FROM MOLECULES TO MEDICINE:
CLINICAL RESEARCH

RARE TOOLKITS

FROM MOLECULES TO MEDICINE: CLINICAL RESEARCH

Introduction

Patients with rare diseases often look to new treatments for help. These treatments are often new drugs but may also be devices, vaccines, or biologics such as cell-based treatments or gene therapy. Sometimes, these drugs or biologics are still being tested to learn how well they work and how safe they are. These tests are called clinical trials or clinical research.

This Global Genes™ Toolkit will offer information surrounding the types of clinical trials, as well as how to find them. It is part of a series on drug development, **From Molecules to Medicine**, with others in the series providing more detail on each step of the process. Details about how patients and their families may share their voices to improve clinical trials can found in **From Molecules to Medicine: Sharing Patient Voices**. For more about understanding the drug development process, take a look at **From Molecules to Medicine: How Are New Drugs & Therapies Developed**.

SECTION 1: WHAT IS A CLINICAL TRIAL?

Clinical trials can be divided into **observational** and **interventional** trials. In an **observational trial**, researchers study a disease or medical treatment without asking patients or their doctors to test specific investigational therapies. A very important type of observational study for clinical research is a **natural history study**. In this type of study, the ways the disease or condition develops or how patients are affected over time is studied. **Natural history studies** provide valuable information that can be used to develop the best design for clinical trials that test investigational therapies, which might make the clinical trials faster.

"When it comes to rare diseases, their natural histories frequently are not fully understood because there are simply not enough cases that have been observed and studied. This lack of knowledge limits researchers' ability to study rare diseases and develop new treatments. Knowledge of natural history is essential for developing more efficient clinical trial designs. It also could help reduce the length and cost of drug development and, possibly, contribute toward greater predictability of clinical development programs," Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research at the FDA (from http://blogs.fda.gov/fdavoice/index.php/2014/10/the-more-we-know-about-rare-diseases-themore-likely-we-are-to-find-safe-and-effective-treatments/).

Interventional trials are what most people think of when talking about clinical trials. In an interventional trial, researchers test specific drug therapies to learn about the risks and how well the therapeutic works. All drug therapies must be tested through a series of interventional clinical trials before being approved for sale by a government regulatory agency, such as the Food and Drug Administration (FDA) in the U.S.

Clinical Trial Designs

Patients in clinical trials do not always receive the drug or biologic being tested. Often, the patients are split into different groups, or arms, which receive different treatments. Different **arms** may receive different doses of the investigational drug or the drug in combination with other drugs. In some clinical trials, there are **control groups** or **control arms** where patients receive another treatment that is currently being used by physicians. In **placebo-controlled** clinical trials, the patients in a control group receive a **placebo**, which looks like the investigational drug or biologic, but does not have any effect.

Most often, the clinical trial is **randomized**, which means the patients are assigned to the different arms randomly. Sometimes, patients stay in one arm throughout the clinical trial, but sometimes patients move into different arms and receive different products at different times during the clinical trial, which is known as a **crossover design**. Patients often do not know which product they are receiving, which is a **blind** trial. This may also be called a **masked** trial. If the clinical research team also does not know which products the patients are receiving, the trial is **double-blind** or **double-masked**. With only rare exceptions, an investigational drug must be tested in at least one randomized, controlled clinical trial to be approved for sale.

SECTION 1: WHAT IS A CLINICAL TRIAL?

Clinical Trial Phases

Several clinical trials must be done before a drug can be approved. Clinical trials are divided into four phases. Phase 1-3 trials are conducted before the drug is approved, and Phase 4 trials are done after the drug has been approved for sale. The differences between the clinical trial phases are the number of patients enrolled and what the researchers are trying to understand (See the table below). Clinical trial phases may be written using Roman numerals for the phase, such as "Phase II" for Phase 2. Clinical trials phases sometimes also include a letter, such as "Phase Ia" or "Phase 2b," which indicates a narrower focus of the purpose of the trial. For example, a Phase 2a clinical trial focuses on determining the best dose of the drug, while a Phase 2b clinical trial is designed to determine the drug's effectiveness.

