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
### Table 1: ISPOR-recommendations for language translation and cultural adaptation of PROs

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<th>Step</th>
<th>Stage</th>
<th>Critical Components</th>
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| 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|
|                           | 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):

- Basic Neuroscience
- Clinical Neuroscience
- Pharmacology
- Psychiatry
- Neurology
- Clinical Trial Design
- Statistics
- Tests & Measures
- Psychology

Weighted Average

No Expertise/Experience

Deep Expertise/Experience

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

- Use in prior trials for the indication of interest (n=70)
- Frequently cited (n=69)
- Existing FDA/CDER qualifications (n=69)
- Psychometric properties (n=69)
- Validated in other languages/cultures (n=69)
- CRO recommendations (n=68)

Weighted Average
Top 3 threats to data integrity in international trials

1. Item/items misunderstood or not relevant in the target culture (e.g., independent living highly rated in a culture that does not) (n=46)
2. Concepts that are difficult or impossible to translate (n=42)
3. Items is well understood, but value of behavior differs across cultures (n=35)
4. An entire rating scale is not culturally appropriate (e.g., sexual activity) (n=32)
5. Cultural impact - honesty is valued less than discretion (n=28)
6. Mistranslation of aspects of the rating (n=27)
Frequency of engagement in the following ClinRo activities (1 - never, / 7 - all the time)?

How often do you engage in the following activities in connection with ClinRo measures (1 - never, / 7 - all the time)?

- Undertake translation and adaptation initiatives (n=69)
  - Never: 3.6
- Utilize guidelines for translation and adaptation (n=68)
  - Never: 3.8
- Analyze the equivalence validity and reliability of adapted measures across international locations (n=69)
  - Never: 3.7
- Resolve issues related to use of measures in different countries, languages and cultural groups (n=70)
  - Never: 4
- Become aware of potential issues related to the use of COAs in different countries, languages and cultural groups: (n=66)
  - Never: 4.7

Weighted Average

Never 1 2 3 4 5 6 7 All the Time Average Rating
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