

A case study: Evaluation of the infantile neuroaxonal dystrophy rating scale (INAD-RS)

Paldeep Atwal¹, Eva Hajdukova Brown², Alessandra Girardi², Kavita Jarodia², Katja Rudell², Jeremy Hobart³

- 1. Retrotope
- 2. Parexel® International, London, UK
- 3. Plymouth University

Background & Objectives

Scale development and evaluation is particularly challenging in rare diseases, due to small samples and heterogenous clinical profiles (1). Recent recommendations support a flexible approach which includes multiple sources, iterative mixed methods and repeated measurements to estimate the psychometric characteristics of an instrument when sample size is small (1,2). Detailed methodological accounts of Clinical Outcome Assessment (COA) evaluation rare disease are still rare. This study describes an iterative mixed method approach for the evaluation of the content validity and psychometric properties of the INAD-RS, a 40-item ClinRO developed to assess the disease progression in children with Infantile Neuroaxonal Dystrophy (INAD) (3).

Methods

- Qualitative interviews with 5 healthcare professionals (HCP), 10 caregivers of children with INAD (mean age of children=5.5, range = 3.6 – 10 years; mean age of caregivers=32.4, range = 28 – 35 years; average years of caregiving = 4.3; range = 1.5 – 10 years).
- Independent experts’ feedback (Advisory Board).
- Secondary analyses of evidence gathered as part of a National History (NH) study conducted in Tunisia, China, and India: exploratory Classical Test Theory (CTT) and Rasch Measurement Theory (RMT) analyses of 39 baseline assessments.
- The results of preliminary psychometric analysis were used to modify the scale. The psychometric properties of the new mINAD-RS26 were evaluated with 57 baseline data from the NH and an ongoing clinical trial.

Results

- Caregivers rated most motor functions as severe/moderate, while ratings of other domains were more homogenous across all response categories. A similar pattern was seen from the interviews with HCPs (range of relevance: GM = 80-100%, FM = 40-100%, BF = 0-100%, OF = 60-100%, TF = 60-100%, ANS= 10-60%).
- Results of the interviews, experts’ feedback and the initial exploratory CTT and RMT highlighted for investigation problematic items and scoring issues, possibly related to developmental and regional differences (Table 1).
- The original 40-item questionnaire was subsequently modified to 26-item scale (mINAD-RS26). The psychometric evaluation of the mINAD-RS26 on 57 individuals provided evidence to support measurement performance (Table 2). Table 1 and Table 2 show the CTT and RMT analyses provided evidence to support measurement performance.

Table 1. Ecological validity (ADL), Content validity from interview data, Reliability testing (PM), Advisory Board review and overall summary to include or exclude items of the INAD-RS40

Item No	Code	Domain, domain number, label	Full item label on scale	ADL	CG INT	HCP INT	PM	AB	OS
Gross Motor Function (GMF)									
1	GM01	1. Head upright	Holds head upright against gravity when sitting	☑	☑	☑	☑	☑	☑
2	GM02	2. Roll over	Roll over	☑	☑	☑	☑	☑	☑
3	GM03	3. Sit with support	Sit with support	☑	☑	☑	☑	☑	☑
4	GM04	4. Sit without support	Sit without support	☑	☑	☑	☑	☑	☑
5	GM05	5. Stand aided	Stand aided	☑	?	☑	☑	☑	☑
6	GM06	6. Stand unaided	Stand unaided	☑	☒	☑	☒	☒	☒
7	GM07	7. Head lag	Does head lag with dynamic change of position	☑	☑	☑	☑	☑	☑
8	GM08	8. Hand contractures	Peripheral limb function: Hand	☑	?	☑	☑	☑	☑
9	GM09	9. Feet contractures	Peripheral limb function: Feet	☑	☑	☑	☑	☑	☑
10	GM10	10. Crawling	Crawling	☑	?	☑	☑	☑	☑
11	GM11	11. Walk aided	Walk aided	☑	☑	☑	☑	☑	☑
12	GM12	12. Walk unaided	Walk unaided	☑	☒	☑	☒	☒	☒
Fine Motor Skills (FMS)									
13	FM01	1. Reach objects	Reaches for objects	☑	☑	☑	☑	☑	☑
14	FM02	2. Grasp objects	Grasps small objects	☑	☑	☑	☑	☑	☑
15	FM03	3. Pick up food/spoon	Pick up food or spoon	☑	☑	☑	☑	☑	☑
16	FM04	4. Ring bell	Ring bell	☑	☑	☑	☑	☑	☑
17	FM05	5. Transfer objects	Transfer objects	☒	☑	☑	☑	☑	☑
18	FM06	6. Place blocks	Place one block on another	☑	?	?	?	☒	☒
Bulbar Function (BF)									
19	BF01	1. Swallow saliva/ drooling	Swallows saliva	☑	☑	☑	?	☒*	☒
20	BF02	2. Swallow pureed food	Swallow pureed food	☑	☑	☑	☑	☒*	☒
21	BF03	3. Swallow solid food	Swallow solid food (including soft food)	☑	☑	☑	☑	☒*	☒
22	BF04	4. Bite strength	Bite strength	☑	☑	☑	☑	☑	☑
23	BF05	5. Liquid by syringe	Nourishes liquids by syringe or tube feeding	☑	?	?	☑	☒	☒
24	BF06	6. Tube feeding	Tube feeding	☑	☒	☒	☒	☒	☒
25	BF07	7. Upper airway	Upper airway	☒	☒	?	☒	☒	☒
Ocular Function (OF)									
26	OC01	1. Nystagmus	Nystagmus	☑	☑	☑	?	☑	☑
27	OC02	2. Strabismus	Strabismus	☑	☒	☑	?	☑	☑
28	OC03	3. Track faces	Tracks human face	☑	☑	☑	☑	☑	☑
29	OC04	4. Track objects	Track object	☑	☑	☑	☑	☑	☑
30	OC05	5. Optic atrophy	Optic atrophy/temporal pallor	☒	☒	?	☑	☒	☒
Temporo-Frontal (TF)									
31	TF01	1. Interact	Interacts with parents or examiner	☑	☑	☑	☑	☑	☑
32	TF02	2. Respond to verbal	Responds to verbal commands	☑	☑	☑	☑	☑	☑
33	TF03	3. Repeat sounds	Repeats simple sounds	☑	☑	☑	☑	☑	☑
34	TF04	4. Smile	Smiles	☑	☑	☑	☑	☑	☑
35	TF05	5. Affect	What is the child's affect	☑	☑	☑	☑	☑	☑
36	TF06	6. Speak words	Speaks individual words	☑	☑	☑	☑	☒	☒
37	TF07	7. Combine words	Puts words together	☑	☒	☑	☑	☒	☒
38	TF08	8. Point to objects in a book	Point to objects in a book	☒	☒	☑	?	☒	☒
Autonomic Nervous System (ANS)									
39	AN01	1. Constipation	Constipation	☒	☑	☑	☑	☑	☑
40	AN02	2. Urinary	Urinary	☒	?	?	☒	☒	☒

