

Methodology To Develop Guidelines For The Management Of Patients With Neuronal Ceroid Lipofuscinosis Type 2 Disease

Authors:
Hendriksz CH¹, Donohue J², Donohue Y², Mole SE³

Author Information:

1. University of Pretoria, Steve Biko Academic Unit, Pretoria, South Africa
2. Care Beyond Diagnosis, Columbia, TN, US
3. MRC Laboratory for Molecular Cell Biology, UCL Institute of Child Health, University College London, London, UK.

The multiple clinical manifestations and progressive nature of CLN2 disease, a major form of the neuronal ceroid lipofuscinoses or Batten disease, make the management of patients challenging. Although guidelines are available, the methodology used to formulate clinical recommendations has come under increased scrutiny, highlighting a need for robust, independent guidance on the benefits/risks of disease-modifying treatments and the medical interventions used to manage this condition. This method will be implemented to develop evidence-based and expert-agreed recommendations for the wide range of interventions currently used to manage CLN2 disease and will be independently managed by Care Beyond Diagnosis, a 501(c)3.

The first part of the project was to develop an expert mapping tool to identify two chairs, who would lead the project to ensure the process is transparent and unbiased. After identifying 1,454 professionals through the KOL tool, after ranking by the “tool”, they were sequentially approached until two were able to commit to participation in this project.

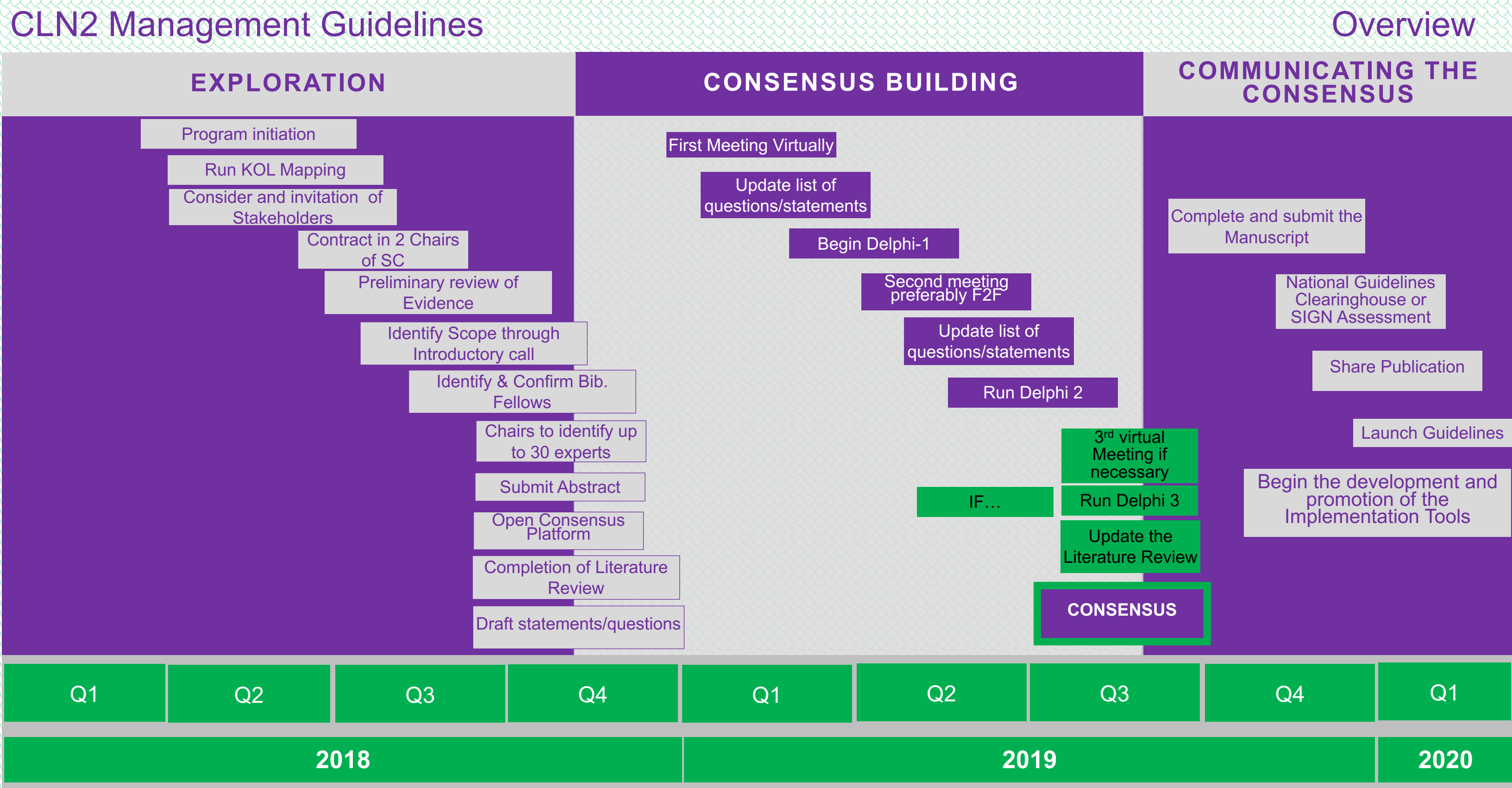
Key statements or questions will be developed and supported by a systematic review of the published evidence using PRISMA guidance to form the basis of an international modified Delphi consensus determination process which will then be conducted.

