Establishing a Core Outcome Set (COS) for CTD & GAMT Deficiency Through Caregiver and Health Professional Collaboration

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Introduction

- Creatine transporter deficiency (CTD) and guanidinoacetate methyltransferase (GAMT) deficiency are cerebral creatine deficiencies (CCDS) that cause intellectual and developmental disabilities, behavior problems, speech delay, seizures, and motor impairments.[1]
- No FDA-approved treatments exist. However, research studies are ongoing to develop and test the effectiveness of new therapies/drugs.[2]
- Clinical trials often differ in how they define and measure outcomes, posing challenges to their interpretation and real-world application.[3] Additionally, research outcomes do not often fully reflect patient priorities.[4]

Objective

- Develop a core outcome set (COS) of 8-10 outcomes for CTD and GAMT deficiency to ensure consistent evaluation of therapies, using clinically significant outcomes for patients and caregivers.

Methods & Results

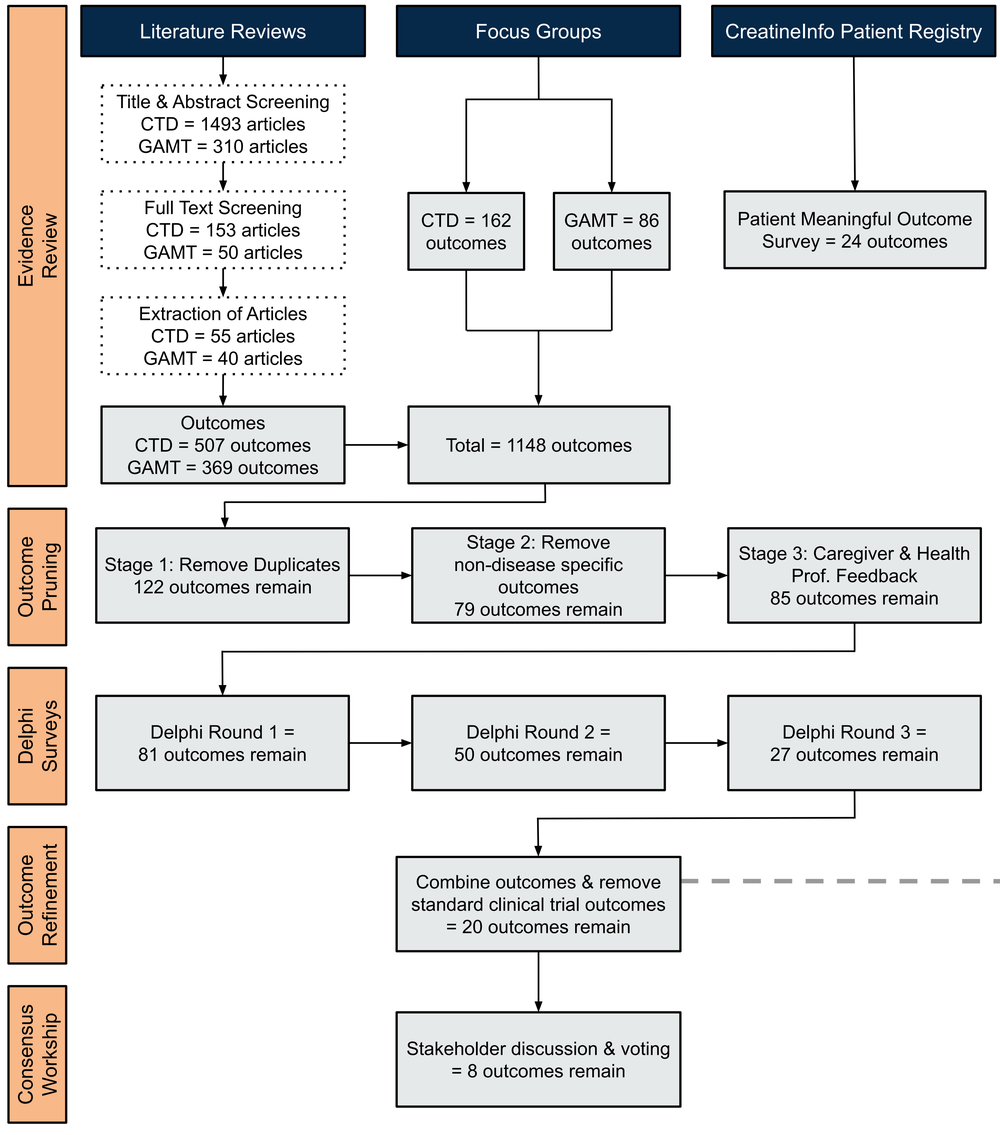

Figure 1. Outcome selection process for core outcome set development for CTD and GAMT deficiency, including the remaining number of outcomes at each step.

