COMBINE Study – Frequently Asked Questions

Questions about the COMBINE Study

What is the COMBINE Study?

COMBINE is a research study looking to answer an important question:

For kids with Crohn's disease who need to start an anti-TNF medication (Remicade or Humira), does adding another medication called Methotrexate lead to better outcomes?

Pediatric Crohn's disease experts are split on whether adding Methotrexate to anti-TNF treatment is better or not.

Some experts think that two medications for Crohn's disease may work better.

Other experts think that two medications may not work better than one and could add side effects.

Why is the COMBINE Study important?

COMBINE is the first study to look at this question in children with Crohn's disease. It is expected that 425 kids from across the US will enter the study. The results of this study will be used to help doctors choose medications that help children the most.

What do I need to know when deciding to participate in the COMBINE Study?

It is important that you understand:

- What this study is about, including why it is being done
- What is required in order to participate
- The potential risks and benefits of being in the study
- The available alternatives for treatment

An informed consent document that you will receive from the research staff will explain this and the major elements of the trial.

On the COMBINE Study website (www.combinetrial.org) you can find more information to help you decide whether to participate in COMBINE. However, the best source of information will be the researchers at your clinic and you should feel free to ask them any questions you have about COMBINE.

What are the eligibility requirements to participate in the COMBINE Study?

To be eligible to participate in COMBINE your child will have to be starting an anti-TNF medication on the recommendation of your clinician and have at least moderate Crohn's disease.

If my child joins COMBINE, what happens?

Children entering this study will be randomly assigned into one of two groups. In one of the groups, the pill form of methotrexate will be added to anti-TNF therapy. In the other group, a look-alike placebo pill will be added to anti-TNF therapy.

During the study, you, your child, your doctors, and the researchers, will not be aware of which group your child is in.

Why include a placebo in COMBINE?

COMBINE is a blinded study. In a "blinded" or "masked" study, participants do not know whether they are getting the drug being tested, or are in a control group, which could be a group getting a placebo. The goal is to prevent the so-called "placebo effect" or any other biases from influencing the results of the study. The placebo effect is the phenomenon of participants feeling better simply because they think they are receiving a helpful drug or treatment.

Sometimes, clinical trials like the COMBINE Study are "double-blind" or "double-masked." That means that neither the participants nor the study staff members know who is receiving the dual therapy drugs and who is in the control group. Studies are performed in this way so that expectations and assumptions about the treatments being studied do not influence observations and results.

As a double-blind study, COMBINE will be able to compare outcomes like safety and tolerability, Crohn's disease activity, and quality of life directly between the two study groups in a way that greatly reduces bias.

Under some circumstances participants and their clinic may be informed if they are receiving methotrexate or placebo before the end of the study. These include cases where this information could significantly affect treatment decision, such as when a major side effect is suspected or when there is progression of Crohn's disease activity while on study treatment. Unblinding decisions will be made on a case by case basis by the leadership of the study.

What will children and their parents be required to do if they participate in the COMBINE Study?

COMBINE is designed to rely on information collected at your routine visits with your Crohn's doctor. So, the results of examinations, blood work, medical history, and tests obtained by your clinic during these visits will be included in a research database that the study team will use. There will also be some phone calls from study staff to make sure you receive your medications and to check with you on how things are going once treatment has started. Your health will continue to be monitored during the study trial period. COMBINE participants will be asked to complete several brief questionnaires each year. A detailed description of what's expected is outlined in consent forms.

What are the benefits of participating in the COMBINE Study?

There may be no direct benefit to your child resulting from participation in this study as no one knows which of the two treatment strategies being compared is best. However, in answering an important question about Crohn's disease treatment, the study may eventually help doctors and patients make more informed decisions when considering treatment options.

How are COMBINE research subjects protected?

The COMBINE Study follows a carefully written and reviewed study protocol, which provides in great detail information about how the investigator is to conduct the study.

http://cedars-sinai.edu/Patients/Clinical-Trials/Clinical-Trials-Frequently-Asked-Questions.aspx#conduct

An Institutional Review Board (IRB) must review and approved this study. This board, which includes scientists, clinicians, and community members, protects your rights and welfare if you take part in a research study.

The study team has also put in place a number of procedures to protect the safety of participants. Most importantly, there are medical staff at your clinic who are responsible for carefully reviewing laboratory and other test results, physical exams, and any information that lets them know about a participant's health. The study protocol spells out what the clinic staff must do when there are findings that are abnormal or concerning. This includes letting the main study team and the IRB know about the problem.

Another important safety measure is a Data and Safety Monitoring Board. This is a group of experts who are not otherwise connected to the study except to review study data at intervals during the trial. The Data and Safety Monitoring Board is not blinded to the treatment assignment of participants; therefore it receives information that can let them decide if there are significant differences in good or bad outcomes in one arm of the study compared to the other. This board can recommend that a study stop randomizing participants to a specific

treatment group, and can even stop the study if there are important differences between the study arms during the trial.

Lastly, during the study, the researchers must share with you any new information that might be expected to influence your decision to remain in the study. This information could be from COMBINE or from another research study.

