

A PARTICIPANT'S GUIDE TO DRUG RESEARCH IN RETT SYNDROME



PURPOSE OF THIS GUIDE

With multiple clinical trials underway that are aimed at changing the biology associated with Rett syndrome or ameliorating symptoms that are common in Rett syndrome, we created this guide to help you understand the importance of clinical trials and what participation means, what to expect, and what your rights are as the parent or legal guardian of a participant in a trial, as well as the rights of your participating child.

The goal of this guide is to both answer common questions and to pose additional ones that may be important for you to consider. The decision of whether to participate in Rett syndrome drug studies should be guided by your goals and values as well as a clear understanding of potential risks and benefits. You will also need to have a clear understanding of the possible demands upon you, your child and your family, including potential time and financial burdens associated with participating in a research study. It may be helpful to write down questions that may come up as you review this material. These questions should be discussed with your family, personal physician and the researchers leading the study you are considering.

WHAT IS CLINICAL DRUG RESEARCH?

Clinical research involves humans. Some early clinical studies involve “healthy” volunteers whose participation enables scientists to understand how the human body processes a drug and to begin to identify potential effective doses. Other clinical trials generally involve participants who are affected by symptoms that the experimental drug may relieve. Until recently, most research in the field of Rett syndrome has involved collecting information on individuals and families affected by this postnatal neurological disorder. Such studies are crucial to better understanding the underlying biology of Rett syndrome. This research has now advanced to the point where scientists are identifying biological mechanisms that can be targeted by experimental drugs – the primary goal being to relieve disabling symptoms. Generally, these experimental compounds are first tested in animal models to gather preliminary evidence of effectiveness and safety.

Early drug research can also involve laboratory studies using human cells and tissues – either cultured or donated after death. Only after considerable tissue and/or animal research do the best drug candidates move into clinical trials with human volunteers. Typically, these studies start off small. If evidence of safety and effectiveness continues to build, a drug may then move into studies with larger numbers of participants. Larger studies are vital to ensure that a perceived benefit is real and not the result of chance or some unidentified influence.

The National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) both have strict rules for promoting drug trial safety and obtaining the informed consent and assent of

participants. In this context, “consent” refers to permission that is typically provided by an adult research participant. In the case of a child participant, or an adult participant unable to “consent” themselves and under legal guardianship of another adult, “consent” can be provided by a parent or other legal guardian. In addition to a guardian’s consent, it is also important to seek a child’s “assent,” or agreement to participate. Both parental consent (permission) and the individual’s assent (agreement) are typically necessary before the individual can participate in clinical drug research, provided that the child has the capacity to understand what she is agreeing to and that she has an effective way to express her agreement.

In some instances, when this is not possible, the parent’s or guardian’s consent becomes the essential step prior to commencing any research-related activities with the individual. All of this should be documented in writing by those overseeing the research. As suggested above, additional ethical considerations arise when study participants are nonverbal or have significant intellectual disability. In these cases, it is particularly important for legal guardians, researchers and, if necessary, other advocates to work together to safeguard the well-being of these vulnerable participants and respect their wishes to the extent possible.

Sometimes, study participation requires changes in the volunteer’s current therapies, including current medicines. Some studies require participants to be monitored with techniques such as brain scans, EEGs, EKGs, behavioral observation, blood samples and other tests. Clear information about these requirements should be part of the “informed consent” that all study participants and/or their legal guardians should receive and review prior to joining a study.

WHY PARTICIPATE IN CLINICAL DRUG RESEARCH?

Many people participate in clinical drug research with the hope of receiving an advanced treatment. At present, there are no FDA approved drugs for relieving Rett syndrome's core symptoms. The decision to administer any medicine to your child, whether it is FDA-approved or experimental, is a highly personal one. For this reason, it is important for the person or family who enters into clinical research to balance the desire for advanced treatment against a number of factors that separate clinical research from conventional medical treatment. These are described in more detail in the section below.

