Electronic Patient-Reported Outcome (ePRO) Consortium Webinars

COVID-19: Risk Assessment and Mitigation Strategies for the Collection of PRO Data through Clinical Sites - Lessons Learned

October 29, 2020

ePRO CONSORTIUM
CRITICAL PATH INSTITUTE

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RECORDING

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COVID-19: Risk Assessment and Mitigation Strategies for the Collection of PRO Data through Clinical Sites - Lessons Learned

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About Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and the U.S. Food and Drug Administration (FDA)
- An independent, non-profit organization
  - Dedicated to implementing FDA's Critical Path Initiative
  - Enables pre-competitive collaboration that includes regulatory input/expertise
- C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.

Funding Acknowledgments

- Critical Path Institute is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) and is 62% funded by FDA/HHS, totaling $14,448,917, and 38% percent funded by non-government sources, totaling $8,669,646. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.
- Support for the ePRO Consortium comes from membership fees paid by members of the ePRO Consortium (https://c-path.org/programs/epro/).
- Additional support for the Patient-Reported Outcome (PRO) Consortium comes from membership fees paid by members of the PRO Consortium (https://c-path.org/programs/proc/).

ePRO Consortium

- The ePRO Consortium was established by C-Path in 2011. 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.

PRO Consortium

- The PRO Consortium was formed in late 2008 by C-Path in cooperation with FDA's Center for Drug Evaluation and Research and the pharmaceutical industry, and formally launched in March 2009.
- The mission of the PRO Consortium is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification of PRO measures and other COAs that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.

Agenda

- Background
- Summary of Recommendations
- Lessons Learned
  - Janssen Global Services, LLC
  - GlaxoSmithKline
  - Clinical Ink
  - .assisTek
- Discussion

Background

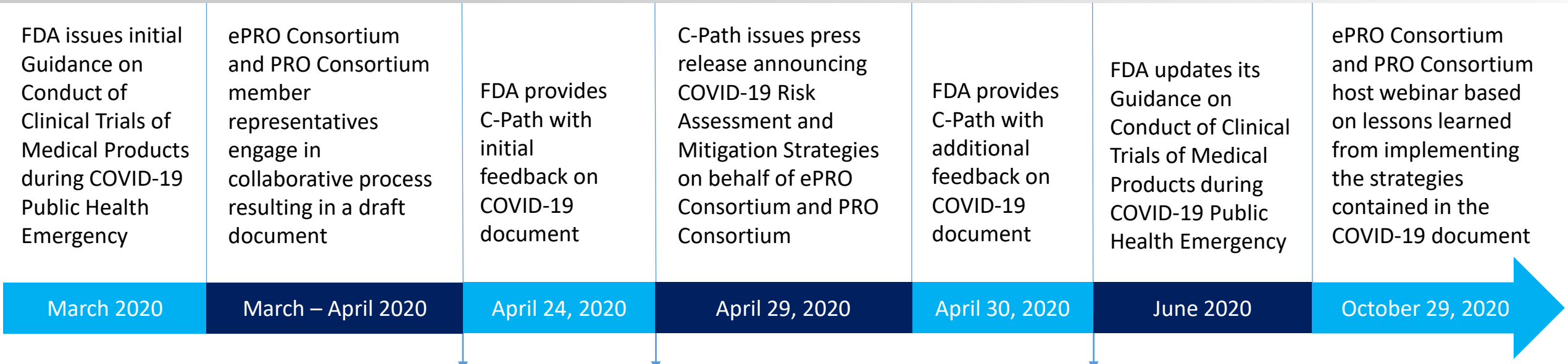
Presenter

Cindy Howry, MS
CEO
.assisTek

Background

- Members of the ePRO Consortium and PRO Consortium were invited to collaborate on a risk assessment and mitigation plan for clinical trials in response to the impact of COVID-19.
- Over a 4-week period in March-April 2020, member representatives participated in a series of teleconferences in which they engaged with others to provide suggestions and mitigation strategies for their firms.
- Resulted in the document titled “Coronavirus Disease 2019 (COVID-19): Risk Assessment and Mitigation Strategies for the Collection of Patient-Reported Outcome Data through Clinical Sites” available under Best Practices Documents at https://c-path.org/programs/eproc/

