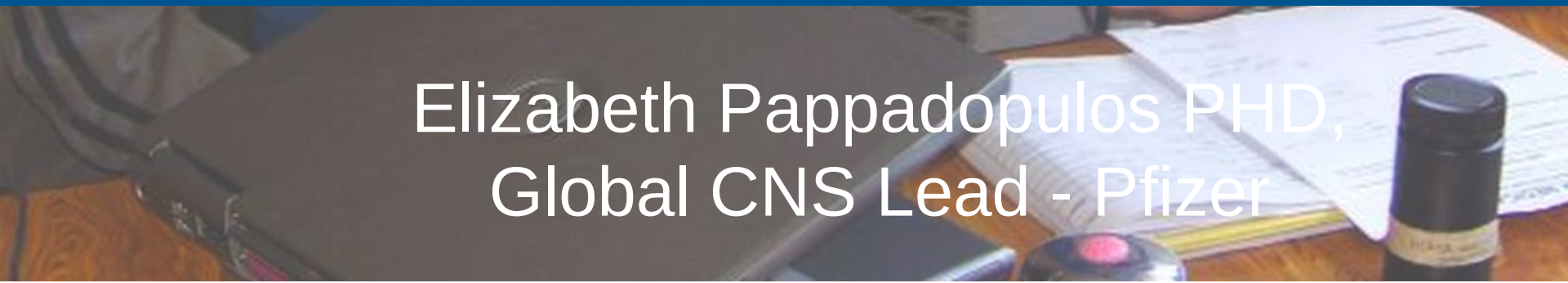
ISCTM Recommendations on the Translation and Adaptation of Clinician Reported Outcomes in International Clinical Trials



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Objective

The ISCTM guidelines are intended to provide practical guidance to industry decision-makers weighing measurement and study accuracy against costs and time.

Consensus Process

1. Workgroup members were representatives from academic & government research, industry and clinical research organization
2. Identified study challenges related to ClinROs used in international trials
3. Informed by existing guidance and literature
4. Survey of 442-person membership

PRO Guidance is Abundant

- FDA PRO guidance document (2009) recommends that, “sponsors provide evidence of content validity and other measurement properties” but does not outline specific methods
- ISPOR (2009) issued decision aid tools and minimum standards for translating and culturally adapting psychometrically valid PROs
- World Health Organization (2011)
- Numerous recommendations by therapeutic area

Expert and/or Regulatory Guidance not available for ClinROs

- Registration trials in psychiatry rely heavily of ClinRO for regulatory approval
- Diagnostic clarity and item sensitivity is critical
- Most ClinROs developed in Western cultures are used in non-western sites

Table1: ISPOR-recommendations for language translation and cultural adaptation of PROs

Step	Stage	Critical Components
Professional Translation	Preparation	• Obtain copyright permission • Concept sheets generated and reviewed by content experts
	Forward and Back Translation	• Two successive translators complete forward translation • Independent back-translation • Quality analyses checks and content expert review for conceptual equivalence • Template draft for use in pilot testing • Feedback from pilot testing and expert review is incorporated prior to finalization
Cognitive & Expert Review	Conduct Cognitive Debriefing Interviews	• Cognitive debriefing interviews conducted with subjects in each country • Abbreviated administration of each test in the battery and administration of Subject Questionnaires • Raters complete Rater Questionnaires
	In-Country Expert Review	• Independent local review of each assessment and pilot testing documents by three psychologists/neuropsychologists in each country
	Final Review and Harmonization of Feedback	• All comments and suggestions reviewed and categorized by language and assessment • Recommended changes reviewed and approved by Lead Neuropsychologists
Finalization	Final Reporting	• Finalize translation and issue certificate • Generate final report

