

# Clinical Research 101: Patients and Clinicians Gearing up to Discover Together

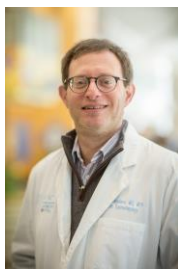
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## Presenters



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## Faculty Disclosures

**Michael Kappelman, MD** has affiliations with AbbVie Inc. (*Speakers Bureau*) (*Grant Support*).

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## Agenda

Today, we will be answering the following important questions about clinical research:

- What is clinical research and why is it important?
- What are the steps to performing a research study?
- How are participants recruited for a study?
- How does the research process protect human subjects?
- What questions should I ask myself, my family, and my healthcare team before joining a clinical research study?

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## Why is Clinical Research Important?

- The field of medicine relies on evidence.
- In the absence of evidence, clinicians can only rely on their judgment and intuition.

Clinical research has the potential to provide new information to take the guesswork out of care and provide insights into:

- Disease trends
- Risk factors for a condition
- Patterns of care, costs, and use
- Discovery of treatments
- Effectiveness and safety of treatments
- Optimization of treatment
- Development and evaluation of diagnostic tests
- Perceptions and preferences of providers and patients
- And more...

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## Why is Pediatric IBD Clinical Research Important?

- More children are being diagnosed with IBD than ever before.
- The risk factors for pediatric IBD remain unclear.
- There is debate about the best treatment approaches for kids with IBD.
- While some kids' diseases are managed well with standard IBD treatments, others with more severe IBD are more likely to:
  - Not grow to their full potential
  - Experience continued active gastrointestinal (GI) symptoms
  - Develop complications that require surgery
  - Need new therapies to control symptoms and disease activity, especially as children often have more severe disease
- For all kids living with IBD, managing a life-long chronic disease presents physical and emotional challenges.



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## Pediatric IBD Research: An Urgent Need

- Few IBD clinical research studies focus on children.
- Kids and families often have to make treatment decisions based only on information provided from adult clinical studies and trials.
- Without clinical trials involving children, doctors may not fully understand the degree to which a treatment studied in adults will be effective for kids.



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## What is Clinical Research?

Clinical research is the way we learn how to prevent, diagnose, and treat illness. A clinical research study tries to answer a specific question by collecting and studying information using a clearly specified, organized approach.



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## What are the Steps to Performing a Research Study?

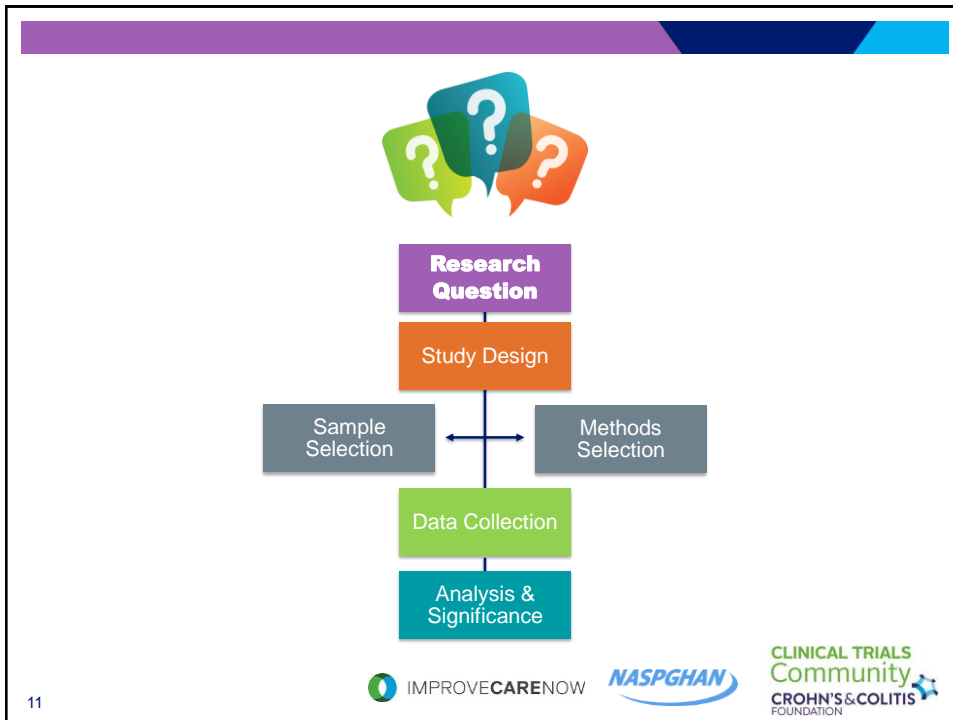
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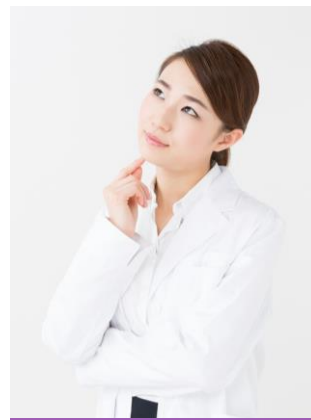
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## Step 1: The Question