*ADL = Activity of Daily Living Videos review, CG INT = Caregiver Interview, HCP INT = HCP Interview, PM = Traditional Psychometric Analyses, AB= Advisory Board Feedback & OS = Overall Summary. A ☑ indicates analysis of the source provided general item relevancy, A ? indicates questionable item relevancy, ☒ indicates item was not generally relevant. In OS, green shading indicates the item was generally relevant across sources and red shading indicates the item was generally not relevancy across sources. * Advisory Board advised that the bulbar items were mostly parent reported and not observed in clinic.

Table 2. Known groups validity: domain and scale total scores in patients with aNAD, INAD, and deceased patients

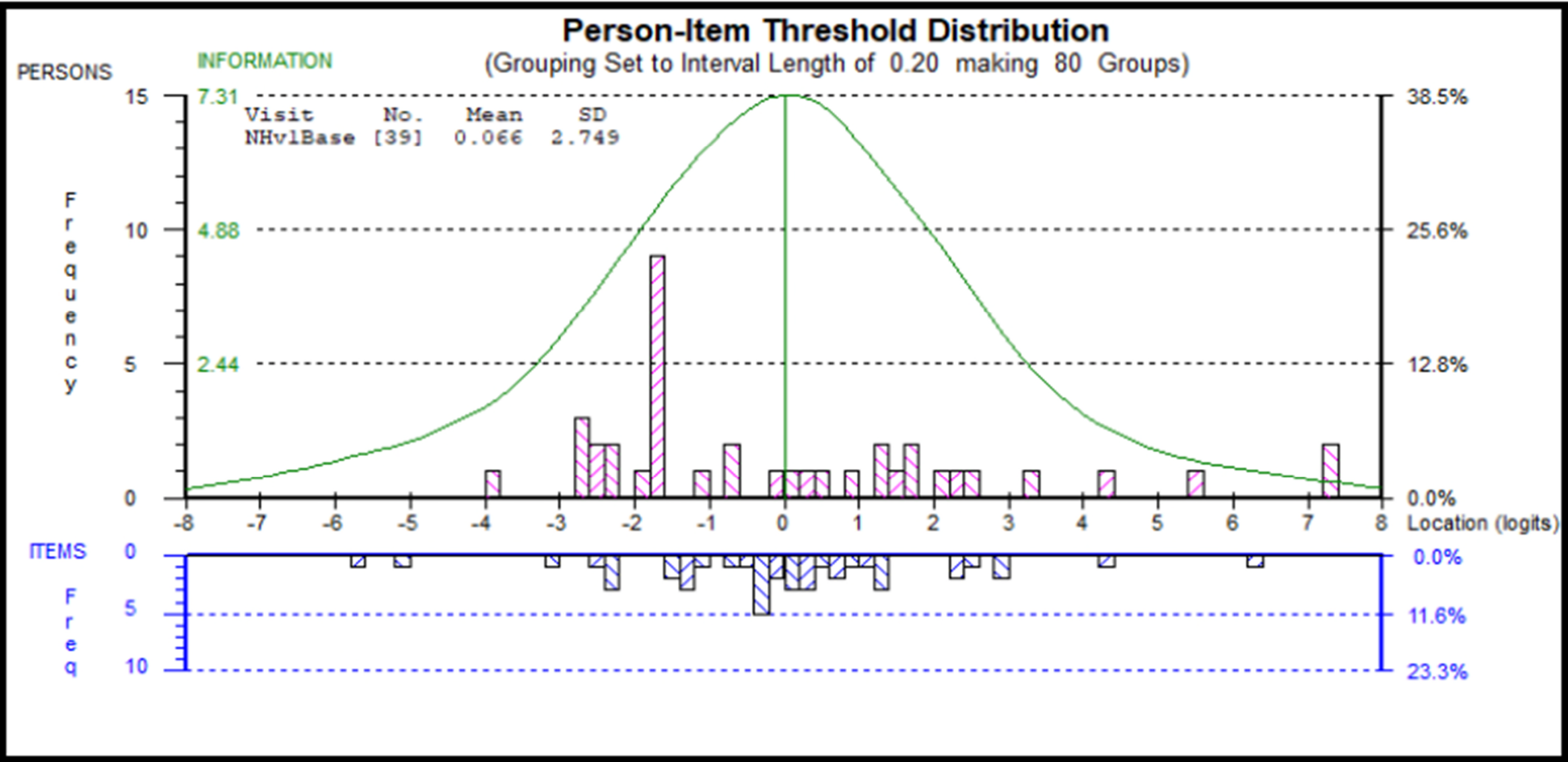
	aNAD (n = 4)				INAD (n =50)				Deceased (n = 7)			
	Mean	SD	Mdn	Range	Mean	SD	Mdn	Range	Mean	SD	Mdn	Range
Gross motor	12.3	2.2	13.0	9;14	4.2	4.3	2.0	0;13	0.9	1.1	1.0	0;3
Fine motor	8.0	0.0	8.0	8;8	3.6	3.5	2.5	0;8	0.7	1.9	0.0	0;5
Bulbar functions	2.0	0.0	2.0	2;2	1.5	0.6	2.0	0;2	1.0	1.0	1.0	0;2
Ocular functions	8.0	0.0	8.0	8;8	5.5	1.9	6.0	2;8	3.0	1.3	3.0	1;5
Temporo-frontal	10.0	0.0	10.0	10;10	5.2	2.7	5.0	1;10	3.7	3.2	2.0	0;7
ANS	1.8	0.5	2.0	1;2	1.6	0.5	2.0	1;2	1.6	0.5	2.0	1;2
Total	42.0	2.0	43.0	39;43	21.7	11.8	19.3	6;43	10.9	6.7	9.0	3;24

Table 3. Internal consistency for the CCT.

	Cronbach's alpha	Cronbach alpha if item removed	ICC	MAS**	CHOP-INTEND**	HINE**
Gross motor	0.93	0.93	0.95	-0.32;-0.70	0.41; 0.89	0.68;0.91
Fine motor	0.95	0.95	0.99			-