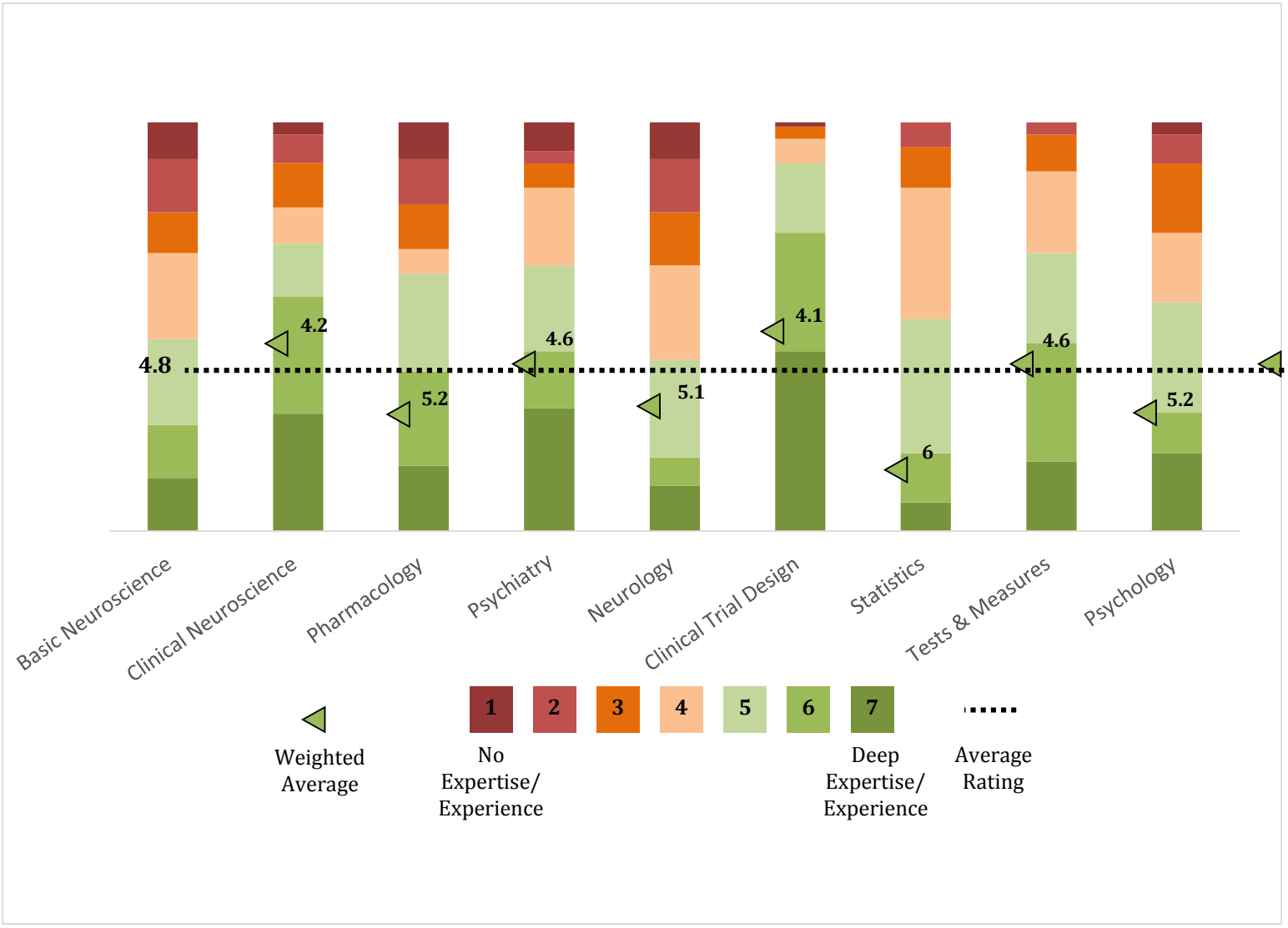
Unique Challenges for CNS ClinRO Validity

- Rater expertise varies widely – training needed to ensure consistency of neuropathological constructs
- Patient/clinician communication around ClinRos may vary by gender/race/ethnicity
- Systematic cultural variation based on norms, taboo or stigma (eg, libido, what is good functioning?)
- Growing interest and investment in “emic” outcomes – mood, QOL, functioning that are culturally sensitive
- Unwarranted confidence that ClinROs administered by a language fluent physician are valid