- Creating a clear question is the first step in every research study. This question typically tries to answer whether the research hypothesis is true.
- A research question focuses the information that a research study should provide.
- Observations during clinical practice often lead to the emergence of a research question



## Developing a Research Question

The PICO model is one method that can help researchers form the questions for a study. The method requires that a question address 4 main elements:

- P** – Population or health problem to study
- I** – Intervention, prognostic factor, or exposure to be studied
- C** – Comparison strategy
- O** – Outcome to be measured, improved, or affected

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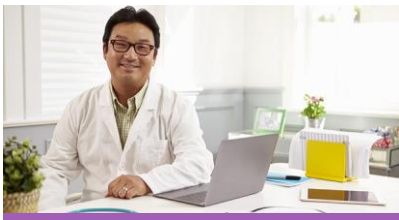
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## Example: Forming a Research Question Using PICO

- A research team is interested in the role of diet in IBD.
- Specifically, the team wants to know how effective the Specific Carbohydrate Diet (SCD) is in kids with symptomatic Crohn's disease.

**Research Question:** *In children with Crohn's disease, is the Specific Carbohydrate Diet more effective than a regular diet in reducing symptoms?*



Applying the **PICO** method:

**Population:** Patients 7 to 17 years of age with Crohn's disease not on the SCD

**Intervention:** SCD

**Comparison:** A regular (non-SCD) diet

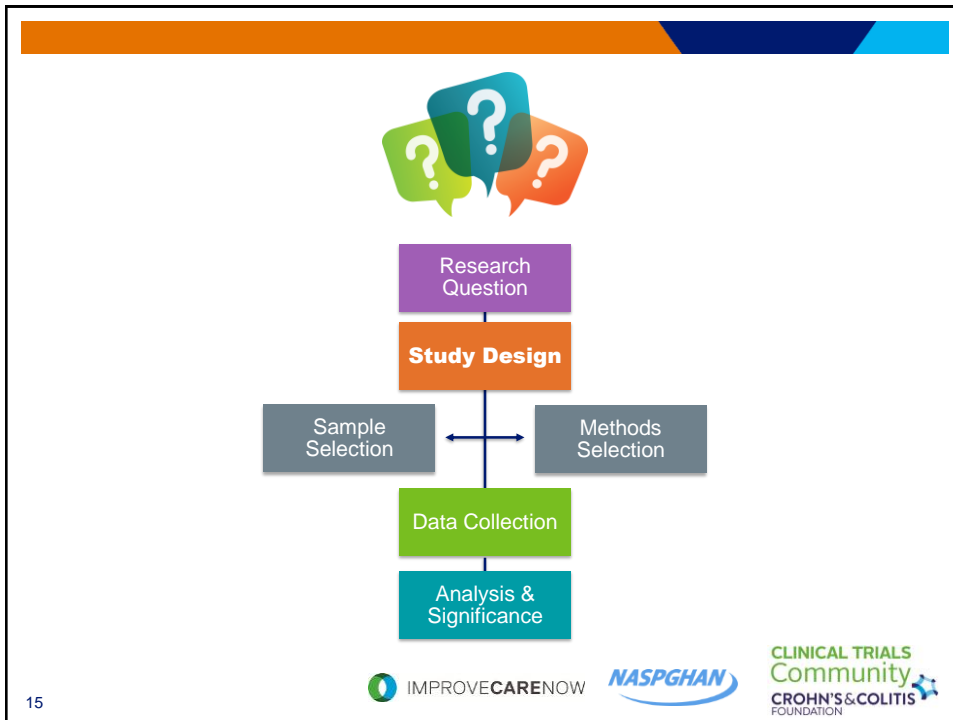
**Outcome:** Improving symptoms as measured by a validated disease activity index

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## Step 2: Study Design Selection

- Once a research question has been formulated, the next step is to choose how the question can be answered.
- Certain types of research questions are best addressed with certain types of study.
- Researchers have to match the research question to an appropriate study design.

