A Family Guide:

Clinical Research for Children with Rare Neurological Diseases

BY CAMILLE CORRE, MD

Introduction

When a child is diagnosed with a rare disease, it is normal for families to have many questions. Some families wonder about whether they should join a research study. This new diagnosis may be the first time a family has thought about clinical research.

Whether your family has been asked to join a research study or you are just curious to explore what research might look like for your family, the goal of this guide is to help you understand your options.

Often, families learn about clinical research from the team running the study. It can be helpful to get information from many different sources and points of view. The goal of this guide is to give you the information you need to make a truly informed decision about what is right for your family.

Throughout the guide, you will find ideas about helpful questions to ask researchers about their study.

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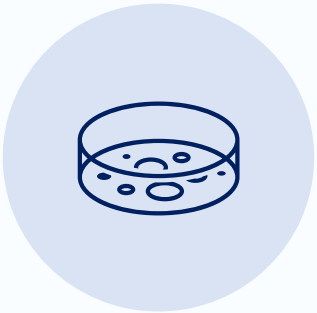
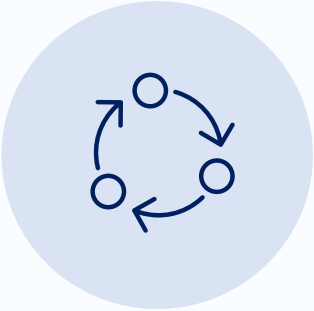
The Basics of Research

The purpose of medical research is to help answer scientific questions about diseases and how to treat them.

Basic Science Research

Basic science research is done on samples in a lab. Scientists can study cells, genes, proteins, and chemicals. They may use samples from animals or from humans, or even cells that they grow in a test tube.





Translational ("Bench-to-Bedside") Research

When basic science researchers make a discovery ("at the lab bench"), translational researchers help find ways to test that discovery in humans (clinical research).

Clinical Research

Clinical research uses data from humans to understand health and disease. This includes clinical trials that test whether a new medicine works, and also many other types of studies.

From Disease to Treatment

Many different people must work together to find a new treatment for a disease.

A doctor discovers a new rare disease. She writes about it in medical journals so that other doctors can learn about it, too.

A basic scientist figures out which gene causes the disease. He publishes this so that others can learn about it, too.

A clinical researcher asks people with the disease to be in a research study. She gives participants a survey to figure out how the disease affects them. She collects blood or other samples from them, to be used for more research.

A basic scientist does testing on those samples to learn more about the disease. He publishes his findings.

Another basic scientist sees that scientist's results and discovers a new medicine that might be helpful to treat the disease.

A translational researcher figures out how to give that medicine to humans. Should it be a pill or a shot? How many times a day does it have to be taken? He looks at the clinical researcher's data to decide how to measure whether the medicine works.

A sponsor (a company or the government) decides it wants to fund a clinical trial for this new medicine.

A clinical researcher leads several clinical trials to see if the medicine is safe and works in humans.

The FDA reviews the results of the clinical trials and decides whether or not to approve the medicine.

Types of Studies

There are many different types of clinical research studies. Some studies might just involve the study team looking at your child's medical records. Other studies might involve a survey that you fill out once or maybe yearly. Some studies involve an experimental medicine and might require many visits to the study site.

Cross-sectional:

A type of study that collects information at a single point in time.

vs

Longitudinal:

A type of study that collects information over a long time.

Retrospective:

A type of study that looks back in time to gather information that has already been collected. Often, study teams will read old medical records to gather information.

vs

Prospective:

A type of study that collects specific, new information from participants at different points in time.

Observational:

A type of study that collects data without giving participants any new medicine or treatment.

vs

Interventional:

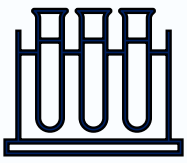
A type of study that is testing a specific medicine or treatment; these studies are called "clinical trials."

