CTD & GAMT
Core Outcome Set Report

The COS Development Process

The CTD and GAMT deficiency Core Outcome Set (COS) study involved:

1. Evidence Review Comprised of

- Two independent rapid literature reviews of the currently reported outcomes for CTD and GAMT deficiency
- In-person and online focus groups with caregivers of individuals with CTD and GAMT deficiency to identify important outcomes
- A review of ACD's CreatineInfo Patient Registry and Natural History Study to extract Patient Meaningful Outcomes

2. Globally Distributed Delphi Survey

- Three rounds of Delphi survey were conducted to systematically reduce the number of outcomes, based on patient, caregiver, and health professionals responses

3. Consensus Workshop Meeting

- A consensus workshop was held to determine which of the remaining 20 candidate outcomes, identified in our Delphi survey, should be incorporated into a Core Outcome Set (COS) for CTD and GAMT deficiency, for use in clinical trials.
- Caregivers of individuals with CTD and GAMT deficiency as well as health professionals including clinicians, laboratory scientists, and researchers attended the Consensus Workshop.
- A decision was made to include 8 outcomes in the final COS.

STAGE 1
Evidence Review:

Reviewed the research and patient reported evidence to identify all outcomes involved in CTD and GAMT.

JUNE 2022 - JANUARY 2023

STAGE 2
Delphi Surveys:

Asked families, health care providers, and researchers to rate outcomes to develop a consensus.

FEBRUARY - OCTOBER 2023

STAGE 3
Consensus Workshop:

Asked survey participants to attend a workshop to help develop a final COS.

NOVEMBER 2023

Thank You!

Thank you to everyone who participated in the PaReNts project, focus groups, Delphi surveys, and the consensus workshop. Your participation helped develop a core outcome set (COS) for CTD and GAMT deficiency!

The Finalized Core Outcome Set

Following one round of voting and several roundtable discussions, the following 8 outcomes were approved by more than 50% of consensus workshop attendees for inclusion in the Core Outcome Set (COS).

Adaptive Functioning
An individual's level of independence in functioning compared to similarly-aged peers, in areas including communication and practical tasks, such as daily living skills involving toileting, eating, dressing, and hygiene

Cognitive Functioning
Specific mental abilities, including the ability to learn, think, remember, problem solve, as well as decision making, and attention

Emotional Dysregulation
Having a difficult time appropriately managing and controlling one's feelings and emotional responses

Expressive Communication
Ability to express one's needs and wants through communication

Fine Motor Functions
Motor skills that involve the smaller muscles (e.g., wrists, hands, fingers) and allow for more precise movement

MRS Brain Creatine*
Amount of creatine in the brain as determined by magnetic resonance spectroscopy (MRS), a technique that shows the levels of chemical components in the brain

Seizure/Convulsions
Sudden and uncontrollable movements and/or loss of consciousness and/or loss of body control; episodes can be self-limiting and last for a few seconds, or they can persist, or come in clusters

Serum Plasma Guanidinoacetate**
Amount of guanidinoacetate in the serum or plasma

*In the case of GAMT deficiency, maintenance of this level is worth noting. However, it is anticipated that this biomarker may remain stable if the patient received oral creatine supplementation prior to the trial.
**This outcome is not applicable in CTD trials.
Note: Although Expressive Communication and Fine Motor Functions did not receive more than 50% of the votes in the Consensus Workshop voting, they were included based on unanimous agreement during group discussions among all attendees.

Other Outcomes of Note

Serum Plasma Creatine

Definition: amount of creatine in the serum or plasma

MRS Brain Guanidinoacetate

Definition: amount of guanidinoacetate in the brain as determined by magnetic resonance spectroscopy (MRS), a technique that shows the levels of chemical components in the brain

While Serum Plasma Creatine and MRS Brain Guanidinoacetate are not in the COS, discussions at the Consensus Workshop emphasized that measuring them in GAMT deficiency trials could provide valuable insights into the maintenance of oral supplementation results.

MRI Brain General

Definition: MRI (magnetic resonance imaging) is a technique that shows the various parts of the brain as an image; parts of the brain which may be affected in CCDS include the basal ganglia and cerebellum (which control the coordination of movement) or the
white matter (which connects brain areas with nerves)

While not deemed appropriate to include in the COS, there was consensus that when an MRI is performed, often at the same time as MRSpectroscopy, it is appropriate to note any abnormalities for comparison later in the trial. Changes have been observed in GAMT patients replenished with creatine supplementation and it is unknown if similar improvements may be observed in successful trials.

Delphi Round 3 Outcomes Considered at Consensus Workshop

The following 20 outcomes were discussed and voted on at the consensus workshop based on results from the Delphi Survey:

- Seizure/Convulsions
- Caregiver Burden
- Emotional Dysregulation
- Aggressive Behaviors
- Cognitive Functioning
- Intellectual & Developmental Disability
- Adaptive Functioning
- Expressive Language
- Receptive Language
- Independence
- Executive Functioning
- Fine Motor Functions
- MRS Brain Creatine
- MRS Brain Phosphocreatine
- MRI Brain General
- MRS Brain Guanidinoacetate
- EEG Epileptic Potentials
- Serum Plasma Creatine
- Serum Plasma Guanidinoacetate
- Life Expectancy

Caregiver Engagement

PaReNts Project

The goal of this project was to recruit and actively engage, train, and empower a group of CTD and GAMT “Family Collaborators” throughout the entire research process. Special focus was placed on patient-meaningful outcomes (PMOs) and the development of a core outcome set (COS).

Delphi Survey Design

Feedback was collected from the Family Collaborators to ensure the survey, used to identify important outcomes, was designed in a way that was easily understandable by caregivers.

Caregiver Meeting

A subset of the Family Collaborators was prepared for the Consensus Workshop in a preparation meeting. They were encouraged to ask questions, and seek clarification, on the remaining 20 outcomes.

Consensus Workshop

The subset of Parent Collaborators, with a similar number of health care professionals, participated in a Consensus Workshop, sharing their expertise and opinions on the remaining outcomes based on their lived, and clinical experiences.

Next Steps

- The “Core Outcome Set for CTD & GAMT” will be published in a peer-reviewed journal.
- A second project is being planned to study “Considerations for CTD & GAMT Outcome Measurement Tools” as a companion to the COS.
- Caregivers, clinicians, scientists, industry, and policymakers will be recruited for participation in the OMT study.

Publish Core Outcome Set for CTD & GAMT in peer-reviewed journal

Study Considerations for CTD & GAMT Outcome Measurement Tools (OMT)

OMT Study will include broad participation, including CCDS caregivers