ALLOWING RESPONDENTS TO SKIP ITEMS DURING ELECTRONIC COLLECTION OF PATIENT-REPORTED OUTCOME (PRO) DATA: DOES IT MATTER?

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INTRODUCTION

Complete and accurate data is the cornerstone of any clinical trial – without it, it is impossible to make sound inferences about the safety and effectiveness of an experimental treatment. Data on the patient's experience of a disease/condition and its treatment in clinical trials has grown in importance over the years, with an industry focus on the development of high quality clinical outcome assessment (COA) tools and, in particular, patient-reported outcome (PRO) measures.

The traditional technology for capturing PRO data has been paper. However, with the recognition of the limitations of paper-based data collection and the increased availability of reliable and relatively inexpensive hardware, the electronic collection of these data (i.e., ePRO) is rapidly becoming the mainstream method of data capture in clinical trials.

These new electronic tools have brought a host of benefits to study teams (Coons et al. 2015). One of the most unique opportunities presented by electronic data capture is the possibility to minimize missing data by requiring subjects to respond to all items in order to complete the measure. Such an approach seems to offer the chance of complete PRO data at the close of the study. However, implementation of such data entry rules can have unintended consequences. For example:

- Subjects confronted with inapplicable items they cannot answer (e.g., questions about work for those who are unemployed) or sensitive items they are unwilling to answer (e.g., questions about sexual health) may lead to subjects providing inaccurate or unreliable data just to move through the measure.
- In the worst-case scenario, a subject might even refuse to continue or even drop out of the study altogether because he or she does not want to answer particular items.
- Ironically, unlike paper where an item can be left unanswered or additional information written in the margins, with ePRO data collection there is no way to know if a subject has provided a random answer just to move on with the questionnaire and thus a complete dataset might not be as accurate as first thought.

OBJECTIVES

The purpose of this poster is to share considerations around requiring subjects to respond to items in a measure and provide data on the prevalence of skipped items in three therapeutic areas and ePRO modes using data collected in three quantitative pilot studies conducted by the Patient-Reported Outcome (PRO) Consortium in collaboration with member firms of the ePRO Consortium.

- Identify the possible risks of requiring subjects to complete all ePRO items
- Identify 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 measures

METHODS

O'Donohoe et al. (2015) identified three possible scenarios for dealing with skipping of items in a study collecting PRO data electronically:

1. Require subjects to complete all items in all measures in the study;
2. Require subjects to complete all items used to derive key endpoints in the study, and allowing the subject to opt-out of responding to some, or all, other items (including sensitive items);
3. Allow subjects to opt-out of responding to any or all items in the study.

Three observational quantitative pilot studies conducted in the United States (US) by working groups within the PRO Consortium allowed participants to skip any item on the measures being evaluated.

- The PRO Consortium's rationale in consultation with the US Food and Drug Administration was that missing data could indicate a problematic item and would provide useful information when evaluating the measurement properties of the items in each measure.
- Use of an "active skip" (see Box 1) ensured that participants indicated they were intending to skip an item, and that it was not missed accidentally.

Data on skipped items were analyzed from the following three measures:

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

- 7 items
- 7-day recall period
- Completed on a tablet in clinic on Day 1 and Day 8

Symptoms of Major Depressive Disorder Scale (SMDDS)

- 36 items in Wave 1 reduced to 16 items in Wave 2
- 7-day recall period
- Completed remotely (e.g., at home) via a web-based data entry portal on Day 1 in Wave 1 and Day 1 and Day 8 in Wave 2

Asthma Daily Symptom Diary (ADSD)

- 8 items completed twice daily (i.e., morning and evening)
- 12-hour recall
- Completed remotely on a handheld device (i.e., smartphone) over 10 days

All three studies were approved by central or local institutional review boards (IRBs) and participants provided informed consent to participate in the studies.

Box 1. ePRO Consortium Best Practice Recommendations for Item Skip Wording

In cases where there is a pop-up heading, the heading would read "No response selected" followed by the message text:

- "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

RESULTS

Table 1 includes the demographic characteristics of the participants in the three quantitative pilot studies.