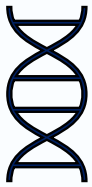
Natural History Study:

A type of study that is done to understand how a disease affects people. This type of study is not studying a medicine or treatment. These studies are important because they make it possible to test medicines or treatments in later studies. By understanding how diseases affect people, in the future we will be able to figure out whether a new medicine or treatment works.

Biorepository/Biobank:

A type of study that collects tissue or fluid samples from participants. The study may collect blood, saliva, or spinal fluid, and sometimes they may ask for details about the person's symptoms or health. Researchers test these samples to better understand a certain disease. Sometimes, researchers only collect samples from people with the disease. Sometimes researchers also collect samples from people without the disease. These participants are called "healthy controls." Sometimes the samples may be studied right away. Sometimes the samples may be stored in a freezer to be studied later, or shared with other researchers for more testing.



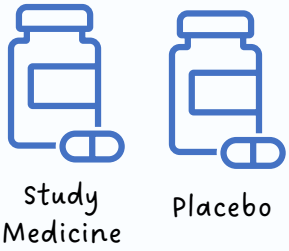


Clinical Trials

Studies that test a new medicine or treatment in humans to see how safe it is and how well it works.

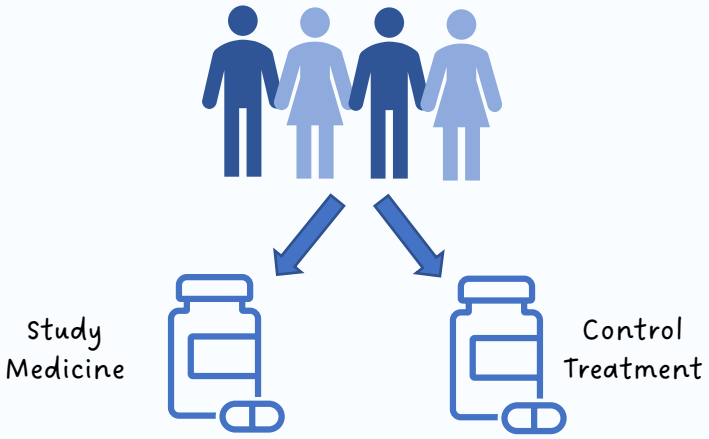
Placebo:

Something that looks and tastes like the study medicine but does not have any therapeutic effect. Placebos are sometimes called "sugar pills." Using them helps researchers understand the "placebo effect." This is a bias that makes people feel better when they believe they are receiving a new treatment, but they aren't.



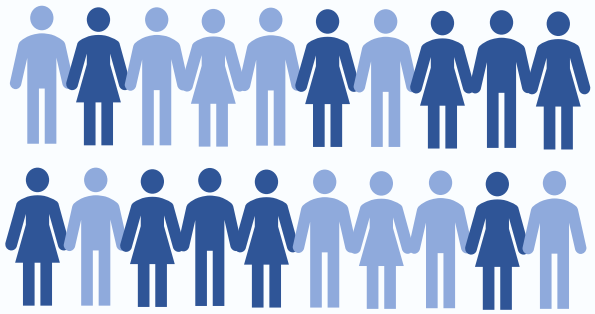
Control Group:

A group of participants in a trial who are assigned to receive the standard-of-care treatment for their disease instead of the study medicine. "Standard-of-care" means the treatment that they would get if they were not in the trial. This type of study tool helps researchers understand whether a new treatment is better than an existing one.

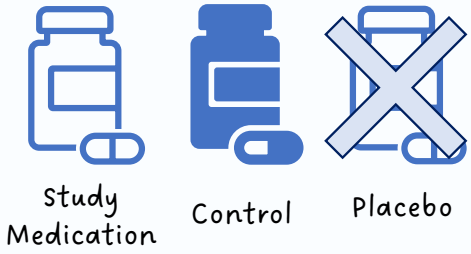


Randomized:

A type of clinical trial where some participants receive the study medicine and some receive a placebo or control treatment. A computer randomly decides which participants are in which group.