Timeline



April 10, 2020
Coronavirus Disease 2019 (COVID-19): Risk Assessment and Mitigation Strategies for the Collection of Patient-Reported Outcome Data through Clinical Sites posted to C-Path's website

April 28, 2020
Based on feedback from FDA and other stakeholders, C-Path updates v2.0 of COVID-19 document on website

June 5, 2020
Based on feedback from FDA and other stakeholders, C-Path updates v3.0 of COVID-19 document on website

Objective and Scope

- Issue:
  - Due to concerns with COVID-19, many patients are either unable or unwilling to travel to sites for scheduled visits or sites have had to close due to social distancing measures.
- Objective:
  - Provide a selection of risk analysis and mitigation strategies for consideration by sponsors and eCOA providers to facilitate the continued collection of PRO data in clinical trials.
- Scope
  - Provide document that focuses on the current challenges of capturing patient-reported outcome assessment data electronically (ePRO) originally intended to be collected in person at site visits.

Core Principles

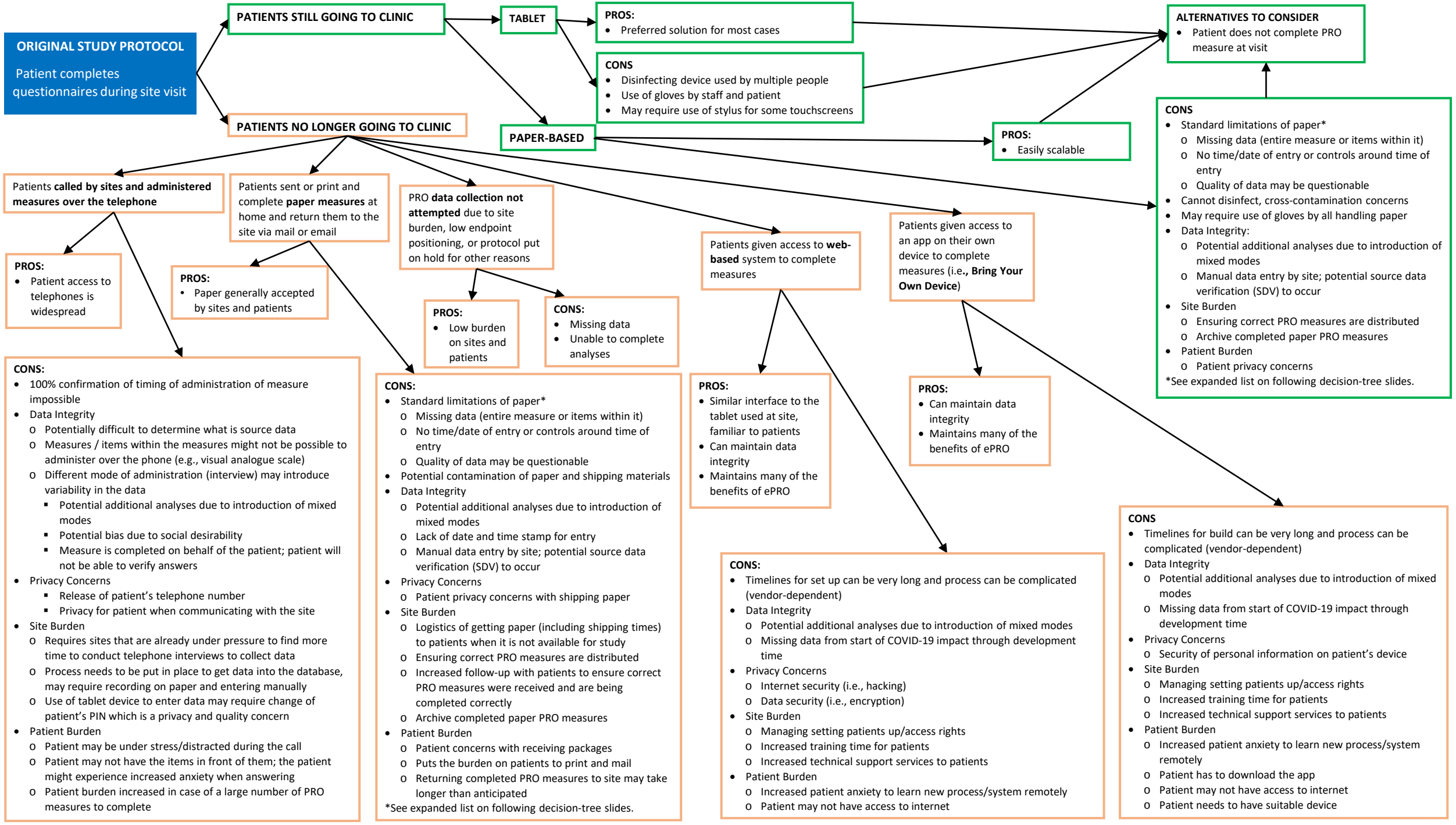
The following are considered core principles and should be kept at the forefront of the decision-making process by sponsors and eCOA vendors.

