Addressing the Problem of Data Missingness: Building on the Legacy of Andy Leon

Larry Alphs,[1] Ibrahim Turkoz,[2] Eric Chan,[3] Carol Jamieson,[3] Leonard Oppenheimer[2]

[1]Janssen Scientific Affairs, LLC, Titusville, NJ; [2]Janssen Research and Development, LLC, Titusville, NJ; [3]Janssen Global Services, LLC, Raritan, NJ

INTRODUCTION

- Subject attrition rates from neuroscience clinical trials range from 20% to more than 50%, leading to data missingness[1,2]
- Data missingness can decrease the statistical power, precision, and generalizability of study results
- The National Research Council[3] suggests developing mechanisms to predict and adjust for patient dropout
- Leon and colleagues developed the Intend to Attend (ITA) scale for this purpose[4]
  - The ITA is a one-item instrument designed to assess subjects' self-rated risk of study dropout at baseline and at subsequent visits
    - At baseline: likelihood of subjects completing the clinical trial
    - Throughout the trial: likelihood that subjects will attend their next study visit
  - The ITA can be used statistically to model missing data processes and convert dropout mechanisms from nonignorable to ignorable
    - If this variable proves to be associated with dropout and is included in the efficacy analysis, the dropout process could be effectively converted from nonignorable to ignorable. As a result, likelihood-based inferences would be valid if the other model assumptions are met
  - The ITA can be used logistically to improve patient retention
    - If the dropout risk is assessed to be high, study staff can ask follow-up questions to help identify the reason for possible dropout or to identify hurdles to study completion
  - The authors are proposing revisions to the ITA to create a version called the ITA-Plus scale in order to
    - Provide clear anchor points to the likelihood of completing the study or making the next visit (for patients)
    - Include a standardized collection of reasons for dropout or failure to make the next visit (for patients), second question
    - Increase the chance of study completion and document responses that may address patient-identified reasons for study dropout or making the next visit (for study staff), second question
    - Provide an instruction manual to explain how to administer the ITA (for sponsor)

OBJECTIVES

- Have experts review the content of a revised version of the ITA scale (ie, the ITA-Plus scale) that has been designed to predict and manage dropout in clinical trials (**Tables 1 and 2**)
- Modify the ITA based on this expert review

Table 1. ITA-Plus Questions at Baseline

Now that you have learned about this trial and how long you will be expected to be in it, consider the things in your life that may get in the way of your completing it. Given those considerations, how likely is it that you will complete this study?	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	I will not complete study	**Very uncertain that I can complete full study**	**Uncertain that I can complete full study**		**Moderately likely to complete full study**		**Likely to complete full study**	**Highly likely to complete full study**	**Extremely likely to complete full study**
If response is 6 or less, answer the following question:									
For subject									
What might prevent you from completing this study? (check all that apply)	Transportation considerations	Treatment side effects	Job or school considerations	Family considerations	Clinical trial burden	Planned move to another area	Other study concerns	Other personal concerns (identify)	
For clinician									
If response was "Transportation considerations," provide potential solutions….	Free text: The following suggestions regarding transportation were provided….								
If response is "Treatment side effects," provide potential solutions….	Free text: The following suggestions regarding treatment side effects were provided….								
If response is "Job or school considerations," provide potential solutions….	Free text: The following suggestions regarding job or school considerations were provided….								
If response is "Family considerations," provide potential solutions….	Free text: The following suggestions regarding family considerations were provided….								
If response is "Clinical trial burden," provide potential solutions….	Free text: The following suggestions regarding clinical trial burden were provided….								
If response is "Planned move to another area," provide potential solutions….	Free text: The following suggestions regarding planned move to another area were provided….								
If response is "Other study concerns," provide potential solutions….	Free text: The following suggestions regarding other study concerns were provided….								
If response is "Other personal concerns (identify)," provide potential solutions….	Free text: The following suggestions regarding other personal concerns were provided….								

Table 2. ITA-Plus Questions at Follow-Up

Given your experience in this trial and how things are going in your life, how likely is it that you will attend your next scheduled study visit?	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	I will not attend the next study visit	**Very uncertain that I can attend the next study visit**	**Uncertain that I can attend the next study visit**		**Moderately likely to attend the next study visit**		**Likely to attend the next study visit**	**Highly likely to attend the next study visit**	**Extremely likely to attend the next study visit**
If response is 6 or less, answer the following question:									
For subject									
What might prevent you from making your next study visit? (check all that apply)	Transportation considerations	Treatment side effects	Job or school considerations	Family considerations	Clinical trial burden	Planned move to another area	Inadequate treatment response	Other study concerns	Other (identify)
For clinician									
If response was "Transportation considerations," provide potential solutions….	Free text: The following suggestions regarding transportation were provided….								
If response is "Treatment side effects," provide potential solutions….	Free text: The following suggestions regarding treatment side effects were provided….								
If response is "Job or school considerations," provide potential solutions….	Free text: The following suggestions regarding job or school considerations were provided….								
If response is "Family considerations," provide potential solutions….	Free text: The following suggestions regarding family considerations were provided….								
If response is "Clinical trial burden," provide potential solutions….	Free text: The following suggestions for clinical trial burden were provided….								
If response is "Planned move to another area," provide potential solutions….	Free text: The following suggestions regarding planned move to another area were provided….								
If response is "Inadequate treatment response," provide potential solutions….	Free text: The following suggestions regarding in adequate treatment response were provided….								
If response is "Other study concerns," provide potential solutions….	Free text: The following suggestions regarding other study concerns were provided….								
If response is "Other personal concerns (identify)," provide potential solutions….	Free text: The following suggestions other personal concerns were provided….								