There are many types of research study designs. These can be broadly placed into categories, including:

- **Observational** – Researcher collects data to look for trends and associations but does not attempt to introduce any changes that could influence outcomes.
- **Interventional** – Researcher introduces an intervention or change to a situation and compares this to control who receives a different or no intervention.



## Considerations When Choosing a Study Design for Observational or Interventional Research

- Feasibility – Is it possible to do?
- Efficiency – Is it possible, but would it be difficult and slow?
- Bias – Are there significant flaws that could lead to an invalid conclusion?
- Cost
- Ethical considerations



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## Two Types of Observational Studies

**Cohort Study** – Researcher collects data from one or more groups (called cohorts) that are followed prospectively to learn more about exposure characteristics and/or risk factors associated with a particular disease or health outcome.



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## Two Types of Observational Studies

**Case Control** – Researcher collects data from a group of individuals with the outcome of interest and then compares the data to a group without this outcome.



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## Example #1: Choosing a Study Design

*Research Question: Do antibiotics increase the risk of getting IBD?*

### Option 1 – Cohort Study (Observational)

Find healthy children and send them a survey every 3 months asking about antibiotic use. Over time, some will develop IBD. Analyze whether those that develop IBD had different use of antibiotics than those that did not develop IBD.

### Option 2 – Case Control Study (Observational)

Find cases of IBD and ask about use of antibiotics prior to diagnosis. Find controls who do not have IBD and ask them the same questions.

### Option 3 – Interventional Study (Randomized Trial)

Find healthy children. Prescribe antibiotics to some and not to others. See whether those who were prescribed antibiotics were more likely to get IBD.

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## Option 1 – Cohort Study

Find healthy children and send them a survey every 3 months asking about antibiotic use. Over time, some will develop IBD. Analyze whether those that develop IBD had different use of antibiotics than those that did not develop IBD.

Advantages	Disadvantages
Considered a relatively strong study design	Requires a lot of time and \$\$
	For a rare outcome (condition), you may need to follow a very large number of people for a very long time
	Subject to confounding, particularly unmeasured <b>confounding</b>

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## Option 2 – Case Control Study

Find cases of IBD and ask about use of antibiotics prior to diagnosis.  
Find controls who do not have IBD and ask them the same questions.

Advantages	Disadvantages
Fast and efficient	Subject to recall bias
Helpful if you are studying a rare condition	If control group does not reflect the population that gave rise to the cases, it introduces another type of bias: "selection bias"

### Recall bias

- If data about the exposure is collected after the fact, 2 groups may remember things differently.
- For example, patients can think that their IBD was caused by prior antibiotic exposure and be more likely to recall having antibiotics than a group of people that do not have IBD.

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### Option 3 – Interventional Study (Randomized Trial)

Find healthy children. Prescribe antibiotics to some and not to others. See whether those who were prescribed antibiotics were more likely to get IBD.

Advantages	Disadvantages
Most rigorous study design	Requires a lot of time and \$\$
Eliminates confounding and many other biases	Trial recruitment would be difficult
	For some research questions, a trial may not be ethical

- Due to ethical considerations, trials are often better suited to study effectiveness rather than etiology
- Randomized trials can be great study design when there is **equipoise** about the value of a medication or other intervention.

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### Equipoise – Funny Word, Important Concept

- Equipoise is when there is uncertainty that an intervention will be beneficial.
- This uncertainty forms the ethical basis for doing research to test a new treatment, like a medication or behavioral therapy.
- For example, the uncertainty of whether a new IBD medication is as good as or better than usual care provides ethical justification for a randomized trial of this new medication for IBD.

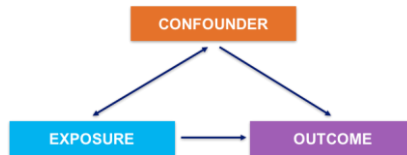


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## Confounding

- An extra factor that influences the study outcome. This factor may be measured or unmeasured.



- Dealing with Confounding:
  - Statistics can sometimes “adjust” for confounding when the confounder is known.
  - In randomized trials, the confounder would probably be balanced between the study groups, reducing their impact on the outcomes of interest.

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## Confounding: Example



A team launches a study to determine whether probiotics improve IBD outcomes.

The study compares outcomes in kids taking and not taking probiotics.

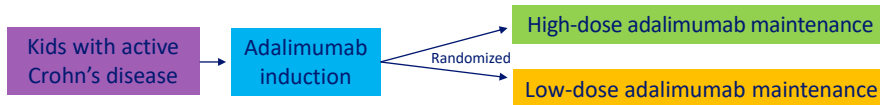
But what if kids getting probiotics are more likely to be in families with higher incomes or medical insurance – characteristics that could influence IBD remission?