Clinical Trial Phases

Phase	Purpose	Estimated Range: Number of Patients
1 or I	To find the highest amount of the drug that can be given that is still safe for patients	20-100 – may be fewer for rare diseases
2 or II	To begin to learn how safe the drug is and how well the drug works to treat the disease or condition	100-500 – may be fewer for rare diseases
3 or III	To show the drug is safe and works well to treat the disease or condition	Hundreds to thousands – may be fewer for rare diseases
4 or IV	To show the drug is safe for long-term use and if there is any more information about how well the drug works	Hundreds to thousands – may be fewer for rare diseases

Clinical Trials for Rare Disease Populations

It's important to note that clinical trials for rare disease populations are not one-size-fits-all, because each disease and patient population is unique. Consequently, trial designs often are individualized and based on the needs of the company and the disease. This not only affects the trial design, but also the number enrolled. With very small patient populations, clinical trials may be smaller in comparison to studies and trials for common conditions.

Data Collected During Clinical Trials

Substantial amounts of information, or data, is collected during a clinical trial. The data are collected during regular visits to the clinical research site and, sometimes, from a patient's medical records. All the information and how it will be collected is described in the informed consent form. Patients should ask any questions they have about how information will be collected. Visit the Toolkit Informed Consent: Important for Treatment Decisions and Advancing Research for more information.

Some examples of information usually collected during clinical trials include the patient's physical condition such as pulse rate, breathing rate, blood pressure, weight, any symptoms related to the disease or condition, and how the patient is generally feeling. Other information may be collected through blood samples, MRI's, CT scans X-rays, tissue samples, or genetic testing.

SECTION 2: WHO IS INVOLVED IN CONDUCTING CLINICAL TRIALS?

Typically a clinical trial involves the participation of many patients and the work of many clinical research staff at numerous locations (See blue Box). Clinical trials also are reviewed by committees to make sure the research is done responsibly, and by regulatory agencies to decide if the product is safe and effective (See green Box next page). For larger trials, especially Phase 3 and Phase 4 trials, the number of people involved can be in the thousands, however for rare diseases, this number may be smaller and based on the size of the patient population as well as other factors.

Individual Roles in Clinical Trials

Patient: The role of the patients is to contribute their time and effort by following the instructions for the clinical trial and telling the clinical research staff of any changes in their condition. Patients should also ask questions at any time during the trial. They can decide to stop participating at any time. In information about clinical trials, participating patients may also be described as “subjects,” “human subjects,” or “participants.”

Sponsor: The sponsor is responsible for every part of a clinical trial. Sponsors are usually pharmaceutical or biotechnology companies. Federal research agencies, such as the National Institutes of Health in the U.S., also often are a sponsor for clinical trials. Sometimes for early phase trials, university medical centers or individual university faculty serve as the sponsor.

Clinical Research Organization: A clinical research organization (CRO) is a company that manages clinical trials for the sponsor. Not all clinical trials involve a CRO.

Research Site: The research site is where the clinical trial is done–where the patients are enrolled, where the patients come for trial visits, and where data are collected. A research site is usually at a healthcare organization such as a medical clinic, an academic medical center, hospital, physician’s office, or at a research site managed by a clinical research organization.

Principal Investigator: The Principal Investigator (PI) is responsible for making sure the clinical trial is done accurately and responsibly at all the clinical research sites. There may also be local PIs who are responsible for the trial at one research site.

Clinical Research Coordinator: Clinical research coordinators manage the details and procedures of the clinical trial under the supervision of the Principal Investigator.

SECTION 2: WHO IS INVOLVED IN CONDUCTING CLINICAL TRIALS?

Committee and Agency Roles in Clinical Trials

Institutional Review Board/Ethics and other review committees: Ethics committees, called Institutional Review Boards (IRBs) in the U.S., review the clinical trial before it begins at a research site to be sure the patients will be treated ethically and safely. Other review committees may also be involved for issues such as medical privacy of patients or use of radiation or gene therapy. Often these review committees are part of each research site and so a review is conducted at each research site. In some instances, central IRBs are used, where one committee conducts the review for research that will be conducted at multiple sites.

Regulatory Agencies: National regulatory agencies review and approve the start of Phase 1 clinical trials and approve the sale of drugs or biologics based on clinical trial data. In the U.S., this agency is the Food and Drug Administration. Although it doesn't happen often, regulatory agencies can put a trial on "clinical hold," which stops the clinical trial until safety issues can be reviewed.