Multiple stakeholders have been identified and approached to support funding this project, including; potential companies developing therapeutics in this area, patient organisations and an international steering committee as recommended by the steering committee chairs.

The guidelines will be assessed against the Appraisal of Guidelines for Research and Evaluation (AGREEII) criteria and multiple tools will be developed to support their implementation and after completion, a written report will be produced.

This approach has been used successfully for development of other rare disorders for example ACMG PKU and the MSUD Guidelines, which led to publication.

CLN2 Management Guidelines



Guidelines Assessment Criteria

Table 1. Notes on use of the AGREE II instrument for guideline quality evaluation in rare diseases

AGREE II Domain	Points to consider
Scope and purpose (Items 1–3)	Rare disease guidelines should be able to address all of the items concerned with scope and purpose.
Stakeholder involvement (Items 4–6)	Although it is likely that one professional group may dominate, comprehensive stakeholder involvement is as important to the development of guidelines for rare diseases as it is for common diseases. Scoring of these items should recognise this principle and reflect the extent to which the guideline addresses each item.
Rigour of development (Items 7–14)	The AGREE II quality rating does not depend on the quantity or type of published evidence but on the rigour of the systematic methods used to identify, select and synthesize evidence and the transparency with which the guideline development group report how they reached recommendations. For item 13 (external review by experts) – the experts should include patients, carers, and/or patient groups.
Clarity of presentation (Items 15–17)	When scoring item 16 there may not be a range of options for management of the (rare) condition or health issue. In this case the item would be considered ‘not applicable’ and scored as ‘1’.
Applicability (Items 18–21)	The extent to which a guideline can provide information on potential facilitators to guideline implementation and describe resource implications may be limited for rare disease guidelines where the implementation setting is likely to encompass diverse healthcare contexts. The information provided may be country-specific, healthcare-system-specific, or generic
Editorial independence (Items 22–23)	For many rare diseases there are likely to be only a small number of experts worldwide. This may limit the potential for editorial independence. Scores should reflect how this was addressed.
Overall guideline assessment	Before selecting ‘yes with modifications’, consider whether resources are available to modify the guideline and any copyright issues. The existence of only a few or only one guideline on a topic should not prevent a judgment of ‘no’ on question 2 as it is worthwhile to indicate that better quality guidelines are needed.
Notes section	Indicate if the guideline is the only (known) guideline on available on the topic. Indicate any research recommendations which the guideline identifies.

Identifying your Key Opinion Leaders without perceived “bias” utilizing novel Expert Mapping tool

1.)

Research and Grading of Experts

2.)

Categorize, Exclude and Engagement of highest ranked experts for Steering Committee Co-Chair (X2) Selection

3.)

Co-Chairs provide feedback on SC Experts

4.)

