

CLINICAL RESEARCH

What is clinical research?

Clinical research is any kind of research that measures something taking place in a patient. Some kinds of research included in this broad category are:

- *Outcome studies* – measure the outcome of a large group of children with a certain disease.
- *Efficacy studies* – measure the response (for example, change in symptoms and signs of inflammation, change in bone destruction) of a large group of children treated with a certain medication.
- *Safety studies* – measure side effects of a medication.
- *Pharmacokinetic studies* – measures the metabolism (absorption and elimination) of a medication
- *Laboratory studies* – doing basic biological research on blood or a tissue specimen taken from a patient, to try to understand the cause for the disease.

Why is clinical research important?

Before new medications are tested in children, they have already undergone testing in adults and found to be safe. In order to be approved by the US Food and Drug Administration (FDA) for use in children, the appropriate dosage must be established and the safety and efficacy must also be documented.

Currently, only some of the medications that pediatric rheumatologists routinely use have been well studied in children, or approved by the US FDA for use in children. As all pediatricians (and parents) know, children are not just small adults! Because children metabolize drugs differently (sometimes faster, sometimes slower than adults, depending on the drug), one cannot always guess accurately at the proper dose on the basis of weight.

Outcome studies are important to determine how children with a specific disease do over the long run, and to try to identify ways in which their care can be improved. Laboratory studies are essential to the understanding of rheumatologic conditions. We can't treat autoimmune and inflammatory diseases properly until we know exactly what has gone awry to cause these dysregulated responses. All of the new biologic drugs on the market for treatment of juvenile arthritis and related conditions are the direct result of basic laboratory research.

Why is there more clinical research on childhood arthritis now than ever before?

1999, the FDA enacted the Pediatric Rule, which says that if the same or an equivalent condition exists in children as in adults, all new drugs approved to treat that condition have to be tested in both adults and children. The FDA also encouraged testing of medications already on the market by allowing companies to extend their patents if they now test these drugs in children.

What are the characteristics of good clinical research?

To determine if a treatment is effective, the research must be *unbiased*. That means it is designed so as to minimize or eliminate the possibility that a patient or investigator may influence the outcome of the study *based on what he or she believes*. For example, to accurately compare two medications, or to compare a medication to no treatment, a good study would have the following characteristics:

- (1) The research must have an objectively measurable hypothesis. For example, testing the hypothesis that a medication reduces swelling in arthritis, and being able to measure the swelling in an unbiased or objective manner, follows the scientific method. Something that is less objective which still might be measured in such a study is the patient's report of how he or she feels.

- (2) There is a control group. In some studies, the control group receives a placebo (something that looks just like the study medication but is inactive). In other studies, the control group receives an active comparator (a medication that has been shown to be effective for the condition being studied, but is different from the medication being studied).
- (3) The study is “double blinded”. The patients do not know which preparation they are taking. The doctors who are assessing the response to the treatment do not know which preparation the patients are taking. This process of blinding is accomplished in two ways: The preparations are made to look and taste just alike (or as nearly as possible), and someone else besides the doctor dispenses and keeps the records of the medications.
- (4) The control and treatment groups are randomized. Patients are assigned to either group in a random fashion as determined by a computer. This is necessary so that there is no unconscious bias in assigning the sicker patients to either group.
- (5) The study is large enough to achieve statistical significance. In other words, there must be enough patients or samples in each group to be reasonably sure the results occurred because of the treatment rather than by chance.
- (6) After the entire study is over, the “code” is broken, and the investigators find out which patients received which treatment. Then the data is compiled and analyzed to see if the study medication had a beneficial effect.

Where are the results of good clinical research reported?

Results of properly performed clinical studies are reported in peer-reviewed journals. The results are written up by the investigator and submitted to the editor of the journal. The editor assigns several experts in the field to review the manuscript. These reviewers are usually academicians (faculty members of colleges and universities) who review manuscripts on a volunteer basis. Each reviewer makes his or her independent recommendations on whether the research was done properly, and how the manuscript could be improved. The editor or editorial board then decides whether the results can be published, and what changes should be made to the manuscript.

There are other kinds of publications that are not peer-reviewed. Research that is published only in a non-peer-reviewed or an industry-sponsored publication should be suspected to be biased. Patients and parents should also keep in mind that information on the Internet is not peer-reviewed.

Who provides the money to conduct research?

Some research is initiated by investigators, who are usually faculty members in colleges and universities. The investigator explains the proposed research in detail in the form of a grant application, which is submitted to a funding organization. Some examples of national organizations that fund rheumatology research include The National Institutes of Health and The Arthritis Foundation. Other sources for funding of investigator-initiated grants include state and local philanthropic organizations, industry, and universities.

Some research is sponsored by pharmaceutical companies. Often this is in the form of a clinical trial of a medication they wish to sell. In this case, the industry contracts with physicians in many locations (often in academic centers) to perform the actual research. Many pharmaceutical companies also sponsor laboratory research.

How are patient rights and safety insured in clinical research?

Universities and hospitals have institutional review boards (IRBs) whose duty is to monitor and insure that research involving patients is performed in an ethical and safe manner. Before such research

can even be started, it must be approved by the IRB – a process that requires documentation that the study procedures should not cause harm, and describing in exact detail how the study will be performed so as to safeguard the rights of the patient. The research is monitored by the IRB, which has the power to halt the research if it is not being conducted properly or if it turns out that patients are being harmed. In trials conducted at numerous places at once (multicenter trials), any adverse events that occur involving patients are required to be reported to the investigators and IRBs at all the participating centers.