Types of Clinical Trials

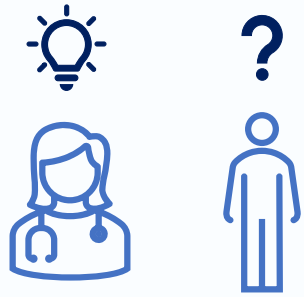


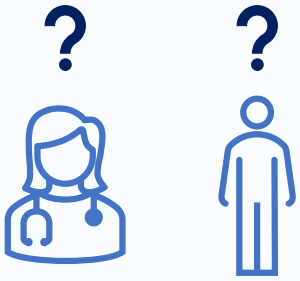
Open-Label:

The participants and the researchers know who is in which group (study medicine or control). No one is receiving a placebo. This type of study is used when it would be unethical to give some people a placebo.

Single Blinded:

The researchers, but not the participants, know who is receiving the study medicine and who is receiving a placebo or control.



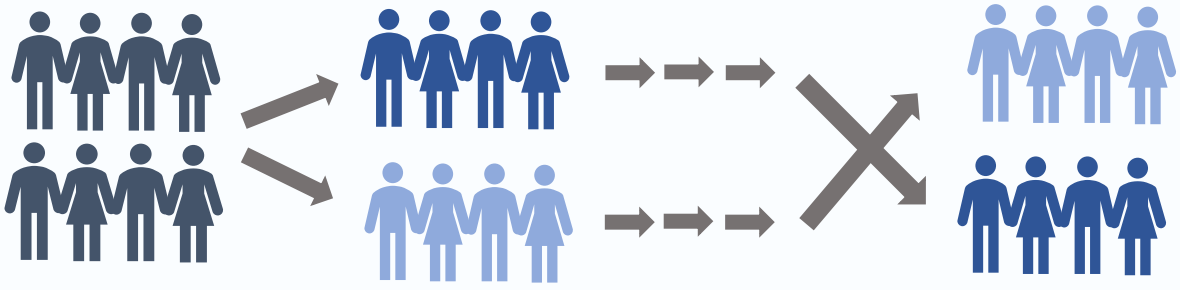


Double Blinded:

The participants don't know who is receiving the study medicine and who is receiving a placebo or control. Neither do the researchers. Someone outside of the study keeps track of this.

Crossover:

After a period of time, participants switch from one group (medicine or placebo/control) to the other.



Phases of Clinical Trials

Phase 1

*Is the medicine or treatment **safe**?*

- Monitors for side effects to find the safest dose
- Small number of participants
- Highest risk, lowest chance of benefit

Phase 2

*Does the medicine or treatment **work**?*

- Studies whether the medicine or treatment is effective
- Continues to monitor safety

Phase 3

*Is the medicine or treatment **more effective** than other options?*

- Compares medicine or treatment to other options
- Larger number of participants

Phase 4

*What are the **long-term effects** of the medicine or treatment?*

- After full FDA approval of the medicine or treatment
- Lasts many years

FDA Approval

For a rare disease, some of these phases might be combined into one study.

Questions to Ask:

- ❑ What type of research study is this?
- ❑ What would we need to as part of the study?
- ❑ Who is the sponsor of this study?
- ❑ How long will this study last?
- ❑ How many participants will be in this study?

<u>For Clinical Trials:</u>

- ❑ What phase is this trial?
- ❑ Will all participants receive the study medicine, or is there a placebo or control group?
- ❑ If there is a placebo or control group, how many participants will be in that group?
- ❑ After the main study is over, is there an opportunity for participants who were in the placebo or control group to receive the study medicine?
- ❑ Are there any early data available about participants who are already in the trial?
- ❑ Has the study medicine ever been studied in other trials? If yes, what were the results?