Bulbar functions*	-	-	0.45	-	-	-
Ocular functions	0.59	0.69	0.74	-	-	-
Temporo-frontal	0.83	0.74	0.76	-	-	-
ANS*	-	-	1.00	-	-	-
Total	0.84	0.78		-0.58	0.71;0.76	0.84

*: One item; ANS: Autonomic Nervous System; ICC = Intraclass Correlation Coefficients; MAS = Modified Ashworth Scale; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. **Spearman correlation coefficients.

RMT person-item threshold plot for mINAD-RS26 in baseline data (n=39)



Conclusions

The mINAD-RS26 was systematically evaluated using an iterative mixed method approach that aligns to the best practices in scale development and evaluation, especially for a rare, ultra-orphan disease. Results were promising given the caveats.

References:

1. Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report. Value Health. 2017 Jul-Aug;20(7):838-855. doi: 10.1016/j.jval.2017.05.015. PMID: 28712612.

2. Morel T, Cano SJ. Measuring what matters to rare disease patients - reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. Orphanet J Rare Dis. 2017 Nov 2;12(1):171. doi: 10.1186/s13023-017-0718-x. PMID: 29096663; PMCID: PMC5667521.

3. Atwal PS, Midei M, Adams D, Fay A, Heerinckx F, Milner P. The infantile neuroaxonal dystrophy rating scale (INAD-RS). Orphanet J Rare Dis. 2020 Jul 29;15(1):195. doi: 10.1186/s13023-020-01479-5. PMID: 32727524; PMCID: PMC7392694.

Acknowledgements:

We would like to thank Ivanna Pavisic from Parexel® International (London, UK) for the invaluable support provided during the poster development