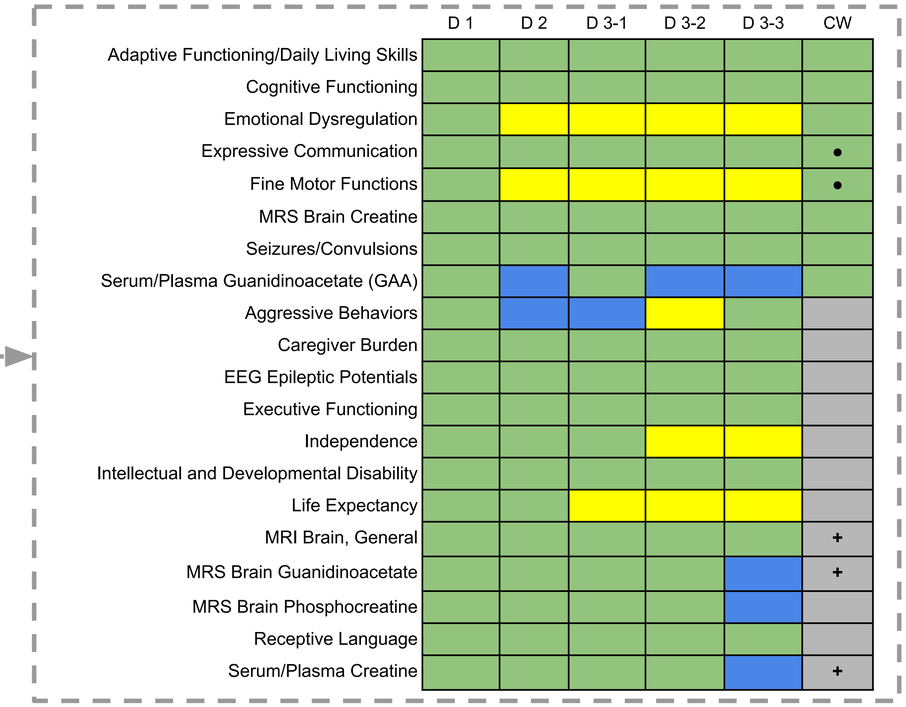

Figure 2. Twenty candidate outcomes were discussed during the consensus workshop. Inclusion criteria for each round were as follows: Delphi 1, rated ≥3 by ≥70% of any stakeholder group; Delphi 2, rated ≥7 by ≥70% of any group; Delphi 3-1, rated ≥7 by ≥70% of any group; Delphi 3-2, mean rating ≥7 for any group; Delphi 3-3, ranked in top 10 by ≥15% of any group; Consensus Workshop, ≥50% voted "1-Definitely In". Outcomes met the inclusion criteria among stakeholders: caregivers (yellow), health professionals (blue), both (green). Two outcomes (●) did not meet the inclusion criteria but were included in the COS based on later unanimous agreement. Three outcomes (+) were excluded but identified as worth tracking as they are often measured in parallel with the required COS.

Patient & Caregiver Engagement

"He gets mad really quickly. He can't seem to control his outbursts. [He's] put his foot through a wall before."

Emotional Dysregulation

"I can see that he gets disappointed when he cannot get his message across to others. And it's frustrating for me because I'm trying to understand him, but I can't."

Expressive Communication

Figure 3. Sample quotes from the CTD and GAMT caregiver focus groups. Caregiver engagement was integral to developing a COS that is not only disease-specific but also patient-centered.

Conclusions & Future Directions

- The CCDS community reached consensus on eight outcomes for the first COS for CTD and GAMT deficiency.
- This COS will 1) facilitate a patient-centered approach for accelerating drug development for CTD and GAMT deficiency, 2) minimize bias, and 3) promote a more efficient use of resources.
- A second project is underway to develop "Considerations for CTD & GAMT Outcome Measurement Tools", to identify appropriate measurement tools that could be used to appropriately measure the COS in CTD and GAMT deficiency patients.

Core Outcome Set

1. **Adaptive Functioning**
2. **Cognitive Functioning**
3. **Emotional Dysregulation**
4. **Expressive Communication**
5. **Fine Motor Functions**
6. **MRS Brain Creatine**
7. **Seizure/Convulsions**
8. **Serum/Plasma Guanidinoacetate**

References & Acknowledgements

1. Stöckler-Ipsiroglu S, van Karnebeek CD. Cerebral creatine deficiencies: a group of treatable intellectual developmental disorders [published correction appears in Semin Neurol. 2014 Sep;34(4):479]. Semin Neurol. 2014;34(3):350-356. doi:10.1055/s-0034-1386772
2. Fernandes-Pires G, Braissant O. Current and potential new treatment strategies for creatine deficiency syndromes. Mol Genet Metab. 2022;135(1):15-26. doi:10.1016/j.ymgme.2021.12.005
3. Gargon E, Gurung B, Medley N, et al. Choosing important health outcomes for comparative effectiveness research: a systematic review. PLoS One. 2014;9(6):e99111. Published 2014 Jun 16. doi:10.1371/journal.pone.0099111
4. Faulkner SD, Somers F, Boudes M, Nafria B, Robinson P. Using Patient Perspectives to Inform Better Clinical Trial Design and Conduct: Current Trends and Future Directions. Pharmaceut Med. 2023;37(2):129-138. doi:10.1007/s40290-022-00458-4

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