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Your Rights as a Research Participant (or Parent of One)

1. To decide **whether or not to participate** in a study
2. To **change your mind** about being in a study
3. To **withdraw** from a study at any time
4. To understand the goals of a study and **what you are agreeing to** if you choose to participate in a study
5. To understand the **risks and potential benefits** from participating in a study
6. To understand your **other options** if you choose not to participate in a study
7. To be able to **take your time** in deciding whether to participate in a study
8. To learn about how your **confidentiality** will be protected, including who will have access to your personal and health information
9. To know **who you can contact** with questions or complaints about the study
10. To continue to receive **medical care** even if you choose not to participate in a study

Informed Consent

A very important part of clinical research is informed consent. This is how people **learn about a research study** and **decide whether to participate**. They should not feel pressured to join a study. The person should be given plenty of time to understand all of the information, to ask any questions they have, and to think about it before making a decision. Some people choose to talk it over with friends or family members before making up their mind. After all of this, if someone chooses to be part of a study, they will sign an Informed Consent Form, and so will the researcher.

Informed consent is more than a one-time conversation. It is an **ongoing process**. At any time, if someone decides they do not want to be in the study anymore, they can withdraw their consent and leave the study. Even after signing an informed consent form, a participant can **leave a study at any time**.

Every hospital has a research ethics committee, called the Institutional Review Board (IRB), that oversees clinical research studies and informed consent. Study teams must get approval from the IRB before beginning a study and any time they want to make a change to the research study. If you have concerns about a research study, feel that you are being pressured to participate, or feel that your rights are not being protected, you can always contact someone at the IRB. Their job is to **advocate on your behalf**.

Sometimes, a research team must make changes to a study while the study is still ongoing. They must **ask for approval** from the IRB. If the change is approved, the IRB might require that they add new information to the Informed Consent Form. If this occurs, the study team will explain these changes to you and ask you to sign a new Informed Consent Form if you agree to continue participating.

Children under 18 years legally cannot provide their own consent. Depending on their age and maturity, children might be able to learn about the study and agree or decline to participate. Agreeing is called **providing assent**. The study team will tell you whether they feel your child is able to learn about the study and provide assent. If they do, they will **explain the study to your child** in a developmentally-appropriate way. They might use pictures, videos, or other tools, depending on how your child learns best. They will let your child ask any questions they have.

Very young children:
Parents/guardians can give consent on behalf of their child

School-age children and teenagers:
Parents/guardians can give consent on behalf of their child, and the child/teenager can agree (provide assent) to participate

For a clinical trial, usually **both parents/guardians** are required to consent for their child to participate. There are exceptions to this rule if one parent is not available or if one parent has sole custody. For studies that are less risky, sometimes only one parent/guardian needs to provide consent.

Alternatives to Research

Participating in research is entirely voluntary. You have several options if you choose not to be in a research study.

Wait and See:

Maybe research is not right for your family right now. You can always say "no" to research and then change your mind later on. There may be a new research study for your child's disease in the future.

Standard Care:

You can always choose "standard care" for your child's disease. "Standard care" might include a treatment that has already been approved by the FDA. But some diseases do not have an approved treatment. In that case, you can talk to your child's doctor about the best way to manage their symptoms. This could include medicines to help with pain, seizures, or tight muscles. Many children also get physical therapy (PT), occupational therapy (OT), or speech therapy.

Questions to Ask:

- ❑ How will you protect my child's confidential health information in this study?
- ❑ What are the risks involved in this study?
- ❑ If we choose not to participate, what other options do we have?
- ❑ Who can I contact with questions or concerns about the study?
- ❑ Do you think my child would be able to learn about the study and provide assent? If so, what tools do you have to help them understand what the study is?

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Eligibility

The goal of clinical research is to understand diseases better in order to find safe and effective treatments. To do this, clinical research has to be done in a consistent, standardized way.