METHODS

- Nine questions addressing the usefulness of and possible improvements to the ITA-Plus scale were sent in a SurveyMonkey questionnaire (SurveyMonkey, Palo Alto, CA) to members of the International Society for CNS Clinical Trials and Methodology (ISCTM) and to attendees of past ISCTM meetings
- Potential respondents were given 2 weeks to reply
- The survey included the following questions:
  - What is your primary activity relative to clinical trials?
  - Is data missingness an important consideration for your work?
  - If yes, what makes data missingness an important or unimportant consideration for you?
  - How difficult was it to understand how to complete the ITA-Plus scale?
  - If anything was difficult to understand, what was it?
  - Could information from the ITA-Plus scale be helpful in addressing your problems with missing data?
  - How might information from the ITA-Plus scale be helpful in addressing problems with data missingness?
  - Are there things that you would modify in the ITA-Plus scale to make it more useful to you?
  - If you would change some of the items in the scale, what would you change and why?
- Responses were structured for both Likert scale and free-text responses

RESULTS

- 2091 invitations to complete the SurveyMonkey questionnaires were sent. Of these, 696 were opened and 63 responses were received
- Of the respondents, 54% self-identified as clinical leaders and 21% as statisticians
- Of these, 65% of respondents regarded data missingness as important or very important, and 69% regarded the ITA-Plus scale as easy or very easy to understand
- Many valuable comments were provided on how to improve the scale, how to use it in special populations, and any potential limitations
  - These comments were then used to revise the ITA-Plus scale (**Table 3**, **Table 4**)

Summary of Responses

- Respondents indicated that data missingness is an important issue because it can
  - Affect the validity of results
    - Influence or compromise the interpretation of clinical trial results
    - Introduce bias and reduce statistical power
    - Decrease sensitivity and precision
    - Affect the integrity of the principles of intent to treat
    - Lead to a skewed sample
  - Delay the identification of data trends
  - Be a barrier to understanding risk and safety signals
  - Have regulatory implications
  - Affect the ability to publish

Summary of ICSTM Survey Responses

- Respondents reported that information from the ITA-Plus scale might be helpful in addressing problems with data missingness because it
  - Provides a systematic structure for identifying factors that may lead to missing data
  - Has the potential to anticipate and prevent future missing data and facilitate the discussion of potential hurdles for trial completion
  - Might help improve compliance by making the subject more aware of the importance of complying with the visit schedule
  - May help assure better informed consent
  - May facilitate the study site's capability to address the subjects' needs and keep them in the study (eg, transportation needs)
  - Can be used as a covariate in the statistical model. This will help inform data models as to whether the data is missing-at-random or missing-not-at-random
- The tested version of the ITA-Plus scale may be valuable for use in other populations (eg, inpatient, outpatient, pediatric, geriatric dementia) but would require review and possible adaptation and testing for these populations
- Additional questions suggested by reviewers:
  - Baseline: Why do you want to participate in this trial (include a follow-up on patient-perceived drivers to stay in trial)?
  - Follow-up: How pleased are you with your progress in this trial?

Table 3. Revised ITA-Plus Questions at Baseline

Now that you have learned about this trial and how long you will be expected to be in it, consider things in your life that may get in the way of your completing it. Given those considerations, how likely is it that you will complete the full study?	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	I will not complete study	**Very uncertain that I can complete full study**	**Uncertain that I can complete full study**	**Somewhat uncertain that I can complete full study**	**Somewhat likely that I can complete full study**	**Moderately likely that I can complete full study**	**Likely that I can complete full study**	**Highly likely that I can complete full study**	**Extremely likely that I can complete full study**
If response is 6 or less, ask the subject to answer this additional question:									
For subject									
What might prevent you from completing this study? (check all that apply)	Transportation considerations	Treatment side effects	Job or school considerations	Family considerations	Length and complexity of study	Planned move to another area	Other study concerns	Other personal concerns (identify)	
For clinician									
For each item identified by the subject as an impediment to completing the study, provide a brief summary of your key responses to address the subject's concerns	Free text: No character limit. Be comprehensive but concise.								

Table 4. Revised ITA-Plus Questions at Follow-Up

Given your experience in this trial and how things are going in your life, how likely is it that you will attend your next scheduled study visit?	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	I will not attend the next study visit	**Very uncertain that I can attend the next study visit**	**Uncertain that I can attend the next study visit**	**Somewhat uncertain that I can attend the next study visit**	**Somewhat likely that I can attend the next study visit**	**Moderately likely that I can attend the next study visit**	**Likely that I can attend the next study visit**	**Highly likely that I can attend the next study visit**	**Extremely likely that I can attend the next study visit**
If response is 6 or less, ask the subject to answer this additional question:									
For subject									
What might prevent you from making your next study visit? (check all that apply)	Transportation considerations	Treatment side effects	Job or school considerations	Family considerations	Length and complexity of study	Planned move to another area	Inadequate treatment response	Other study concerns	The Study Medication has not worked
For clinician									
For each item identified by the subject as an impediment to attending the next visit, provide a brief summary of your key responses to address the subject's concerns	Free text: No character limit. Be comprehensive but concise.								

CONCLUSIONS

- **Data missingness represents an important problem for many members of ISCTM**
- **Feedback from ISCTM members and attendees of past ISCTM conferences has provided useful input for modification of the ITA-Plus scale**
- **The ITA-Plus scale provides potential statistical advantages to the management of data missingness**

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