. This is why investigators and research sites are screened for experience prior to being selected to participate in a clinical trial. Clinical trials require extensive specialized testing and careful monitoring. Also, the research nursing specialists, research pharmacy requirements, and specialized laboratory and testing equipment may only be available at specific research centers.

The new Blood Cancer Research Partnership will test whether trials can be done safely in smaller settings with practitioner/researchers in order to reach more patients not able to travel to big academic centers. This type of program may be particularly important for rare diseases where no center has enough patients to perform a trial. This concept may have the benefit of bringing more "real world" patients onto clinical trials, but it also runs the risk of having trials stopped too soon due to the inexperience of investigators and staff. This novel program will be watched closely as a new model for the future.

Do drug companies perform trials with drugs they know aren't good?

Given the extraordinary costs of drug development and the goal of getting approval and recuperating costs of development and research, there is no incentive for a company to start a large Phase 3 trial without a reasonable belief in its success. Also, this decision is only made after careful scrutiny of Phase 2 data, in discussion with regulatory authorities. Lacking promising Phase 2 data, companies favor saving money by stopping development or making new adjustments rather than initiating a Phase 3 trial for approval. Often this cost/benefit analysis has meant that drug developers have chosen to proceed with Phase 3 trials primarily in larger indications (more prevalent diseases) that have a greater market potential. However, with the recent trend to more specific and targeted therapy, this model is changing.

How can rare diseases be better represented?

New models of clinical trial participation, including cooperative groups, consortia, and clinical trial networks through disease-specific advocacy groups, are ways to provide access to new drugs for patients with rare diseases. Regulatory incentives such as Orphan Drug Designation may also provide a stimulus for researchers to study rarer indications. Incentives for sponsors include grants and guidance for clinical trials. This program is particularly designed for treatments of diseases/disorders that affect fewer than 200,000 people in the U.S., and thus are not expected to recover the costs of development and marketing.

What are the FDA and other health authorities doing to improve the drug development process while maintaining safety?

The FDA has several new programs to help speed promising agents through development. One program, Breakthrough Therapy Designation, is intended to expedite development of drugs for serious or life-threatening conditions. A Breakthrough Therapy Designation requires preliminary clinical evidence that the drug may have substantial activity. If a drug receives this, the FDA has an organizational commitment to work with the sponsor to get the data necessary for approval as efficiently as possible.

Accelerated approval is intended for drugs that demonstrate an effect on a "surrogate endpoint" that is reasonably likely to predict clinical benefit and that can be measured earlier than an effect on survival. Accelerated approval may require additional trials after approval, and approval can be withdrawn if the benefit is not verified.

Priority review was initiated as part of the Prescription Drug User Fee Act (PDUFA). If a drug receives a priority review, the FDA agrees to complete the review and act on an application within 6 months rather than the standard review timeline of 10 months.

FINAL THOUGHTS

Drug development is undergoing dramatic change. As we understand the biological differences between patients with the same disease and the biological differences between individuals, our approach is becoming more patient specific rather than disease specific. This poses a new set of challenges for research scientists and requires new paradigms for drug development and approval. Novel ways to conduct trials, new endpoints for success, new ways to collaborate, and new regulatory processes are just the start. It is an exciting time for clinical research. Should you participate? For each individual it is a risk/benefit question. For those of us involved in drug development, we hope that for many patients the answer will be yes.

Dr. Nichols is a member of the IWMF Scientific Advisory Committee and has presented at several IWMF Educational Forums.

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