All clinical research studies have a set of "eligibility criteria" that people must meet to be in the study. This is important so that the researchers can understand how the research results may affect different groups of people. Eligibility criteria are designed to keep everyone as safe as possible and to best measure how well a medicine works.

Many studies will have a set of "inclusion criteria" and a set of "exclusion criteria."

Inclusion Criteria:

Traits that a person must have to be part of a study. Some examples are a confirmed diagnosis, a specific age range, and a willingness to return to the study site for follow-up visits.

Exclusion Criteria:

Traits that mean a person cannot be in a study. Some examples are other medical conditions, abnormal labs, or reasons the study would be unsafe for that person.

Eligibility criteria can be a big **source of stress** for families. Clinical trials often have a long list of specific eligibility criteria. The first few visits for these studies are called **"screening visits."** At these visits, a lot of data (like lab tests, imaging, and surveys) are collected to figure out whether a person is eligible. The study team uses these data to decide whether a child can be part of the study. This process can take days to weeks.

Often, clinical trials state that people who have had an experimental therapy in the past are not eligible. **"Experimental therapy"** means a medicine or therapy that was part of a research study and is not FDA-approved. Sometimes this rule is waived after a certain period of time. For example, an exclusion criterion might be "people who have received another experimental therapy within the past 3 months."

When research studies are started, they are approved to enroll a **certain number of participants**. This number can vary greatly, from under ten to hundreds of participants. The exact number depends on the goals of the study and how rare the disease is. Once the study enrolls that many people, the study team cannot enroll any more participants.

Sometimes, research studies also need to enroll people without the disease **("healthy controls").** Other studies may enroll family members who are carriers of a genetic disease but are not affected themselves.

Questions to Ask:

- ❑ What are the eligibility criteria for this study?
- ❑ Do you anticipate that my child would be eligible for this study?
- ❑ What types of tests and procedures will be done at the screening visit for this study?
- ❑ How long does it usually take to figure out whether a child is eligible to enroll in this study?
- ❑ How quickly do you expect this study to fill up? If we say "no" now and later change our mind, is there a chance our child may no longer be able to participate?
- ❑ If my child is not eligible for this study, can we still be considered for future studies?
- ❑ Do you think that participating in this study could make my child ineligible for future studies for their disease?
- ❑ Beyond just my child, would any other members of my family be eligible to participate, either as "healthy controls" or unaffected carriers of the disease?

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Impact on the Family

Time Commitment

It can be overwhelming to consider being in a study with many study visits over weeks to months or even years. Study visits themselves may be many hours long. Are there any commitments or family activities you would have to sacrifice to participate in the study?

Travel

Being in a study might require frequent, long-distance travel to a study site. How much will this cost your family? How does your child do with travel? Do they have special medical equipment you'll need to bring with you?

Siblings

It can be challenging to balance the needs of multiple children, even before thinking about research! Will your other children travel with you to visits? How much school will they have to miss? Are there activities for them to pass the time while you are busy? If they stay home, who will watch them?

Impact on Medical Care

If your child is in a research study, they will still receive all of the medical care that they need. But some medicines and activities might be restricted because of the study.

Coping with Study Visits

Study visits can be long and sometimes stressful. How does your child generally do in medical settings? Are they afraid of hospitals or tests? What about their siblings? Are there any things you or the study team can do to make visits easier for your family?

Child Life

Some hospitals have a team of Child Life Specialists. Their role is to help children cope before and during medical procedures. Some strategies they might use with your child include distraction, practicing the procedure on a doll or stuffed animal first, numbing creams before blood draws, etc.

"Paying It Forward"

Some types of research aren't likely to directly help the participants. Instead, researchers hope that the study will help them learn about the disease to help people in the future. Some families feel it is important to "pay it forward" and help with research so that other families in the future can benefit. But this can also feel like a big burden. What do you think?