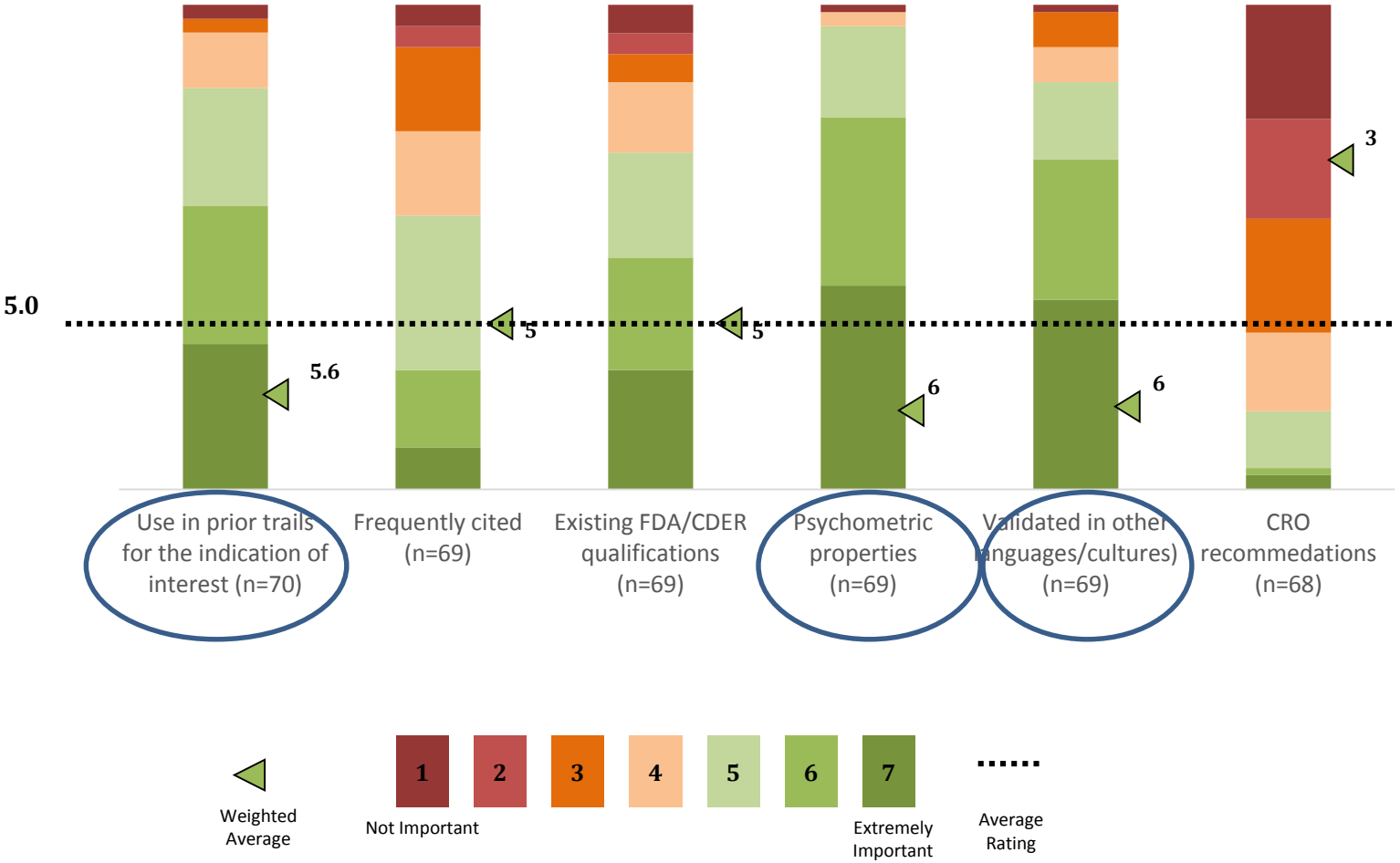
Survey of Membership

- 14 - item survey of practices and perceptions of international trials
- 78 responders
- Sent to 442-person ISCTM membership