Importantly, participation in clinical research offers individuals and families the opportunity to help advance the development of treatments that can improve the lives of all those affected by Rett syndrome. New medicines cannot be brought to market without clinical trials and those who volunteer to participate in them. Related to this, researchers may request permission to collect biological samples such as blood or saliva for genetic testing and future research. You are in no way obligated to provide such samples, but by doing so you can further advance research into the causes and potential treatments of Rett syndrome and related disorders.

HOW IS PARTICIPATING IN RESEARCH DIFFERENT FROM SEEING A DOCTOR?

While every researcher has the responsibility of safeguarding study participants, enrolling in clinical research is not the same as seeing a personal physician. Here are some of the key differences to consider:

The researcher's goal is to learn about your child's illness. The doctor's goal is to treat your child's condition.

The researcher must use standardized procedures. Your child's doctor will change/customize her treatment as needed.

In research studies, your daughter may be randomly assigned to a group taking a standard treatment or a placebo (an inactive substance or preparation used as a control) versus the group taking the new treatment. In contrast, a patient always receives an active drug, typically the best standard treatment available from a personal physician.

The safety and effectiveness of experimental medicines are not fully known. Typically, physicians prescribe FDA-approved medicines whose side effects and benefits have been studied. However this can involve "off label" use, which means the medication, may not have been tested in the context of the patient's particular condition (e.g. Rett syndrome) or age group.

Your child may be asked to undergo procedures (such as blood tests, EEGs, imaging scans, etc.) and you may be asked to complete questionnaires important for research but not necessary for your child's care. In contrast, during routine clinical care of your child, testing procedures and questionnaires are restricted to those necessary for your daughter's optimal medical care.

Medical and other costs associated with participation in a research study may be partly or fully covered. However, travel-related costs (if one is travelling from a far distance) may or may not be covered in research studies. In contrast, you are likely to be responsible for treatment costs and/or the cost of health insurance coverage/co-pays associated with the routine medical care of your daughter, pending the availability of Medicaid and Medicare (as examples).

WHAT DO RESEARCHERS MEAN BY CLINICAL TRIAL “PHASES”?

Clinical trials are often conducted in four, graduated phases. Each of these four phases has a different primary purpose.

Phase I trials

Phase 1 trials tend to involve a relatively small number of participants, and these participants may or may not be affected by the condition the drug is hoped to relieve. The primary goal is to evaluate whether an experimental medicine is safe and well tolerated and to identify potential side effects. Often these trials examine different doses to determine which works best. Building confidence in safety is a key goal at this stage of research.

Phase II trials

The design of phase 2 trials is guided by the knowledge of safety, tolerability and dose gained in phase 1 trials. The goal of a phase 2 trial is to gain insight into the safety and tolerability of a new medicine in participants with the particular medical condition under study, and to determine whether the new medicine shows promise in alleviating specific symptoms. For this reason, these trials enroll volunteers who are affected by this condition or symptoms.

Phase 2 trials usually involve more participants than do phase 1 studies. This increases the researcher's ability to detect benefits and potential side effects and also increases reliability of their results. To gauge the drug's ability to relieve symptoms, researchers typically apply tests called “outcome measures” throughout the trial. If these measures show that the treatment produces significant benefits, then it is said that the study achieved “proof of concept.” In essence, this means that there is sufficient reason to believe that the treatment will have real world benefits and has the potential to

become a medicine used in actual clinical practice. Although encouraging, phase 2 “proof of concept” is not, by itself, sufficient to support a new treatment's approval for medical use. Further study is needed to assure safety and effectiveness.

Phase III trials

The goal of phase 3 trials is to provide definitive evidence that an experimental medicine has real life benefit for a particular group of patients. Guided by the findings of phase 2 trials, researchers provide the experimental treatment to still larger groups of patient volunteers who represent the broad population of individuals affected by the disorder or disease being studied. Phase 3 trials can also refine the most effective dose for one or more groups; better identify the symptoms most responsive to the medicine; improve detection of side effects; and compare the medicine's benefits and side effects to those of commonly used treatments.

This information is vital to refining what is known about a drug that may eventually be introduced into widespread use. If the safety and benefits documented in a phase 3 trial confirm and expand confidence in a favorable benefit to risk balance, the next step becomes application for approval by the FDA. The application itself is known as a “New Drug Application”, or “NDA”.