SECTION 3: HOW DO I BEGIN PARTICIPATING IN A CLINICAL TRIAL?

To begin participating patients must find a clinical trial for their disease or condition, match the requirements for enrolling and decide to participate. In certain cases, patients may be able to receive an experimental therapeutic without participating in a clinical trial, such as expanded access (also known as compassionate use) or under "right-to-try" laws in some U.S. states.

Finding a Clinical Trial

One of the biggest hurdles for a patient looking to participate in a clinical trial is finding a trial located nearby and for the right disease or condition.

There are several resources patients and families who are interested in participating in a clinical trial can consult. Although there are several ongoing efforts to provide a central place where clinical trials can be listed, there are often still some delays, meaning clinical trials are not always being listed in one place. As a result, patients should still consider looking at several resources for available clinical trials.

One of the first resources is your own physician who may be aware of clinical trials for a particular disease or condition. Other resources are searchable databases from sponsors, clinical research sites, or patient advocacy organizations. A large database of trials is available with search functions at www.clinicaltrials.gov and the **WHO International Clinical Trials Registry Platform** (http://www.who.int/ictrp/en/).

Several other websites list clinical trials being conducted at a specific place or clinical trials being conducted for a particular disease. Medical centers often have a list or searchable database of clinical trials being conducted at their site. Sponsors, such as nonprofit organizations or pharmaceutical companies, also list clinical trials linked to their organization's website.

Many other organizations also provide a list of certain types of clinical trials. For example, CenterWatch has a database of industry-sponsored clinical trials, and the American Cancer Society maintains a database of cancer clinical trials.

Enrollment Criteria

Once you find a clinical trial for your disease or condition, the clinical research staff will check to be sure you meet the **enrollment criteria** for the trial. Enrollment criteria are certain requirements that have been set by the clinical trial sponsor and usually have to do with your physical condition or previous medical history. Often you will also hear the terms inclusion and exclusion criteria for participation in a trial or study. These terms further describe enrollment criteria. **Inclusion criteria** are characteristics that prospective subjects of the study must have if they are to be included. **Exclusion criteria** are those characteristics that disqualify someone from inclusion in the study. Common examples of enrollment criteria include age, physical condition (for example, able to sit, able to walk a certain distance), not having received certain medical treatments recently such as other drugs or surgeries, or not having some other conditions or diseases.

SECTION 3: HOW DO I BEGIN PARTICIPATING IN A CLINICAL TRIAL?

Deciding to Participate in a Clinical Trial

If you meet the enrollment criteria for a clinical trial, you then make the decision whether you want to participate. You may want to consider many things in making your decision (See the box below), and you should discuss these carefully with the clinical research coordinator, the principal investigator, and your own physician.

Before Deciding to Participate in a Clinical Trial

Before agreeing to participate in a clinical trial, patients should think about:

- The effectiveness of treatments that are clinically available already;
- The time and commitment needed to participate in the clinical trial;
- The location of the clinic visits and how far you must travel to the clinic site;
- The lab and clinical tests involved; and
- The known potential risks of the investigational drug or biologic.

Enrollment in a clinical trial is always voluntary and you can decide to stop participating in a trial at any time. However, if you leave a clinical trial, you may not be able to enroll later in the same clinical trial or even another clinical trial because you might not meet the enrollment qualifications.

All patients considering enrolling in a clinical trial will be given written information and an opportunity to discuss the clinical trial with the clinical research coordinator and/or principal investigator through the **informed consent process**. The informed consent process includes a discussion of what the researchers hope to learn through the clinical trial, how often you will need to come to the clinic and what instructions you will need to follow Informed Concent also outlines the risks and benefits of the drug being tested and for participating in the trial, and what other medical treatments are available.

Be sure to think of questions before enrolling in a clinical trial. Some examples can be found on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/info/understand). Also, visit **Informed Consent: Important For Treatment Decisions and Advancing Research** (https://globalgenes.org/toolkits/informedconsent/introduction/), for information and guidance.