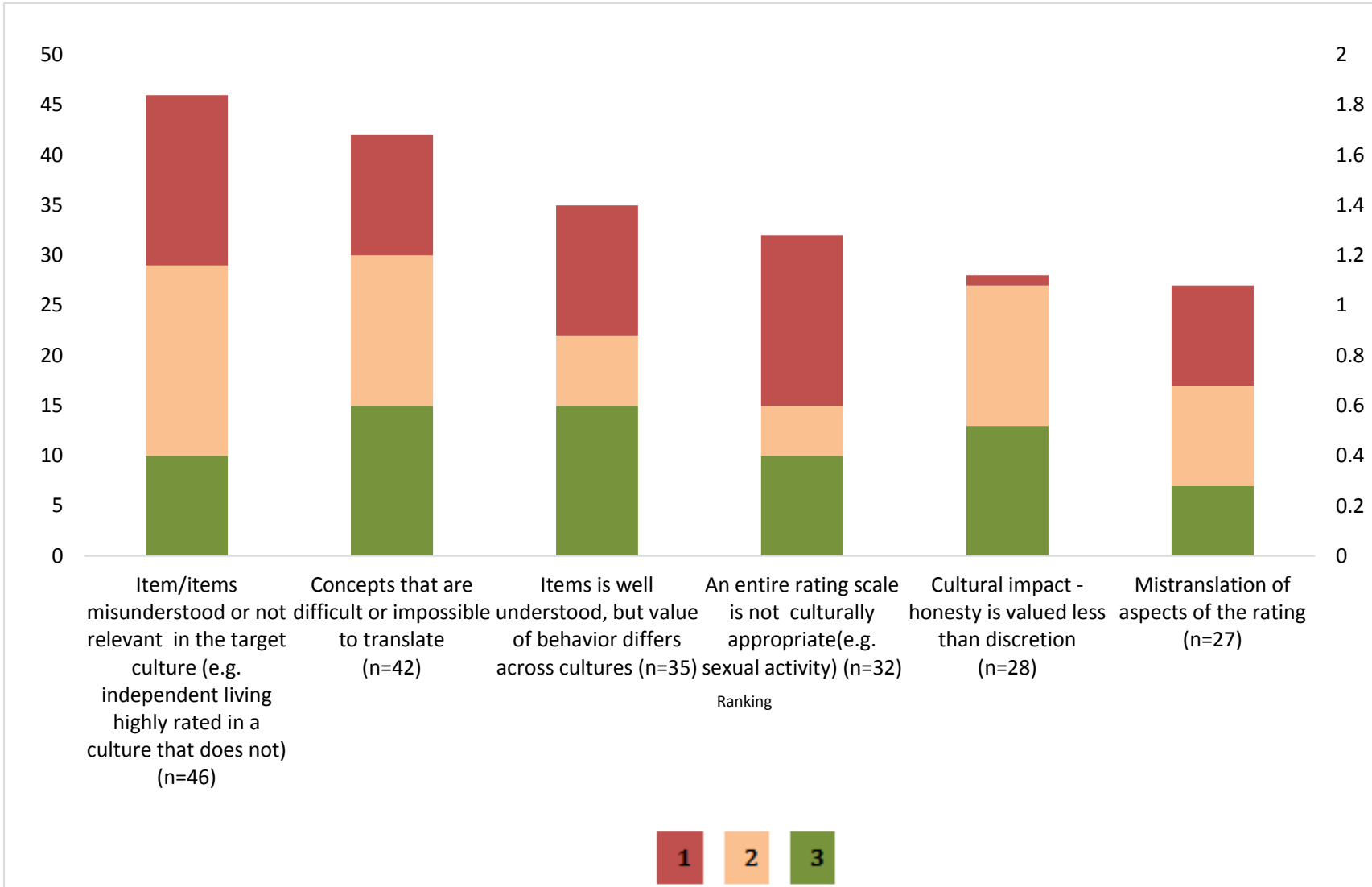
Experience/expertise in the following areas (1-no experience/ 7-deep expertise):