Phase IV trials

The goal of phase 4 is to ensure that safety and effectiveness continue to be monitored after the FDA approves a medicine for use. These “post marketing” studies generally involve newly approved drugs and gather additional safety and effectiveness information as more and more people use the drug under the care of their personal physicians. In some instances, additional studies in specific populations, like the very young, are undertaken in phase 4.

WHY DO WE USE PLACEBO CONTROLS IN CLINICAL RESEARCH?

The guidelines for biomedical research published by the Council for International Organizations of Medical Sciences have established that a clinical trial cannot be justified unless it is capable of producing scientifically reliable results. Therefore, it is important to keep in mind that one must have a scientifically valid study in the selection of a “control group”. The Food and Drug Administration has historically withheld its approval of a number of drugs when proper controls were not used.

The placebo-controlled clinical trial has a long history of being the standard for clinical investigations of new drugs. By blindly and randomly allocating similar patients to a control group that receives a placebo and to an experimental group receiving the new therapy, investigators can ensure that any possible placebo effect will be minimized in the final statistical analysis. When there is a “standard of care” available for a particular disorder often the new therapy is compared against the “standard of care”. In the case of Rett syndrome there is no “standard of care” drug therapy, so the placebo control type of trial design becomes one of the best scientific choices for clinical trials in Rett syndrome. This is

due, in large part, to the potential of a placebo-controlled trial to render a clear answer as to whether or not a potential new medicine drug is worthy of further development.

There are numerous examples in the literature regarding studies that have demonstrated initial findings that were subsequently proven wrong because of a lack of a proper control group. We do not want to fall into this category with our clinical trials. Therefore, the use of placebo controls in trials is a common practice at this time for investigators to prove or disprove the efficacy of these new treatment possibilities.

Placebo-controlled trials are recognized and needed to justify that there is adequate evidence to support or not support the efficacy of the “first-generation” therapies. Rettsyndrome.org does not design clinical trials, but we do evaluate all the elements of a trial when asked. Even though we know that it can be frustrating to think that your child might receive the placebo after all the effort of participating in a clinical trial, we hope that it will not discourage participation.



WHAT QUESTIONS SHOULD I ASK THE RESEARCHER?

It is important to always ask questions, whenever they arise. Study participants and their families become essential partners in research. So it's important for you to understand what will be asked of you and your child, and how those conducting the study will safeguard the health of your loved one. You are encouraged to ask the study physician and his or her staff questions before you agree to participate as well as any time afterwards. Importantly, the researchers should welcome your questions and answer them fully. Below are some suggested questions that you may wish to ask.

- What previous studies have been done on this medication and to what degree has this clarified its risks and benefits?
- How might this study help my child?
- What side effects are possible?
- What comparable standard treatments are available?
- Is there a chance that my child will NOT receive the experimental treatment (become part of a placebo or "control" group)?
- Will this study involve any change in my daughter's current medications or other treatments? If so, what risks does this pose?
- How will participation affect my daily life and/or that of my daughter?
- What tests will I or my daughter be asked to undergo and how often? What discomfort or risks, if any, do they pose?
- What steps are being taken to reduce the inconvenience, discomfort or risks associated with this testing?
- What other measures are being taken to ensure the health and safety of participants in the study?
- How long will the study last, and how often will we need to visit the research clinic?
- What should I do/what will happen if I or my child experiences side effects or begins to feel worse during the trial?
- Has the design of this study been assessed by an independent ethics committee? What were their recommendations for improving the likelihood of benefits and reducing risks for participants, and how were these suggestions implemented?
- Are participants asked to bear any costs? What related costs (travel, lodging, etc.) will be reimbursed?
- Will you support my/our decision to withdraw from the study at any time?
- Will my child be allowed to continue receiving the experimental medicine after the trial has ended? Can you foresee the costs of obtaining this medicine after the trial?
- How will this research help other persons affected by Rett syndrome?