Questions to Ask:

- ❑ Does this study involve scheduled study visits?
- ❑ What will happen at each study visit?
- ❑ How long will each study visit be?
- ❑ Can any of the study visits be performed remotely (either over the phone or via a video visit)?
- ❑ How does scheduling work? Is there a strict time window when each visit needs to take place?
- ❑ If there will be blood draws, will my child need to be fasting (not eat/drink for several hours before)?
- ❑ If my child also needs to have blood draws done as part of their regular medical care, can you coordinate these blood draws with the ones for the study?
- ❑ Will any of the study procedures be painful, uncomfortable, or scary for my child? What supports do you have to help my child through these procedures? Do you have Child Life Specialists or numbing ("EMLA") cream available for blood draws?

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Financial Considerations

There are often costs involved in clinical research studies. Some costs are direct, like the cost of study procedures such as lab draws and imaging. Some costs are indirect, like the cost of travel to a study site or overnight lodging for multi-day visits. Before deciding whether to participate in a study, it is important to understand the potential costs, stipends, and reimbursement that might be involved.

Direct Costs:

Cost of medical exams, labs, imaging, and other study procedures.

- These costs are often covered by the study. In some cases they are billed to your health insurance. This might involve costs to you through a co-pay, co-insurance, or your deductible.
- It is helpful to understand upfront how direct costs will be managed in a study.
- If your health insurance will be billed for anything, it is helpful to ask whether the study site is in-network for your health insurance and what your out-of-pocket costs will be.

Indirect Costs:

Costs involved in participating in a study outside of study procedures themselves. This includes transportation to the study site, overnight lodging, meals, childcare for other children, time away from work, etc.

- Often, these costs are covered by a study. This may be in the form of a stipend or as reimbursement for expenses.
- Sometimes, a study might have a person available to book travel and hotels for your family, so that you do not have to cover the cost upfront.
- For other studies, you might be expected to book your own travel and hotels and save your receipts. After the visit, the study team may reimburse you based on your receipts.
- In other cases, you might be given a stipend that you can use to cover your costs. It can be helpful to estimate what your actual expenses will be and make sure that the stipend will cover those costs. Remember to consider transportation, hotels, meals, and childcare.
- If overnight lodging is not provided by the study, hospital social workers may have resources in the area where families can stay for low to no cost.

Questions to Ask:

- ❑ What potential expenses would be involved if we choose to participate in this study?
- ❑ Who on the study team can I reach out to if I receive a bill in error?
- ❑ Will any parts of the study be billed to our health insurance?
- ❑ How many visits does the study include, and how often will we need to travel to the study site for visits?
- ❑ Does the study cover the cost of travel for study visits? What about overnight lodging if a multi-day stay is required?
- ❑ Does the study cover incidental costs during our study visits, like meals?
- ❑ Is there a daily stipend provided by the study team?

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Gene Therapy & More

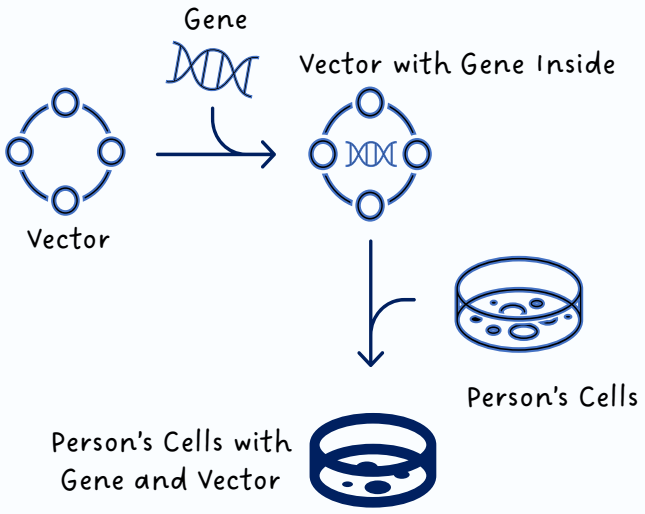
Several new types of treatments have gotten a lot of attention in the past few years. They have all shown promise for treating neurological diseases. Some of them have already been approved by the FDA for certain diseases. There is a lot of new research using these tools to treat new diseases.