What will be done with the information gathered from the COMBINE Study?

http://www.nih.gov/health-information/nih-clinical-research-trials-you/basics#8

After the COMBINE Study is completed, the researchers will carefully examine information collected during the study before making decisions about the meaning of the findings and about further research. Results from clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which experts review the report before it is published to ensure that the analysis and conclusions are sound. If the results are particularly important, they may be featured in news media and discussed at scientific meetings and by patient advocacy groups before they are published. Once a new approach has been proven effective in a clinical trial, it may become the standard of medical practice.

How will my child's information be kept confidential?

Data collected during the study and shared with the researchers is de-identified. This means that information that could lead to the identification of a participant is removed. In place of names, the study assigns a unique ID number to each participant and this number is used on data forms.

A study pharmacy will be used to send study medication to participants. This pharmacy will have the names and contact information of participants but will keep this information private.

Can I withdraw my child from COMBINE after it has begun?

Yes, participation in COMBINE is always voluntary and your child may leave it at any time - either before the study starts or at any time during the study or the follow-up period. There is no penalty for withdrawing from the study and leaving this study will in no way affect your child's clinical care.

Will it cost me anything if my child participates in COMBINE?

Costs for the study medication and any special study procedures that are not part of your child's routine care will be paid for by the study sponsor. Since the study will occur in conjunction with your child's routine doctor visits for Crohn's Disease, you will be responsible

for paying for your child's doctor visits, routine laboratory tests, and anti-TNF medication prescribed by your child's doctor in the usual way. Your clinic can assist you with this process.

How long will my child be participating in the COMBINE Study?

Your child may be in the study for as long as two years.

What happens after the COMBINE Study ends?

At the end of the study, you, your child, and your clinician will be told which study group your child was in. This information can be used to help you make treatment decisions. Children who were assigned to receive active methotrexate can be prescribed this medication by their clinician at the end of the study.

The results of the study will be shared with participants and the families and also with the medical community.

Who is conducting the COMBINE Study?

The University of North Carolina at Chapel Hill is sponsoring the study. This research study is partially funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (PCS-1406-18643). The study is also being supported by ImproveCareNow, an organization working to improve care, health and costs for all children and youth with Crohn's disease and ulcerative colitis. Additional funding is provided by The Leona M. and Harry B. Helmsley Charitable Trust, Grifols Diagnostics Solutions Inc. and the National Institutes of Health.

Parent partners who have children with Crohn's disease are also part of the study team. Parent input for the COMBINE Study has been instrumental in making the study better for children and families.

Questions about Research

What is research?

http://cedars-sinai.edu/Patients/Clinical-Trials/Clinical-Trials-Frequently-Asked-Questions.aspx#research

Research is a way to answer a question and to gain knowledge. We use knowledge gained from research to come up with new treatments. Medical practice is different from research. The main purpose of medical practice is to care for the health and well-being of patients. The main purpose of research is to test new scientific ideas or new treatments. Research may help individual participants, but this is not always the case.

How does the outcome of clinical research make a difference?

http://www.nih.gov/health-information/nih-clinical-research-trials-you/basics#8

Only through clinical research can we gain insights and answers about the safety and effectiveness of medications and other therapies. Groundbreaking scientific advances in the present and the past were possible only because of participation of volunteers, both healthy and those diagnosed with an illness, in clinical research. Clinical research requires complex and rigorous testing in collaboration with communities that are affected by the disease. As clinical research opens new doors to finding ways to diagnose, prevent, treat, or cure disease and disability, clinical trial participation of volunteers is essential to help us find the answers.

What is a protocol?

http://cedars-sinai.edu/Patients/Clinical-Trials/Clinical-Trials-Frequently-Asked-Questions.aspx#protocol

A protocol describes the rules to follow during the research. For example, a protocol states why it is important to study the research question and how the research team will answer the research question. A protocol also states how the research team will protect the health and well-being of the research volunteers. A protocol includes information on the study procedures, medications to be used, possible risks and benefits, possible adverse events, and data analysis methods.

What is informed consent?

http://clinicaltrials.gov/info/resources

Participation in the COMBINE Study is completely voluntary. Before your child can enter the study you will receive an informed consent document that explains the details of the study. It also includes the potential risks and benefits, as well as your rights and responsibilities. A member of the research team will discuss the study with you and answer your questions so you can make an informed decision about whether or not to participate. In addition, you have the right to ask questions throughout the course of the study and may withdraw your consent (stop participating) at any time.

Questions about the Study Medications

What is Anti-TNF medication?

Tumor Necrosis Factor, or TNF for short, is a chemical made by certain immune cells in the body. Medications that block TNF have been found to be effective in treating Crohn's disease in

adults and kids. These medications are also called 'Biologics'. Examples include infliximab (Remicade) and adalimumab (Humira).

What is Methotrexate?

Methotrexate is a medication that interferes with the vitamin folic acid inside of cells and is an immunomodulator – meaning it can have effects on the immune system. Methotrexate has been used in both adults and kids to treat Crohn's and a number of other diseases. It comes as a pill or a shot. People taking Methotrexate also take folic acid to protect healthy cells and prevent any side effects of the medication. All participants in COMBINE will receive folic acid tablets.

How do I learn more?

On the COMBINE Study website (combinetrial.org) you can find LINKS to other resources and MORE INFO that can help you decide whether to participate in COMBINE.