Engage the Steering Committee Prospects



Tools	Method:	Weighted Score
PubMed literature search	A search of PubMed for all relevant articles to CLN2	2 3 - 5 6 - 9 10+
SCOPUS H-Index Review	Using SCOPUS Database, Record H-Index of Author	>30 <30
Patient Organization Event Search of last ‘five’ Years	Involvement at Patient Organization Events as Speaker or Chair	>3 <3
Scientific Conference/Event search of last ‘five’ Years	Involvement at Scientific Congress/Events	2-5 6-9 <9

Care Beyond Diagnosis

US, Non-Profit Organization: Tax ID : 38-4040391

Steps A, B, C, and D Details and Outcomes

Criteria



a Clinician whom works directly with CLN2 patients*



Retired clinicians will be considered



Must include '1' clinician as chair from Europe, and '1' from the rest of the world



Animal Experts excluded from consideration for Chair



Industry professionals excluded

Criteria created in an effort to identify experts with the most on-hands patient experience, remove bias and to be geographically balanced.

***Exception to Criteria: process to run through leading clinicians and once leading clinicians with geographic contrast are exhausted, all experts on list to be reconsidered in order of total score: regardless of geographical separation or clinical experience.**

1454 Total Candidates identified through process

Highest and lowest individual scores: '1' Low--- '21' High

Exclusions were made, and list was populated

2 Chairs selected with individual scores of 20 and 16

Invite experts to join as a co-chair in order of their scoring, excluding only for reasons listed here, making note of any exclusion or expert's decision not to participate

Grading Existing Literature

Table 2. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Question	Step 1 Level 1	Step 2 Level 2	Step 3 Level 3	Step 4 Level 4	Step 5 Level 5
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-Series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or “poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (treatment benefits)	Systematic review of randomized trials or n- of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-Series case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the common harms? (Treatment harms)	Systematic review of randomized trials, systematic review of nested case control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (Fr long-term harms the duration of follow-up must be sufficient.)*	Case-series, case control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational studies with dramatic effect			
Is this (early detection) test worthwhile? (screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

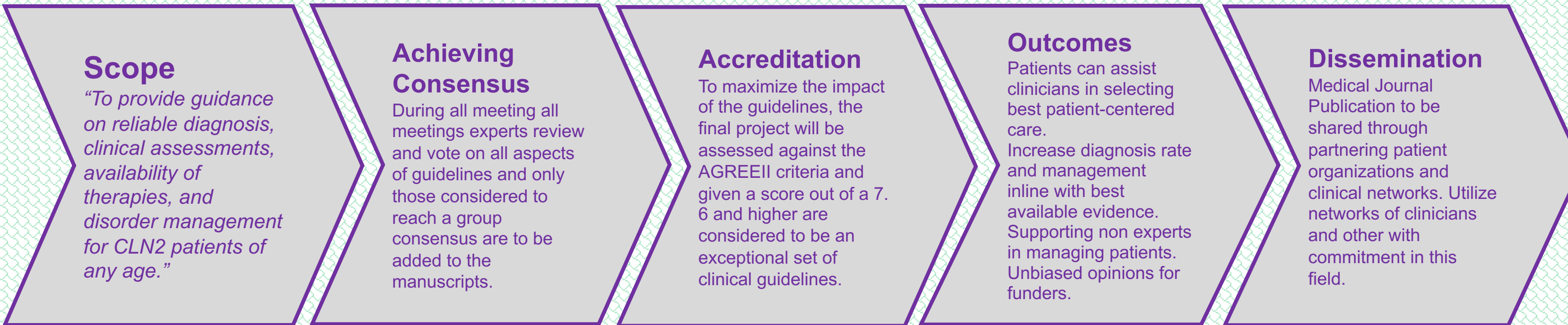


Table 1.) Hilton Boon M, Ritchie K, Manson J. Improving the retrieval and dissemination of rare disease guidelines and research recommendations: a RARE-Best Practices initiative. Rare Dis Orphan Drugs 2014;1(1):20-9

Table 2.) OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653> * OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson