Institutional Implementation of Individualized Clinical Trials

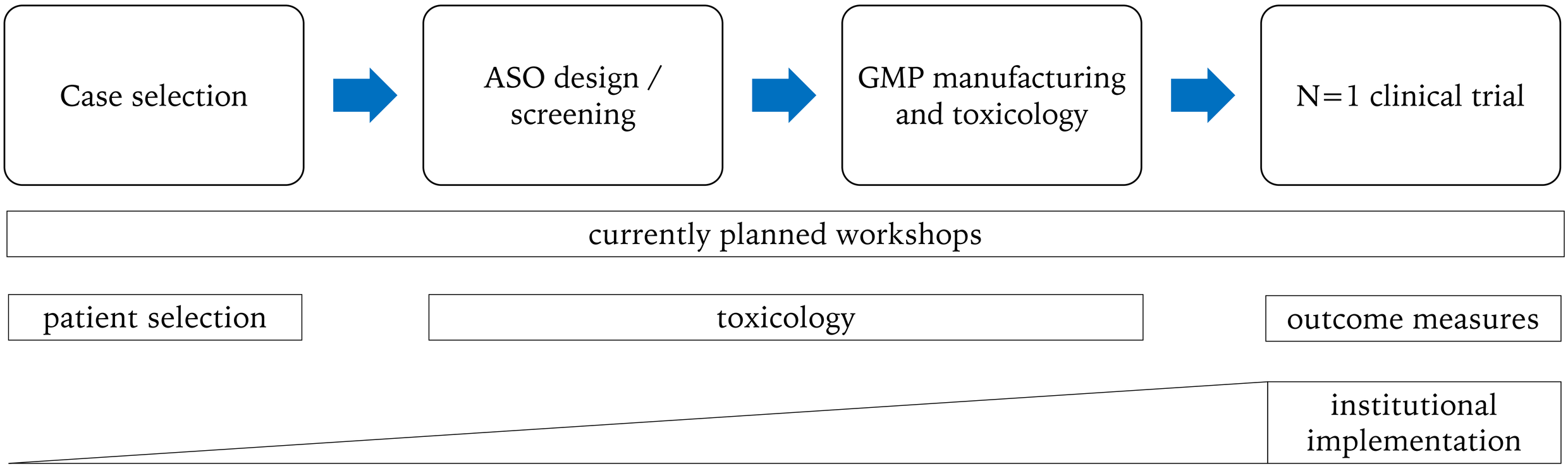
Collaborative Meeting Workshop

14 October 2021

Agenda and goals

- Agenda
  - Study team makeup
  - Institutional oversight
  - Required approvals
  - Key documentation
  - Informed consent
  - Potential issues and challenges with case examples
- Goals
  - Help investigators in N=1 Collaborative with implementation at their own institutions
  - Discuss how the N=1 Collaborative can iteratively improve the content and dissemination of these materials

Process overview



Study team makeup

- Research team
  - Principal investigator
  - Clinical disease expert
  - Regulatory expert
  - Preclinical coordinator(s)
  - Clinical coordinator(s)
- Drug administration
  - Investigational pharmacy
  - Anesthesiology
  - Research nursing
- Outcomes and assessments
  - Neurology, neuroradiology, and neuropsychology
  - Physical, occupational, and speech therapists

Institutional oversight

- IRB / Regulatory
  - Institutional review board
  - Regulatory specialist(s) in communications with FDA
- Clinical and scientific
  - Data and safety monitoring committee (DSMC)
  - Oversight committee for personalized experimental therapeutics (OCPET)
- Other
  - Legal
  - Compliance
  - Ethical
  - International office
  - Hospital and departmental leadership

Required approvals

1. Oversight committee for experimental therapeutics (OCPET)
   - Reviews and oversees case selection and management
2. FDA investigational new drug (FDA / IND)
   - Approvals can happen in parallel with OCPET process
   - Often involves pre-IND meetings and submission of briefing packages
3. Institutional review board (IRB)
   - Approvals typically happen after OCPET and FDA processes
   - Involves submissions of study protocols and consent documents
4. Data safety monitoring committee (DSMC)
   - Monitors the study throughout the trial

Key documentation

1. Clinical protocol
2. Clinical consent form
3. FDA IND application
4. Clinical report forms
5. Pharmacy protocols

Informed consent: unique n=1 considerations

- Overviews
- Procedures and study schedule
- Drug-related risks
  - Class related
  - Individual drug related
  - Unknown risks
- Limitations
  - Unknown efficacy
  - Stopping criteria
- Potential benefits
- Billing considerations

Overview

If you decide to enroll your child in this expanded access protocol, the following things will happen:

- Some screening tests will be done first to determine if they are eligible to participate.
- If your child is eligible to receive the investigational drug, they will be admitted to Boston Children's Hospital, where a lumbar puncture (LP) will be performed. This LP will do two things: 1) withdraw a cerebrospinal fluid (CSF) sample for biochemical analysis and 2) inject the investigational drug, AT008, into the fluid surrounding their spinal cord, via what is called an intrathecal injection. This procedure is done under sedation.
- After the injection, they will stay at Boston Children's Hospital for 24 hours of observation, during the escalation and loading phases. During this observation period, they will have blood and urine safety tests, neurological assessments, and general monitoring for any adverse events or unwanted effects on their health.
- Additional doses will be administered according to the planned schedule below. Once they reaches the maintenance phase, they may be discharged a few hours after receiving the injection.
- More information and details about what will happen during this study is discussed below.

Procedures and study schedule

If your child is eligible to receive the investigational drug, they will be admitted to Boston Children's Hospital. Prior to the procedure, they will receive sedation to help keep their comfortable. Once they are sedated, a licensed and trained medical doctor will perform a lumbar puncture (LP) to administer the investigational drug, AT008, into the fluid surrounding their spinal cord, via what is called an intrathecal injection. After the injection, they will stay at Boston Children's Hospital for 24 hours of observation, during the escalation and loading phases. During this observation period, they will have blood and urine safety tests, neurological assessments, and general monitoring for any adverse events or unwanted effects on their health. Additional doses will be administered according to the planned schedule below. Once they reaches the maintenance phase, they may be discharged a few hours after receiving the injection.

A CSF sample will be withdrawn just before drug injection, to measure drug concentration levels for pharmacokinetic (PK) measurements. PK assessments are usually done when medications are first administered, to monitor how their body handles the investigational drug. The investigators will also take blood samples for PK measurements. These small blood samples (approximately 0.5 mL at each time point) would be obtained when they first receives the drug, then again at 4, 12, and 24 hours after the medication administration. Blood samples will be taken from an IV that will be placed once they are under sedation.

Risks associated with drug

What are the risks of this expanded access treatment? What could go wrong?

Some procedures or treatments used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research.

There two primary ways this expanded access treatment may introduce risk to your child: (1) risks from the drug itself and (2) risks of medical procedures and delivering the drug.

The most critical risks from drug administration would seem to include:

- Your child could have an unexpected or adverse reaction to AT008. In animal studies, intrathecal (spinal) injection oligonucleotide drugs like AT008 have been observed to cause nerve damage and/or leg weakness, impairing the ability of animals to walk (see below); while these reactions have not been seen in humans to date, they are important to know about.
- Your child could be exposed to contaminants unrelated to the drug that may result in neurologic injury following administration.
- Based on drugs related to AT008, there is a low risk of proteinuria/kidney problems and platelet/bleeding problems.
- There is chance of physical harm from the intrathecal injection (lumbar puncture/spinal tap), blood draws, and MRI associated with the study. Intrathecal injection carries a risk of headache, pain or numbness in the legs and lower back, or bleeding into the spinal canal.

Risks associated with drug

AT008 has never been used in humans, so it is very difficult to predict the risks or side effects of this investigational drug. The usual safety studies in animals have not been performed; therefore, there is limited information on the possible side effects of AT008 in animals. To date, the one completed study in rats demonstrated that a single intrathecal injection of AT008 caused injury to nerves in the spinal cord.

We can also infer other potential risks or side effects of AT008 from those seen in similar drugs of the same class. Based on comparisons with those drugs, we expect that side effects could also include headache or lower limb weakness. Rats or monkeys receiving doses of this class of drug have been observed to have transient incoordination and/or weakness of the lower legs, making it difficult to walk. While these observed effects typically last for 24 hours or less, repeated administration can lead to permanent gait difficulties. Additionally, rare side effects reported with this class of drugs included increased seizures, proteinuria/kidney problems, and platelet/bleeding problems. There may also be unknown risks that occur for AT008 but are not seen with other ASOs.

Stopping criteria

Your child will be in this expanded access protocol for approximately one year. This protocol may be extended if their disease does not progress as quickly as other children with A-T after receiving the AT008. It is also possible the drug may be stopped during the year.

Research funds will cover the investigational costs associated with the study. We may bill your child's health insurer for routine items and services they would receive even if they did not take part in this expanded access protocol, and for these non-research services, your family will be responsible for what insurance doesn't cover. You will not receive any financial compensation for taking part of this expanded access protocol.