Don't hesitate to ask for further explanation if you don't understand or are unsatisfied by the answers you receive. And you can always ask the same question or questions again, at any time. Researchers have the responsibility to help you understand. Be wary if you feel they are less than forthcoming or impatient. You also have the right to directly contact the study's ethics committee or institutional review board with any concerns. Their contact information should be in the informed consent form.

WHAT RIGHTS DO ALL PARTICIPANTS HAVE?

“Informed consent” is vital to participation in clinical studies, and you will be asked to read and sign a related document. At a minimum, it should include the following information, which should be clarified for you, as needed, by the researcher(s).

- A clear explanation of all significant risks and benefits.
- Assurance of confidentiality (you and your daughter's identity and personal medical information must be protected; medical data from the study should be anonymous, or “de identified.”)
- A clear explanation of how the study will be carried out and what is expected of you or your daughter as a participant, including the location and length of the study, and what each visit is likely to involve.
- Any anticipated costs to you or your daughter's health insurer.
- Details of expense reimbursement and/or financial compensation.
- After your daughter joins a clinical study, you have the right to:
 - Leave the study at any time. Though you should not enroll if you/your daughter do not plan to complete the study, you retain the right to refuse any request and/or withdraw at any time.
 - Receive any new information that may affect risks, benefits and your decision to continue your daughter's participation.
- Continue to ask questions and get answers.
- Maintain your privacy.

- Once the study is completed, find out about your daughter's treatment assignment (experimental/active or placebo, as examples). This concerns “blinded” studies that randomly assign participants to one or more treatment and/or control groups without disclosing the assignment to the researchers or participants until the results have been analyzed.
- Ask who you can contact – outside the research team – if you have concerns that are not being addressed or have misgivings about how the study is being conducted.

WHAT RIGHTS DO CHILDREN HAVE WHEN PARTICIPATING IN RESEARCH?

Only legal guardians can give informed consent for a child to participate in a clinical trial. However, whenever possible and appropriate, ethics and regulations require that a child's participation be informed and voluntary. The evaluation of a child's ability to give assent, or agreement, should not be based solely on age, but also other factors such as developmental stage and intellectual and/or psychological maturity. Researchers should provide separate information sheets for adult guardians and children, each prepared with age appropriate language. Importantly, objections raised by a child at any time during a trial should be considered and respected. Children should not be forced to provide reasons for their objections. They should be informed of their right to freely withdraw from a trial at any time for any reason. When providing children with the above information (at an appropriate developmental level), their responses should be acknowledged and documented by the researchers.

OUR COMMITMENT

The decision to become a participant in drug research is an important one, all the more so if you are making this decision for your child. It is an option that is becoming a reality for individuals and families affected by postnatal neurological disorders, including Rett syndrome. This is because research into the causes and biology of Rett syndrome is advancing quickly, such that potential medicines are being identified that may relieve disabling symptoms and improve quality of life. **It is very important to remember that a clinical trial is not a form of individualized medical therapy.** Clinical trials are a scientific tool for evaluating treatments in groups of research participants with the aim of proving whether a particular form of care is effective. Often individuals want to enter a clinical trial because they see it as the quickest way to a treatment, but the clinical trial is not yet a treatment. It is a research project designed to determine whether a certain form of care is effective or not. Entering a trial believing it is a form of therapy is entering it for the wrong reason. But we also want to reassure readers that Rettsyndrome.org would not entertain funding any clinical trial that we thought was ill-designed; would put patients with Rett syndrome at undue risk; or didn't hold promise to be *effective*.

Rettsyndrome.org is dedicated to funding research for treatments and a cure for Rett syndrome while enhancing the overall quality of life for those living with Rett syndrome. Rettsyndrome.org will continue to work with families and researchers by providing information, programs, and services. We envision that researchers will bring more medicines into clinical trials, and Rettsyndrome.org will actively provide the participants and their families information and the support they need for them to feel secure and well-educated as they embark on these studies.

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We also encourage readers to visit [ClinicalTrials.gov](https://clinicaltrials.gov) for more information about participating in clinical research and about specific Rett syndrome clinical research in progress.