Access to Experimental Therapeutics Outside of a Clinical Trial

All countries provide some ways for patients who meet certain qualifications to have access to experimental drugs when a clinical trial is not available. In Europe, these programs are called “named patient programs,” “named patient supply,” or “temporary authorization for use.” In the U.S., there are expanded access programs for single individuals, intermediate-size populations, and widespread use. Also, certain U.S. states have passed “right to try” legislation that provides a way to bypass the U.S. FDA in gaining access to experimental therapeutics. The Access to Unapproved Medicine: Is This An Option for Me? (USA) toolkit focuses on the specifics of programs in the U.S. Access to Unapproved Medicine: Is This An Option For Me? (Canada).

SECTION 4:

WHY DO INVESTIGATIONAL DRUGS OR BIOLOGICS FAIL TO MAKE IT THROUGH CLINICAL TRIALS?

Not all investigational therapeutics are found to be safe and effective.

It has been estimated that fewer than 10 percent of drugs entering preclinical research eventually are approved. So what are the reasons clinical trials are unsuccessful?

Investigational therapeutics may not work well enough to be approved. This may be because there is another effect of the disease or condition that the drug does not work on. It may also be because the investigational drug or biologic only works for some patients, and it is not known which patients will benefit. In the larger Phase 2 and Phase 3 trials, the therapeutics may not work in enough patients to be considered effective.

Investigational drugs or biologics may have serious side effects that outweigh any benefits or which make too many patients drop out of the trial.

Finally, clinical trials may fail because of design and operations issues. For example, sponsors sometimes develop trials where it is hard to show that the drug or biologic had the desired effect. The sponsor and clinical research staff may not find and enroll enough patients in the trial. The clinical trial may require too much time or effort from patients so that patients do not enroll or drop out.

SECTION 5:

HOW DO I FIND RESULTS OF A CLINICAL TRIAL?

Right now, companies and researchers have publicly released results from less than 20 percent of clinical trials. In the U.S., some clinical trials are required to be registered and to submit a summary of results, and there are efforts to expand these requirements. The World Health Organization (WHO) recently called for all clinical trial results to be made available in a registry within 12 months after a study is completed and published within 24 months of completion. Although not all clinical trial results are currently available, results from some trials may be found online (See below).

Where to Search for Clinical Trial Results

ClinicalTrials.gov (https://clinicaltrials.gov/ct2/help/how-find/find-study-results)

WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/)

PubMed (http://www.ncbi.nlm.nih.gov/pubmed)

National Cancer Institute: Sponsored clinical trials (http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=6204240)

Trials Central (http://www.trialscentral.org/)

Social media/Twitter: Major scientific journals (e.g., New England Journal of Medicine, Journal of the American Medical Association), pharmaceutical and biotechnology companies, and Principal investigators may reference clinical trial results

SECTION 6: NEW OPPORTUNITIES

Many people involved in the clinical trials process think that there might be ways to make clinical trials faster and less expensive. These include new ways of designing clinical trials, changing the regulatory process, developing more consistent expanded access programs, and repurposing available drugs.

New Ways of Designing Clinical Trials

Sponsors and regulatory agencies are exploring new clinical trial designs including enrichment design, adaptive design, and virtual clinical trials.

Clinical trials using an **enrichment design** focus on enrolling patients who are most likely to benefit from the drug being tested. Researchers use greater knowledge of diseases and conditions and technological tools such genetic sequencing to find these patients.

Adaptive design modifies the clinical trial design during the trial. The best treatment arms can be identified while the trial is still being done. Then, the process of randomizing patients can be changed so that more patients are assigned to the clinical trial arm(s) that appear to be most effective. This can reduce both the time and cost of clinical trials.

Although not very common, drug companies are beginning to conduct clinical trials with remote monitoring, or **virtual clinical trials**. Instead of physically visiting a clinic, patients can be monitored via wireless devices. This saves the patient time and the cost of travel to an often far-away clinical site for participation in a clinical trial.

Changing the Regulatory Process

The clinical trial process is often long and traditionally involves large numbers of patients, however there is some flexibility granted at times for small patient populations with unmet medical need. In addition, once the drug is approved, often additional information regarding safety and efficacy is not collected. The European Medicine Agency in 2014 adopted regulations allowing for the faster approval of drugs where there is an unmet medical need with clinical trials involving fewer patients. The process is called **adaptive licensing**. Initial marketing approval is granted for a limited indication. Once approved, the drug is available but closely checked through additional clinical studies to confirm the safety and effectiveness of the drug and to expand its approval to other conditions. A full marketing approval is given only when the drug is shown to work well for long-term effects. Currently, this process is not available in the U.S.