Potential benefits

The most important potential benefits to know about are:

- There is a theoretical possibility this investigational drug could slow the progression of their neurological symptoms; as your child is young and relatively asymptomatic, there is a chance that AT008 will:
  - Make the neurological course of their A-T slower and more mild than expected or;
  - Prevent them from developing neurological symptoms of A-T.
- AT008 is anticipated to act only on the neurological symptoms associated with A-T. Again, there is no expected impact on the cancer risk and/or immunodeficiency associated with A-T.
- There is also a possibility that treatment with AT008 does not help and does not slow the progression of your child's neurological symptoms

Billing considerations

Are there costs associated with this expanded access treatment? Will we receive any payments?

Although research funds will pay for some expanded access treatment items and services, Boston Children's Hospital may bill their health insurer for routine items and services they would have received even if they did not take part in this expanded access treatment. their guarantor (most likely one of their legal guardians) will be responsible for payment of any deductibles and co-payments required by the insurer for this routine care or other billed care. If you have any questions about costs to the guarantor (the person claiming financial responsibility for any medical costs uncovered by an insurance plan) that may result from your child's participation in this expanded access treatment, please speak with the staff.

We will offer your child the care needed to treat any injury that directly results from taking part in this expanded access treatment. We reserve the right to bill their insurance provider and/or other third-party payors, if appropriate, for the care they receives to treat the injury. We will try to have the insurance provider pay these costs, but the guarantor may be responsible for some or all of them. For care billed to their insurer, the guarantor will be responsible for payment of any deductibles and co-payments that are required by their insurer.

Injuries sometimes happen in expanded access treatment, even when no one is at fault. There are no plans to pay you or your child, or give you or your child other compensation for an injury, should one occur. However, you and your child are not giving up any of your legal rights by signing this form. If you think you and/or your child have been injured or have experienced a medical problem as a result of taking part in this expanded access treatment, tell the person in charge of the expanded access treatment as soon as possible. The name and phone number are listed in this consent form.

Other considerations

Are there other things we should know about?

If we find out about new information from this expanded access treatment or other research that may affect your child's health, safety, or could change your willingness to continue to participate in this expanded access treatment, we will let you know as soon as possible. The FDA is responsible for defining and enforcing standards for how commercially distributed and investigational drugs are made and tested. As an investigational drug, AT008 falls under FDA regulation. The manufacturing practices used for AT008 fell under "Good Manufacturing Practice" (GMP) guidelines. The FDA was informed of all methodologies used for the manufacturing and testing process. The FDA agreed with these manufacturing decisions and deemed them safe for human use.

In the future, it is possible this technology will be sold commercially, and the results of this research will be important in securing government approval or contracting with a business to manufacture or develop the technology. If this were to occur, Boston Children's Hospital and/or the researcher(s) might receive financial benefits. As in all research studies, the hospital has taken steps designed to ensure this potential for financial gain does not endanger research participants, or undercut the validity and integrity of the information learned by this research.

Case 1: Research rigor vs compassionate care

It is important to collect substantial data for reviewing safety and efficacy of the study drug.

However, long and multiple visits can be laborious for families. It may require them to take time off of work, travel to and stay at the hospital, find other childcare, or other burdens.

Additionally, changes to the protocol may be needed, due to new scientific and/or clinical information. N=1 cases have a high regulatory burden per patient.

1. How can research rigor and protocol compliance be balanced with compassionate care? How can families best be supported in these scenarios?
2. Like clinical care is customized over time, how can protocol changes be adapted in a timely yet sustainable manner? How can the study be rigorous yet flexible?
3. Should there be division between research roles and clinical roles for personnel?

Case 2: Transfer between institutions

A patient began an N=1 investigational trial at one institution, but due to family circumstances would like to continue in the trial at a different institution.

1. What needs to be done to coordinate this transfer?
2. What institutional agreements need to be set up?
3. Which personnel and groups need to communicate and collaborate about this?
4. How can this communication be facilitated by the study team?

Case 3: Funding

A clinical research group is in the process of implementing an individualized medicine trial at their institution, and navigating potential funding sources.

1. What funding sources could be available for them? Consider hospital discretionary funds, billing to insurance, advocacy foundations, or grant funds, among others.
2. What personnel, groups, and processes at the hospital should be engaged in the determination of n=1 trial funding?
3. How might these considerations differ in N=1 vs “N=some” scenarios?