Table 1. Demographic Characteristics

Variable	DEPRESSION Wave 1 N=315	DEPRESSION Wave 2 N=207	NSCLC N=152	ASTHMA N=219
Age, years				
Mean (SD)	44.4 (13.8)	45.3 (14.0)	64.3 (9.8)	25.8 (17.0)
Range	18-65	19-66	41-85	12-74
Gender, n (%)				
Female	225 (71.4)	152 (73.4)	86 (56.6)	120 (54.8)
Male	90 (28.6)	55 (26.6)	66 (43.4)	99 (45.2)
Race, n (%)				
White	255 (81.0)	169 (81.6)	132 (86.8)	98 (44.7)
Black or African American	41 (13.0)	25 (12.1)	12 (7.9)	65 (29.7)
American Indian or Alaskan Native	1 (0.3)	1 (0.5)	0 (0.0)	1 (.5)
Asian/Native Hawaiian / Pacific Islander	5 (1.6)	5 (2.4)	3 (2.0)	11 (5.0)
Other	11 (3.5)	6 (2.9)	5 (3.3)	44 (20.1)
Missing	2 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)
Highest level of education completed, n (%)				Adults (n=89)
Less than high school	21 (6.7)	11 (5.3)	24 (15.8)	10 (11.2)
High school graduate	69 (21.9)	42 (20.3)	55 (36.2)	20 (22.5)
Some college	108 (34.3)	78 (37.7)	39 (25.7)	20 (22.5)
College graduate	64 (20.3)	40 (19.3)	25 (16.4)	19 (21.3)
Graduate or professional school	53 (16.8)	36 (17.4)	9 (5.9)	19 (21.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
School grade, n (%)	N/A*	N/A*	N/A*	Adolescents (n=130)
6th grade				15 (11.5)
7th grade				26 (20.0)
8th grade				31 (23.8)
9th grade				14 (10.8)
10th grade				14 (10.8)
11th grade				15 (11.5)
12th grade				10 (7.7)
I have graduated				3 (2.3)
Missing data				2 (1.5)

*N/A This variable was not collected.

NSCLC-SAQ

- 152 participants with non-small cell lung cancer were enrolled to complete the questionnaire at two clinic visits roughly 7 days apart.
  - There were no missing items and no participants skipped items.

SMDDS

There were two waves of testing of the *SMDDS*.

- In Wave 1, 315 participants with major depressive disorder were enrolled to complete the 36-item version once.
  - A total of 10 items were skipped: 9 items skipped by one participant each (one of whom skipped two items); 1 item skipped by 2 other participants.
  - A total of 10 participants skipped items: 9 participants skipped 1 item each; one participant skipped 2 other items
- Following Wave 1 the *SMDDS* was reduced to 16 items
- In Wave 2, 207 participants were enrolled to complete the 16-item *SMDDS* twice, roughly 7 days apart.
  - A total of two items were skipped: 1 item skipped by one participant; 1 item skipped by two participants.
  - Three participants skipped 1 item each.

ADSD

219 adolescents and adults with asthma were enrolled to complete the *ADSD* twice daily on a provisioned smartphone over 10 days. Missing data were analyzed at the form and item level for Day 3 to Day 10, as the first two days were considering training days. Only participants with at least one response on the *ADSD* Morning or Evening Diary were included in the analysis.

As shown in Table 2:

- Morning Diary
  - Eight participants skipped 1 item only on different days
  - One participant skipped 1 item on different days (Item 3 and Item 7)
  - Three participants skipped 2 items within a diary on different days
- Evening Diary
  - 11 participants skipped 1 item only on different days
  - One participant skipped 1 item on different days (Item 3 and Item 7)
- Two participants skipped Morning and Evening Diary items on different days
- There was no pattern over time (tendency to skip more items later in the study)
- Out of all the participants who completed their *ADSD* when it was due, over 98% of them completed all *ADSD* items

Table 2. Quality of completion: number of missing items on the *ADSD* per subject by study day for the total sample (n=212)

	Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Total	
	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n (%)	Morn n (%)	Eve n(%)
0	197 (99.5%)	196 (99.0%)	191 (99.0%)	202 (99.0%)	199 (99.0%)	195 (99.0%)	192 (98.0%)	207 (99.5%)	193 (99.0%)	204 (98.1%)	201 (100%)	202 (99.5%)	203 (100%)	193 (100%)	190 (99.0%)	182 (99.5%)	1,566 (99.2%)	1,581 (99.2%)
1	-	2 (1.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	4 (1.9%)	-	1 (0.5%)	-	-	2 (1.0%)	1 (0.5%)	10 (0.6%)	13 (0.8%)
2	1 (0.5%)	-	1 (0.5%)	-	-	-	1 (0.5%)	-	-	-	-	-	-	-	-	-	3 (0.2%)	-

A few differences were noted between the study *designs* that could have contributed to the difference in missing data observed.

- The *NSCLC-SAQ* was completed in a supervised clinic setting, while the *SMDDS* and *ADSD* were completed remotely, so supervision may have helped prevent missing *NSCLC-SAQ* data.
- In addition, there were only two opportunities to complete the *NSCLC-SAQ* and *SMDDS*, while the *ADSD* was completed twice daily over 10 days, which provided many more opportunities for items to be skipped.
- However, for both the *ADSD* study and Wave 2 of the *SMDDS* study, which had comparable sample sizes, the maximum number of items skipped by an individual participant within a given assessment time point was 2 items.

Table 3. *ADSD* Missing Data at the Item Level between Day 3 and 10

	Total	
	Morning n (%) *	Evening 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 3 represents number of participants who skipped each item between Day 3 and Day 10, broken into Morning and Evening Diary assessments.

- Item 4 (chest pressure) and Item 7 (cough) were skipped more than other items

Importance of Questionnaire Quality

- Careful consideration should be given to the quality of questionnaires or measures being used in a study.
- United States Food and Drug Administration guidance documents on the use of PRO measures to support product labeling claims (2009) and on the qualification process for drug development tools (2014) highlight the importance of selecting concepts and measures that are appropriate for the target populations and context of use.
- Proper consideration should mitigate a respondent's desire to skip items.

CONCLUSIONS

- Requiring completion of items may reduce missing data but can result in questionable data if respondents randomly select a response to advance through the measure because they, for whatever reason, do not want to respond to the item. Careful implementation of skipping rules and the use of well-designed questionnaires assessing relevant and appropriate concepts for the context of use may reduce respondents' desire to skip items when allowed to do so.
- Data from three quantitative pilot studies demonstrated that participants' propensity to skip items is quite low. No items were skipped on the *NSCLC-SAQ*, while rates of item-level skipping ranged from 0.09% to 2% of possible completions on the *SMDDS* and *ADSD*, respectively. Missing data appeared to be at random and did not indicate problems with the items skipped.
- While skipping of items in well-designed measures appears to be of limited concern, it should be recognized that certain countries, jurisdictions, or IRBs may not allow researchers to require study subjects to respond to items they do not want to complete. Hence requiring completion may not be an option.
- When designing an ePRO solution, consideration should be made around the kinds of questions being asked, the quality of the measures being used, and the ultimate use of the data to identify the appropriate skipping strategy (if any) that should be taken in any particular case.

ACKNOWLEDGMENTS

Critical Path Institute and the PRO Consortium are supported, in part, by Critical Path Public-Private Partnerships Grant Number U18 FD005320 (effective 2015-2020) from the U.S. Food and Drug Administration. Additional support for the PRO Consortium comes from membership fees paid by members of the PRO Consortium (https://c-path.org/programs/pro-collaborators/). Support for the ePRO Consortium comes from membership fees paid by members of the ePRO Consortium (https://c-path.org/programs/epro/). The data used for the analyses described in this poster were collected in studies funded by the following PRO Consortium member firms: AbbVie, Allergan, AstraZeneca AB, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly and Company, EMD Serono, Genentech, Inc., GlaxoSmithKline, LLC, Janssen Global Services, LLC, Merck Sharp & Dohme Corp., Novartis Pharma AG, Pfizer, Inc., Sanofi, Sunovian Pharmaceuticals, Inc., and Takeda Pharmaceuticals International. The ePRO data collection for these studies was completed by ePRO Consortium member firms.

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ISPOR 20th Annual European Congress
Glasgow, Scotland
4-8 November 2017