Clinical Trials: Understanding their importance and how to participate
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Until recently, most clinical research in the field of Rett syndrome has involved collecting information on individuals and families affected by this disorder in a study call the Natural History Study. The Natural History Study of Rett Syndrome is crucial to better understand 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. Now we are at an exciting point where these experimental drugs are moving into human clinical trials.

Why are Clinical Trials Important?

It is a simple question and the answer is simple; clinical trials are the only mechanism to bring new drugs and treatments forward for approval to address the challenges of any medical condition. The answer is simple but unfortunately, clinical trials are not easy. Clinical trials involve humans and which bring forward many regulatory rules governing what can be done in any clinical trial.

Why participate in clinical drug research?

Many people participate in clinical drug research with the hope of receiving an advanced treatment, but it is very important to remember that clinical trials are still experiments to determine if something works. At present, there are no FDA-approved drugs for relieving Rett syndrome's core symptoms. 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.

Importantly, participation in clinical research serves to help advance the development of treatments that can improve the lives of 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. Participants are in no way obligated to provide such samples, but by doing so these samples can further advance research into the causes and potential treatments of Rett syndrome and related disorders.

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Phases of clinical trials

Some early clinical trials might only involve "healthy" volunteers (Phase 1). Their participation enables scientists to understand how the human body processes a drug to begin to identify potential effective doses. Later clinical trials generally involve participants who are affected by symptoms that the experimental drug may relieve (Phase 2 and 3).

For more information on the phases of clinical trials, please visit:
https://clinicaltrials.gov/ct2/help/glossary/phase

How complicated is participating in clinical trials?

Each clinical trial has its own set of inclusion and exclusion criteria for participation. These criteria could be age, sex, weight, medical history, current health status, and many other medically important circumstances. The first thing we always suggest when thinking about participating is going to the website clinicaltrials.gov and reading about the trial. Review the inclusion and exclusion criteria and see if you or your loved one meets the criteria to participate.

Once you understand the clinical trial, what is being monitored, what the inclusion and exclusion criteria are and you want to proceed and participate, your next step is to contact the clinic that is conducting the trial. There may be multiple sites conducting the trial so you next have to evaluate whether you want to participate at the closest site to you or with a particular medical center. This choice is yours and you should choose were you would be most comfortable with the physicians doing the clinical research.

Just because you want to participate does not mean you will be chosen to participate. The clinical team will do evaluations and make a determination of who they want to include in the trial. This is important to keep in mind, medical professionals are looking at many criteria and sometimes they have to say no to a willing participant. Their reasons can be many but the driving rationale is safety and the health of the participant.

How do I sign up?

This is the simple part if you know where the study is being conducted. Again, we suggest you visit clinicaltrials.gov to find locations. On that site, the contact information is published and all you have to do is follow the instructions and contact the named individual for consideration to enter the trial. Clinical trials, sites and enrollment contacts are also listed on Rettsyndrome.org under “Research”.

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 (permission) and assent (agreement) of participants. Both consent and the individual’s assent are typically necessary before the individual can participate in clinical drug research, provided that the child has the capacity to understand what they are agreeing to and that they have an effective way to express her agreement.“

- 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, “consent” can be provided by a parent or legal guardian.
- It is also important to seek a child’s “assent,” or agreement to participate. 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.

How am I chosen?

As described above, the clinical team will evaluate you or your child in regard to their inclusion and exclusion criteria. If you meet all the inclusion and exclusion criteria, then it is a matter of how many individuals that individual center has agreed to study. Because Rett syndrome is a rare disease, for many of the Phase 2 trials, the number of participants is small (between 40 & 60). If multiple sites are involved, the number of patients at each site may be small. To this end, it is always best to enroll early so that if you meet all the criteria you have a good chance of being chosen.

Will I get compensated?

To date, individual participants have not been compensated for participating in clinical trials studying Rett syndrome.

Are there travel provisions?

Because these trials are usually at medical centers conducting other clinical research you have to be willing to travel to your preferred site. Travel expenses are usually not covered by the trial site so you have to provide your own travel and cover your housing and food costs. However, we in the Rett syndrome community are fortunate to have a group called RettLand that will help cover these costs. You have to contact Rettland (http://rettland.org or colleen@rettland.org) and apply for assistance but it is worth the time and effort to help cover your costs.

How long will it take?

Each individual trial makes its own determination on how long the trial will be. This is usually done in coordination with the Food and Drug Administration. It is important to know the time commitment (duration of the study) and the actual daily commitment (administering drugs and making observational assessments) required. We encourage you to read about the trial on clinicaltrials.gov to be fully informed about the duration of the study and the daily commitment. You will also need to consider how long you might have to be at the study site for evaluation and how many visits you will make to the clinical study site.

What are the expected outcomes?

Again, we encourage you to visit clinicaltrials.gov and read the expected outcomes. More importantly this should be one of your number one questions to the clinical researchers when you interview for the clinical trial. You should never be embarrassed to ask questions 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 family member participating in a trial, and how those conducting the study will safeguard the health of your loved one. You are encouraged to ask the study physician and staff questions *before* you agree to participate as well as any time afterwards. The researchers should welcome your questions and answer them fully. Below are some suggested questions for you to ask. We also put

together Guidelines to Clinical Trials: http://www.rettsyndrome.org/file/Clinical-Trial-Guide-for-Participants-2015.pdf

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- 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 child'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 child?
- What tests will I or my child 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?

Conclusions

Clinical trials, by design, are experiments and not all experiments work. You have to understand and embrace this concept. To build treatments leading to a cure for Rett syndrome, we have to run trials. Be aware that trials may have mixed results. It is only by conducting these trials will we learn and move forward. We cannot be intimidated by the possibility of mixed results. We must take the leap and move forward if all the supporting data give us some faith that the trial will work. The clinical trials we are sponsoring and backing are first steps to what we want…….a better life for all of those suffering with Rett syndrome…….and a future cure.