Gene Therapy

- Genetic diseases are caused by copies of genes that are missing or not working properly.
- Gene therapy is a way of giving people a new, working copy of the gene that is missing or not working.
- Scientists use something called a vector to get the working copy of the gene into the cells in the body.
- A vector is like a vehicle that brings the working copy of the gene where it needs to get in individual cells.
- Sometimes, the vector is put into a person's cells outside of the body (ex vivo), and sometimes it enters the person's cells inside the body (in vivo).

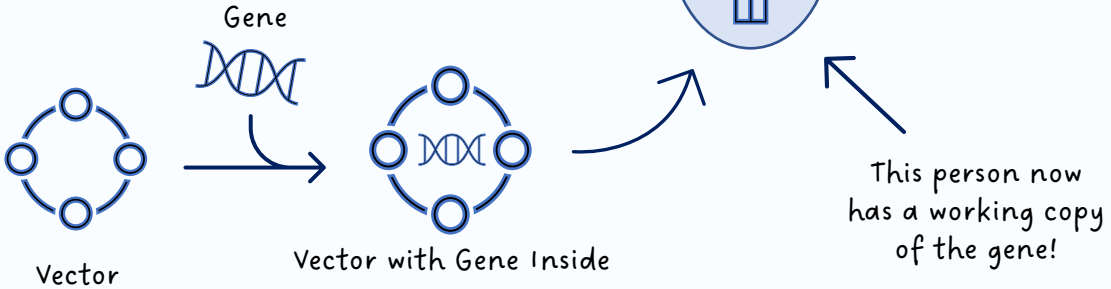
Ex Vivo:

vector goes into cells outside the body



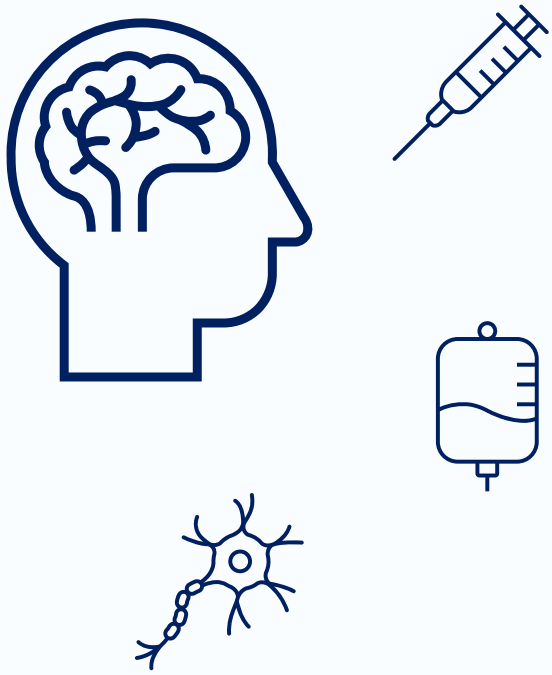
In Vivo:

