Considerations for Requiring Subjects to Respond to PRO Instruments Collected Electronically

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Biographies

Paul O'Donohoe, **MSc**, is Director of Health Outcomes at CRF Health. He is responsible for developing the company's internal health outcomes expertise and supporting clients across the range of scientific issues that can arise during the course of a clinical trial. He is passionate about developing the field of eCOA through research and active involvement in industry consortia.

Sonya Eremenco, **MA**, is Associate Director of the Patient-Reported Outcome (PRO) Consortium at the Critical Path Institute (C-Path). Sonya has over 20 years of experience in PRO (and other clinical outcome assessment) instrument development, with a focus on multicultural development, linguistic validation, and electronic implementation. Sonya holds a Bachelor of Arts in Cultural Anthropology from Duke University and a Master of Arts in Multicultural Communication from DePaul University in Chicago, Illinois.

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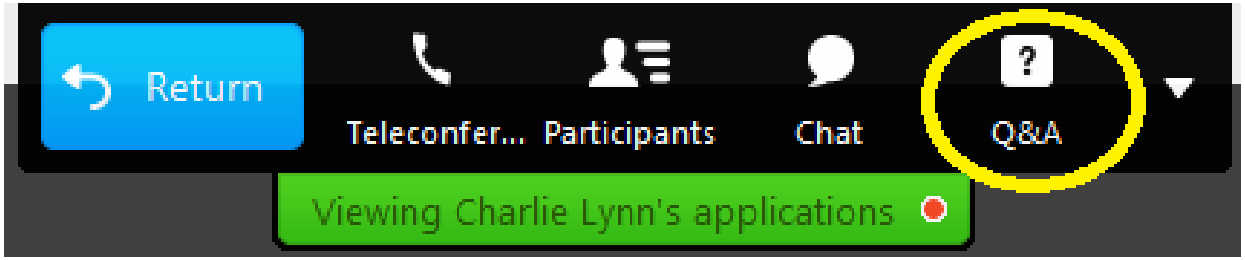

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ePRO Consortium

- The Electronic Patient-Reported Outcome (ePRO) Consortium was established by the Critical Path Institute (C-Path) in 2010. Along with C-Path, the members of the ePRO Consortium are firms that provide electronic data collection technologies and services for capturing patient-reported outcome (PRO) and other clinical outcome assessment (COA) data in clinical trials.
- The mission of the ePRO Consortium is to advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

ePRO Consortium members

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Agenda

1. Requiring Responses with ePRO
2. Key Considerations and Recommendations
3. Skipping Items – How much of an issue in reality?

Goals of Manuscript

- Identify the possible risks of requiring subjects to complete all ePRO items
- Identify the various different approaches that could be taken to requiring subjects to complete ePRO items
- Offer considerations and recommendations around opt-out for study teams implementing ePRO

Scene Setting

- Complete and accurate data – cornerstone of any trial
- Paper has recognized issues with missing or inaccurate data
- Electronic solutions are increasingly popular data capture tools
- This has provided study teams a powerful way to collect high-quality patient-reported outcome data

ePRO and Missing Data

- These new tools have also brought new possibilities
- Key strength of ePRO is the ability to prevent subjects from progressing to the next item in an instrument until they have provided a response to the current item
- Seems to offer the chance of complete PRO data at the close of the study

ePRO and Missing Data

- HOWEVER, what if a subject is confronted with:
  - Inapplicable questions they cannot answer
    - Questions about work for those who are unemployed
  - Sensitive questions they are unwilling to answer
    - Questions about sexual health
- Risks inaccurate or unreliable data
- Worst case scenario - subject could refuse to continue or even drop out

ePRO and Missing Data

- Unlike paper, when using ePRO, there is no way to know if a subject has provided an answer just to move on with the questionnaire

- Suddenly our lovely complete dataset is looking a bit too good to be true…

Three possible approaches

1. Requiring subjects to complete all items in all the instruments in the study;
2. Requiring subjects to complete all items used as key endpoints in the study, and allowing the subject to opt-out of responding to some, or all, other items (including sensitive items);
3. Allowing subjects to opt-out of responding to all items in the study.

Importance of Questionnaire Quality

- Careful consideration should be given to the quality of questionnaires being used in a study
- FDA PRO Guidance and the guidance for the Qualification Process for Drug Development Tools highlight the importance of selecting concepts and measures that are appropriate for the target populations and context of use
- Proper consideration should mitigate a subject's desire to skip questions

Recommendations

- Weigh up the importance of data in relation to its support of endpoints, versus the potential difficulty for subjects to answers questions
- Identify:
  - Items or questionnaires supporting primary or secondary endpoints
  - Items that may potentially be “unanswerable” or “sensitive”

Recommendations

- Expectations for subjects to provide answers should be explicit in the informed consent form
- The approach taken will help in the development of an appropriate statistical analysis plan

Active Skipping

- Regardless of the approach taken, if some form of opt-out is allowed, the electronic system should be programmed such that subjects actively have to confirm their intent to skip an item

ePRO Consortium best practice skip wording

- In cases where there is a pop-up heading, the heading would read – followed by the message text:
  - **“No response selected”**
  - **“Do you want to continue without providing a response?” – Yes/No**
- In cases where no pop-up heading is used, the message text would read:
  - **“No response selected. Do you want to continue without providing a response?” – Yes/No**

ePRO Consortium best practice skip wording in practice

Jurisdictions/IRBs

- It must be recognized that certain countries, jurisdictions, or institutional review boards may not allow researchers to require study subjects to respond to questionnaire items they do not want to complete
- Hence requiring completion may not be an option

PRO Consortium Experience

- Through the electronic implementation process of the instruments under development by the Patient-Reported Outcome (PRO) Consortium, FDA communicated their preference that subjects in clinical trials be allowed to skip items and provide confirmation that they intended to skip the item
- Sponsors will still decide on a case-by-case basis whether or not to allow subjects to skip items in their studies

But how much of an issue is skipping really?