Or what if kids with more symptoms were more likely to be treated with probiotics?

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## How Randomization Deals With Confounding

The IMAGINE 1 Trial compared 2 doses of adalimumab maintenance therapy in kids with Crohn's disease.



Kids who had previously been on infliximab could enter the trial. Prior infliximab experience could reduce the response to adalimumab (ie, previous treatment with infliximab is a confounder).

But with randomization, prior infliximab exposure was balanced between the study groups:

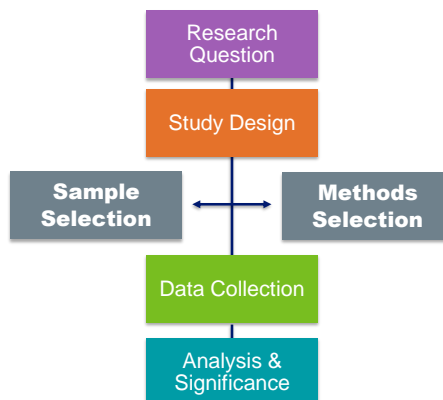
- 43% of the high-dose group
- 45% of the low-dose group

If there was an imbalance in the proportion of kids with previous infliximab, it could have biased the results since in this study such kids did have a much lower rate of remission and response to adalimumab.

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### Step 3a: Sample Selection

- Who will participate, and where will the data come from?
- Since a study cannot include everyone, a sample of people must be selected that represents the type of patients researchers want to learn about (the P in PICO).

**Sample size =  $N$**  = the number of people to be enrolled in the study



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### Step 3b: Outcome Selection

- What are the study outcomes (the O in PICO)?
- Must have specific measures and time points.
- May have primary and secondary endpoints.



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## Choosing a Sample & Outcomes

*In children with Crohn's disease, is the Specific Carbohydrate Diet more effective than a regular diet in reducing symptoms?*

### Participants will be patients with IBD

- Patients with Crohn's disease
- Ages 7 to 17 years
- Mild-to-moderate disease

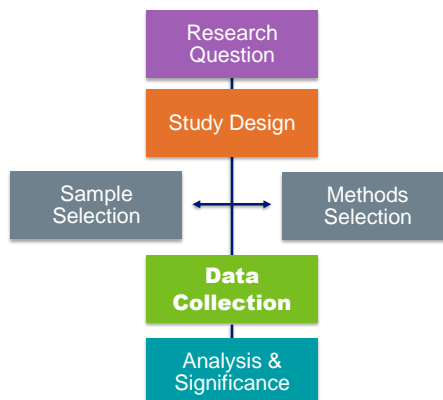
The characteristics of the participants you choose will impact who your study results can apply to.

### Collect data on patient reported IBD symptoms

- Based on a CD Activity Index
- At 6 weeks and 3 months after diet initiation

The types of measures that are collected will impact what is learned.

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## Step 4: Collect the Data

- Implement the procedures and collect the data as specified by the research protocol.
- Implement checks on data quality.
- In some cases, such as interventional treatment trials, data may be shared with an independent group to look for big differences in outcomes between groups or safety issues.



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## Step 5: Analysis and Significance

- Analyze the data using statistical methods to make sense of the information.
- **Power** is a study's ability to detect a statistically significant difference between the outcomes of different interventions.
  - The amount of statistical power is based on the number of people in the study (the **sample size**) and the number of outcomes experienced by the people who received an intervention.
- **Statistical Significance** is used to determine whether the study findings are likely to be true or whether they may have occurred by chance.
- **Clinical Significance** is whether research findings are of practical use to patients and clinicians.



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## Turning Research Into Clinical Practice

- After completion of a study, the knowledge gained must be **Disseminated** and **Implemented**.
- **Dissemination** means "Getting the word out"
- **Implementation** means "Taking action"

### Medical Audience

- Presentation at scientific meetings and publication in medical journals
- Incorporated into Practice Guidelines
- Quality Improvement strategies can be used to ensure that patients are treated based on "current professional knowledge"

### Patients and Caregivers

- Lay press, web, and social media
- Patient education materials and programs
- Shared decision-making tools

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## Other Things to Know About the Clinical Research Process

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## Informed Consent

- Choosing to volunteer in a research study is a personal decision.
- Through a process called **informed consent**, a potential study participant can learn about the research and make an informed decision about whether to join a study.
- Informed consent is more than just signing a form. Informed consent is a learning process to help a person understand the study being done and their role. A member of the research team will help communicate this information.
- The consent process includes opportunities for the asking of questions of the research team.
- Only when the participant has received all the required and requested information should the consent be signed.