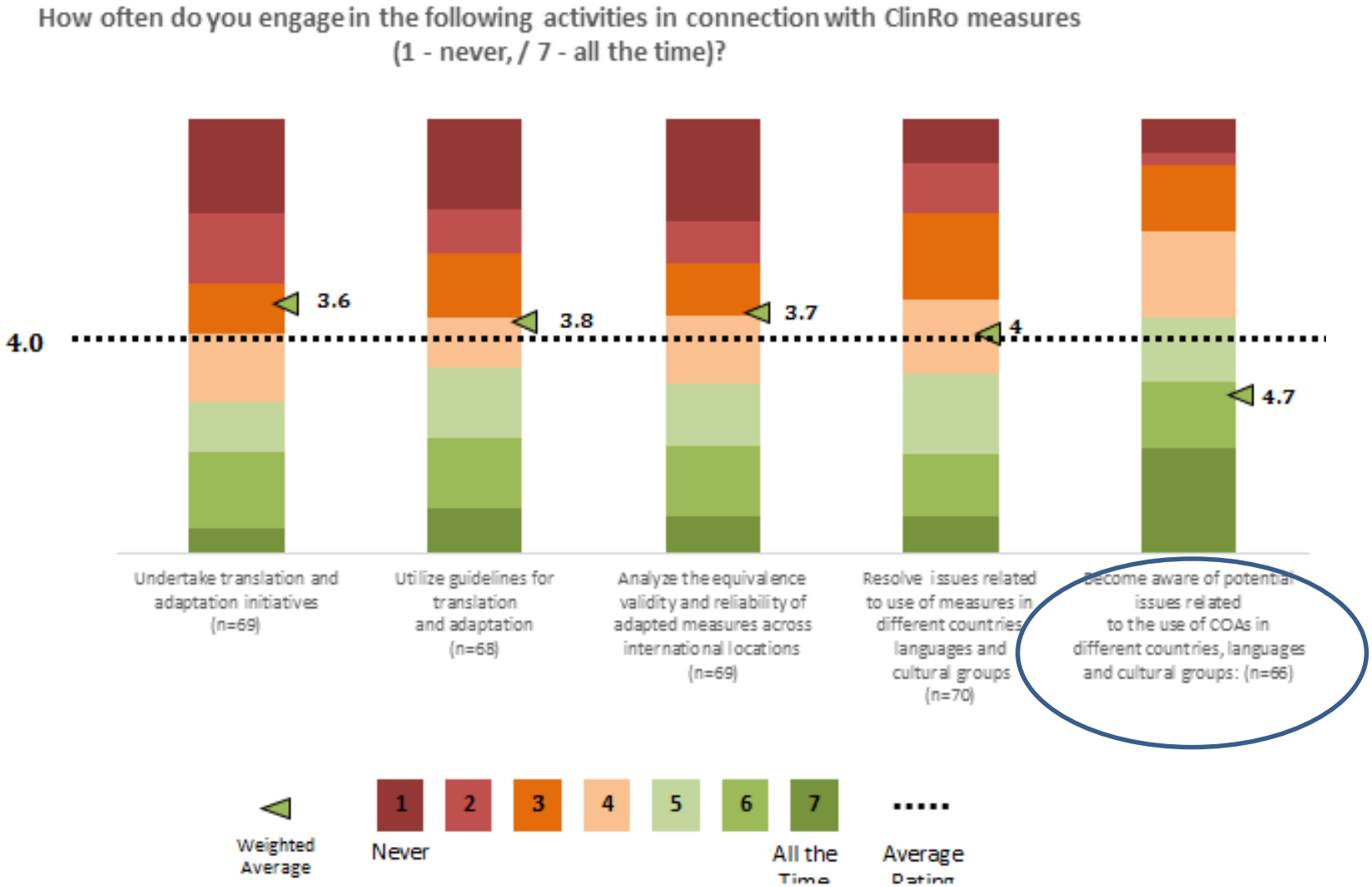
Rate the importance of the following factors when selecting a ClinRo measures for CNS clinical trials (1-not important, 7-extremely important):



Top 3 threats to data integrity in international trials



Frequency of engagement in the following ClinRo activities (1 - never, / 7 - all the time)?



Survey Summary

- Culturally relevant and sensitive ClinRos are a concern to the research community and critical to accurate clinical evaluation
- Too few investigators prioritize cultural translation and validation studies
- Reliance on established measures without evidence of cultural validation seems the norm
- Data integrity becomes a concern only after there are problems
- Bottom-line / Rigor with ClinROs is lacking despite being critical to a successful trial
- Addressing these risks prospectively can mitigate threats to study outcomes

Recommendations for Sponsors

- Consider cultural adequacy and statistical integrity of ClinRO before initiating the study
- Invest early in rigorous translation and validation activities with understanding of the potential risks to data integrity given the TA, ClinRo and study objectives
- Evolve study SOPs that reflect the current state of international trials and will ensure consistency despite ever-changing industry leadership
- Consult with experts where internal expertise of translation, adaptation and statistical validation is limited

Recommendations for the Research Community

- Develop an open repository of translated and validated ClinRos and PROs to encourage the use of the same adaptations across trials
- Provide incentives and resources for underserved indications that will have high impact on the global healthcare economy – schizophrenia, neurodegeneration, etc.
- Setting regulatory standards for ClinRo integrity would adjust priorities
- Publications on measurement are not attractive to journals – but they are critical to advancing the field. Journals could devote a few pages a year to such issues
- Journals could request that translation and validation methods be outlined in published trial results

Challenges to Implementation

- Sponsors fail to prioritize ClinRO cultural adaptation and validation despite spending millions on a development program (small-investment can reduce measurement error)
- Business leaders must weigh the risks of inadequately validated ClinRos against other business and research needs requiring investment – with eyes half open

Conclusions

- More works is needed to educate and guide on the translation and adaptation
- Shifting sponsor judgement on the importance of investing in cultural adaptation of ClinROs is a major challenge
- Persuading the research community to share measures with rigorous adaptation and statistical validation is unlikely