PRO Consortium: Evidence from Three Quantitative Pilot Studies

- Purpose of the studies: to collect data with draft measures to assess item performance and initial measurement properties
- Active skipping at the item level is allowed for PRO Consortium-developed measures in these studies
  - Participant must indicate skip was intentional
  - Excessive skipping is a potential indicator of a problematic item
- Studies have been completed in asthma, depression, and non-small cell lung cancer to date

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)

- 7-day recall period
- Completed on a tablet in clinic
- 7 items
- N=152
- 0 missing items
- 0 participants skipped items

Symptoms of Major Depressive Disorder Scale (SMDDS)

- 7 day recall period
- Web-based measure completed from participant's home
- **Wave 1** (N=315): 36 items
  - 10 items total were skipped by 10 separate participants
  - 9 items skipped once, one item skipped twice
- 7 of the 10 skipped were removed from the SMDDS due to redundancy or other issues not related to missing data concerns

Symptoms of Major Depressive Disorder Scale (SMDDS)

- Item reduction and cognitive interviews took place to refine the SMDDS before Wave 2 of data collection
- **Wave 2** (N=207): 16 items
  - 2 items total were skipped by 3 separate participants
  - 1 item skipped once, one item skipped twice
- No further changes to items after Wave 2

Asthma Daily Symptom Diary (ADSD)

- 8 items completed twice daily, 12 hour recall
- Handheld smartphone completed from participant's home over 10 days
- N=212
- Missing data were analyzed at the subject and item level

ADSD Missing data by subject

- Quality of completion: number of missing items on the ADSD per subject by study Day for the total sample (n=212)
- Morning diary
  - 10 subjects skipped 1 item on different days
  - 3 subjects skipped 2 items on different days
- Evening diary
  - 13 subjects skipped 1 item on different days
- Over 98% of participants completed all ADSD items at each completion window

ADSD Missing data per item for total sample (n=212)

	Total	
	Morn n (%) *	Eve n (%) *
Item 1	-	1 (0.5%)
Item 2	3 (1.4%)	-
Item 3	2 (1.0%)	2 (1.0%)
Item 4	1 (0.5%)	4 (1.9%)
Item 5	3 (1.4%)	1 (0.5%)
Item 6	2 (1.0%)	-
Item 7	4 (1.9%)	4 (1.9%)
Item 8	1 (0.5%)	1 (0.5%)

*Percentage of total number of participants completing the ADSD Morning and ADSD Evening diaries, respectively

- Table represents number of participants who skipped that item between day 3 and 10
- Item 4 “chest pressure” and item 7 “cough” were skipped more than other items
- Item 4 “chest pressure” removed due to redundancy with item 5 “chest tightness” and poor performance

Conclusions

1. While ePRO is powerful tool to ensure complete PRO data collection, it can lead to inaccurate data if subjects are unwilling or unable to answer
2. Allowing skipping of items may be appropriate depending on the study, but any skip must be "active"
3. A well designed instrument, that addresses relevant concepts for patients and is appropriate for the context of use, is likely to result in high compliance rates ensuring that the issue of allowing skips is not one of significant concern

Useful References

- O'Donohoe, P., Lundy, J., Gnanasakthy, A., Greene, A. Considerations for Requiring Subjects to Provide a Response to Electronic Patient-Reported Outcome Instruments. Therapeutic Innovation & Regulatory Science, November 2015, 49: 792-796
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Questions?

http://c-path.org/programs/epro

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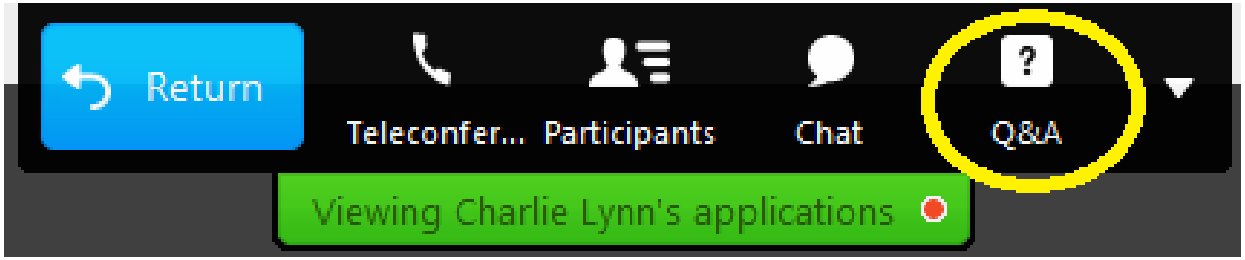

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