The FDA and many companies have been including patients earlier in the drug development process to improve the design of clinical trials, such as the initiative at the FDA called **Patient-Focused Drug Development**. Through this program, the FDA is engaging patients to provide benefit-risk assessments and new measures for the effectiveness of a drug. This may allow clinical trials to improve design and may get the FDA to consider what risks patients are willing to take on for a new

SECTION 6: NEW OPPORTUNITIES

drug for a serious disease or condition. FDA also will engage in externally-led patient focused drug development meetings and is open to participating in well designed and conducted meetings as part of its commitment to receiving patient input on drug development and evaluation. For more details on how to pursue and externally-led meeting, visit http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

More Consistent Expanded Access Programs

Although the FDA has a regulatory process for patients to access investigational drugs outside of a clinical trial, sponsors, which are most often companies, have had difficulties responding to requests. The effort to get the drug to the patient may slow down the clinical trials due to the time needed or because there is often only a small amount of the investigational drug. There may also be risks for the patient if the patient is in worse health than those in the clinical trial. One pharmaceutical company has recently developed a bioethics panel with ethicists, physicians, and patient advocates to consider requests for Expanded Access. This, hopefully, will lead to a better understanding of how sponsors can and should respond to patient requests.

Repurposing Drugs

In many past clinical trials that failed, there were some patients who appear to have been helped tremendously. Until recently, not much could be done to learn why these patients responded when others did not. But with technological advances in genetic and protein sequencing, some researchers are looking to see if the causes for these patients' responses can be identified. There are not yet many organized efforts to explore these "**exceptional responders**," and some researchers have begun to ask for a national registry of these responders. The National Cancer Institute also has begun to conduct a study of up to 200 exceptional responders.

Sometimes drugs that already are approved for marketing or which have failed clinical trials are found to have potential in new indications. The NIH National Center for Advancing Translational Sciences has a program to develop collaborations between pharmaceutical companies and researchers to test drugs in new indications. Because these investigational drugs have already gone through some testing, this will speed the development process.

CONCLUSION

Patients with rare diseases often actively look for clinical trials. They may also be asked by physicians or researchers to consider participating. Patients should be fully informed about the clinical trials process and key considerations prior to enrolling. New advances in clinical trial designs and regulatory processes may help make clinical trials faster and with a higher success rate. As a best practice, patient engagement at every stage of trial design and the trial phases, helps inform the sponsor regarding meaningful outcomes and strengthens understanding and participation of the community.

RESOURCE GUIDE

ClinicalTrials.gov is a registry and results database of clinical trials around the world. This site also includes an overview and definitions of key terms used in clinical research and a list of important questions to ask when considering participating in a clinical trial, https://clinicaltrials.gov/ and https://clinicaltrials.gov/ct2/about-studies/learn#Questions

The Drug Development Process: Clinical Trials from the FDA, an overview of the clinical research process with an emphasis on the role of the FDA, http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

Clinical Trials: What Patients Need to Know from the FDA, provides an overview of what patients should think about when considering clinical trials and how patients are protected during clinical trials, http://www.fda.gov/ForPatients/ClinicalTrials/ucm20041753.htm

About **New Therapeutic Uses from NIH National Center for Advancing Translational Sciences** describes their funding program for repurposing therapeutics, http://ncats.nih.gov/ntu/about

TrialReach provides a searchable database of clinical trials, https://trialreach.com/patients/
Trials Central provides a searchable database of clinical trials, http://www.trialscentral.org/

WHO International Clinical Trials Registry Platform provides a searchable registry of clinical trials, http://www.who.int/ictrp/en/

PubMed provides a searchable database of scientific articles of the results of basic and clinical research. The full text of many of the articles that are older than one year is also freely available, http://www.ncbi.nlm.nih.gov/pubmed

Global Genes Drug Development Roadmap, https://globalgenes.org/wp-content/uploads/2016/02/Toolkit-Roadmap_web_112415.pdf

Global Genes From Molecules To Medicine: How Are New Drugs And Therapies Developed?, https://globalgenes.org/toolkits/

Global Genes From Molecules To Medicine: How Patients Can Share Their Voices Throughout The Drug Development Process, https://globalgenes.org/toolkits/

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