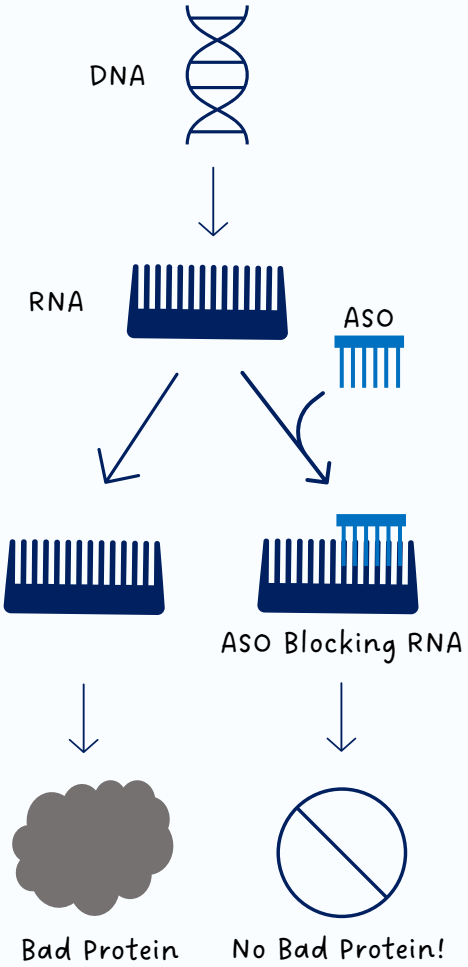
vector goes into cells inside the body



Enzyme Replacement Therapy

- Some genetic diseases are caused by a missing enzyme (a protein that helps cells perform chemical reactions quickly).
- Enzyme replacement therapy gives the missing enzyme to patients in the form of a drug.
- One challenge is getting the drug where it needs to go in the body. It is difficult to get the drug to travel to the brain without putting it there directly.





Antisense Oligonucleotide (ASO) Therapy

- In some genetic diseases, the problem is that cells make a protein that is harmful to cells.
- RNA is the type of building block that is used to make proteins.
- Antisense oligonucleotides (ASOs) are short strands of RNA. They attach to the RNA that makes the harmful protein.
- Because the ASOs are attached, they block the RNA from making the harmful protein.
- ASO therapy only works for diseases that make a protein that is harmful to cells.

Additional Resources

If you're looking for more information after reading this guide, there are many resources you can explore:

ClinicalTrials.gov

- A website that has a page for each clinical trial taking place in the US, and many around the world.
- Great resource to explore what types of research studies exist for your child's condition, even before you meet with a study team.

Your Child's Pediatrician or Neurologist

- Your family's trusted medical providers can provide a helpful perspective on the research study.
- Some families bring their Informed Consent Form to discuss with their child's doctor before deciding whether to participate.

Institutional Review Board (IRB)

- While deciding whether to be in a study, you can always contact the study site's research ethics board.
- If you have complaints about a study or feel that your child's rights are not being protected, you can report this to the IRB. They will investigate and advocate on your behalf.

Study Sponsor

- If a study has a sponsor, they may have a website for research participants. You can visit the site to learn more about the study.
- Remember that these websites are written and paid for by people who want participants to join their studies.

Patient Support and Advocacy Organizations

- There are a huge number of patient support and advocacy groups for families affected by specific diseases. Many more than could be listed in this guide!
- Many of these groups have email lists, Facebook groups, and even meetings (virtual or in-person) to connect with other families.
- If you don't know where to start, ask your child's specialist if they are familiar with any groups for your child's diagnosis.

Other Families/Participants

- It may be possible to talk to other families who have decided to participate in the study.
- Sometimes this is not possible due to strict confidentiality policies. You can always ask the study team if there are families who have agreed to be contacted.

Acknowledgements

Family Experts

This guide would not have been possible without the perspectives offered by several family experts. These parents shared their own experiences with clinical research in order to help support the next generation of families.

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Jennifer & Matt Steichen

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About the Author

Camille Corre is a resident physician training to be a child neurologist. She has been continually inspired by the dedication, love, and resilience of families affected by rare diseases. She is motivated to support families as they face uncertainty, and to empower them with the information they need to make the best decisions for their families. Contact: camillecorre24@gmail.com.

This guide is dedicated to Camille's little sister, Caroline. Caroline was spirited, determined, and silly. She spoke her mind freely and was infamous for her pranks and mischief. She had a rare disease called ataxia telangiectasia (A-T). Her lifelong dream was for researchers to find a cure for A-T. She leaves behind a legacy of embracing one's own abilities to live a full life.