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## Informed Consent/Assent for Kids

- A parent/legal guardian will need to sign the informed consent to give permission for a child under 18 years old to participate in research.
- Children who are able will need to give their verbal or written assent to participate. However, in some situations, a child's assent may not be required for proceeding with participation.
- Informed consent is not a contract – the participant is free to stop participation at any time.



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## Institutional Review Board (IRB)

- External committee of persons with relevant experiences and expertise that is responsible for making sure that human subjects are protected during participation and that the research conducted meets the basic requirements of federal regulations for research.
- The IRB reviews and then approves or disapproves research proposals.
- Each year the IRB needs to approve the continuation of the study and they must be told about any major changes in the study that can impact their previous decision to approve it.



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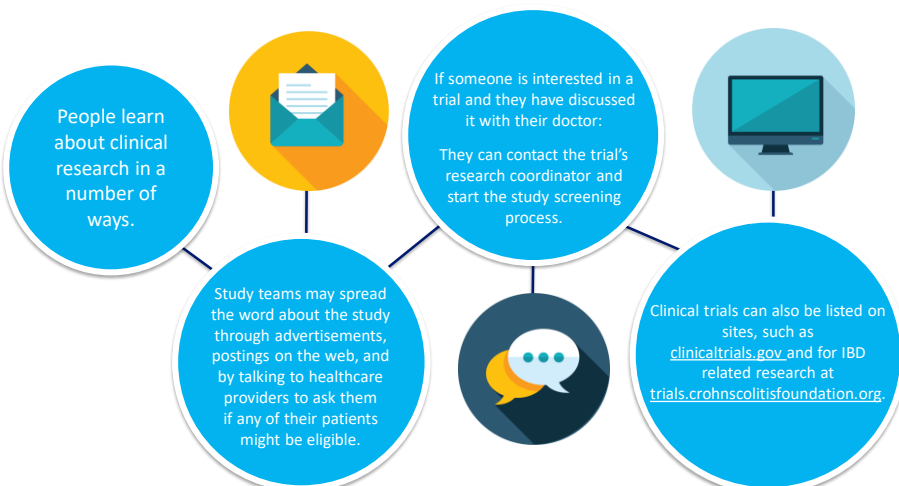
## Placebo

- Placebos are used to control for the ‘placebo effect’ – that is when a benefit is produced independently of the properties of the intervention/medication.
- Placebos provide a control situation that an experimental intervention or treatment can be compared to.
- There are ethical considerations guiding the use of placebos:
  - Participants must be informed that they might receive a placebo.
  - A placebo cannot be used in treatment studies when there is a standard of care that is known to be effective.



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## How are Participants Recruited for a Clinical Research Study?



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## What Should I ask Before Considering Joining a Clinical Research Study?

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>• What is the purpose?</li><li>• Why do the researchers think the approach may be effective?</li><li>• Who is the funder?</li><li>• Who has reviewed and approved the study?</li><li>• Are study results and safety being checked?</li><li>• How long will the study last?</li></ul> | <ul style="list-style-type: none"><li>• What are the risks?</li><li>• How do the risks and benefits compare to my current treatment?</li><li>• Will there be any costs to me?</li><li>• Will extra clinical visits be required? Or additional procedures?</li><li>• Will the results of the trial be given to me and when?</li></ul> |
|--|--|

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## Final Thoughts

- ❖ Clinical research helps the IBD community better understand many aspects of Crohn's disease and ulcerative colitis and how to most effectively prevent and treat these diseases.
- ❖ Clinical trials can be the most rigorous method of evaluating treatment effectiveness and safety.
- ❖ By participating in clinical research and clinical trials, patients directly contribute to the future of IBD care and in turn, help other patients and their families!

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## Where Can I Find More Information?

### Crohn's & Colitis Foundation's Clinical Trials Community

[www.crohnscolitisfoundation.org/clinical-trials-community](http://www.crohnscolitisfoundation.org/clinical-trials-community)

### Clinical Trials and You

[www.nih.gov/health-information/nih-clinical-research-trials-you](http://www.nih.gov/health-information/nih-clinical-research-trials-you)

### Clinical Trials FAQs

<https://www.cedars-sinai.edu/Patients/Clinical-Trials/Clinical-Trials-Frequently-Asked-Questions.aspx>

### Clinical Trials 101

[www.ccfa.org/resources/clinical-trials-101.html](http://www.ccfa.org/resources/clinical-trials-101.html)

### Which Medication is Best?

<https://rompethics.iths.org/video-which-medication-is-best/>

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## Clinical Research 101: Patients and Clinicians Gearing up to Discover Together



**Thank you!**