1. **Ensure Patient Safety**
   - Non-negotiable
   - To reduce risk of exposure, patients should visit clinics only if absolutely necessary for treatment reasons.
2. **Minimize Patient Burden**
3. **Ensure Transparency (i.e., changes to protocol and new processes are clearly documented)**
   - Non-negotiable
   - Transparency with respect to all aspects of changes to the protocol, new processes, and compliance with regulatory guidance and ethical body requirements.
4. **Minimize Site Burden**
   - To the extent possible, there should not be a significant increase in site burden associated with the alternative approaches to collection of clinical outcome assessment data.
5. **Maintain Data Integrity**
   - Integrity of data is of paramount importance; strategies should be employed to ensure data integrity to the greatest extent possible.

Summary of Recommendations

Presenter

Paul O'Donohoe, MSc
Scientific Lead, eCOA and Mobile Health, Medidata Solutions
Industry Vice Director, ePRO Consortium


ORIGINAL STUDY PROTOCOL
Patient completes questionnaires during site visit
PATIENTS STILL GOING TO CLINIC
TABLET
PROS:
Preferred solution for most cases
CONS
Disinfecting device used by multiple people
Use of gloves by staff and patient
May require use of stylus for some touchscreens
PAPER-BASED
PROS:
Easily scalable
CONS
Standard limitations of paper*
Missing data (entire measure or items within it)
No time/date of entry or controls around time of entry
Quality of data may be questionable
Cannot disinfect, cross-contamination concerns
May require use of gloves by all handling paper
Data Integrity:
Potential additional analyses due to introduction of mixed modes
Manual data entry by site; potential source data verification (SDV) to occur
Site Burden
Ensuring correct PRO measures are distributed
Archive completed paper PRO measures
Patient Burden
Patient privacy concerns
*See expanded list on following decision-tree slides.
ALTERNATIVES TO CONSIDER
Patient does not complete PRO measure at visit
PATIENTS NO LONGER GOING TO CLINIC
Patients called by sites and administered measures over the telephone
PROS:
Patient access to telephones is widespread
CONS:
100% confirmation of timing of administration of measure impossible
Data Integrity
Potentially difficult to determine what is source data
Measures / items within the measures might not be possible to administer over the phone (e.g., visual analogue scale)
Different mode of administration (interview) may introduce variability in the data
Potential additional analyses due to introduction of mixed modes
Potential bias due to social desirability
Measure is completed on behalf of the patient; patient will not be able to verify answers
Privacy Concerns
Release of patient's telephone number
Privacy for patient when communicating with the site
Site Burden
Requires sites that are already under pressure to find more time to conduct telephone interviews to collect data
Process needs to be put in place to get data into the database, may require recording on paper and entering manually
Use of tablet device to enter data may require change of patient's PIN which is a privacy and quality concern
Patient Burden
Patient may be under stress/distracted during the call
Patient may not have the items in front of them; the patient might experience increased anxiety when answering
Patient burden increased in case of a large number of PRO measures to complete
Patients sent or print and complete paper measures at home and return them to the site via mail or email
PROS:
Paper generally accepted by sites and patients
CONS:
Standard limitations of paper*
Missing data (entire measure or items within it)
No time/date of entry or controls around time of entry
Quality of data may be questionable
Potential contamination of paper and shipping materials
Data Integrity
Potential additional analyses due to introduction of mixed modes
Lack of date and time stamp for entry
Manual data entry by site; potential source data verification (SDV) to occur
Privacy Concerns
Patient privacy concerns with shipping paper
Site Burden
Logistics of getting paper (including shipping times) to patients when it is not available for study
Ensuring correct PRO measures are distributed
Increased follow-up with patients to ensure correct PRO measures were received and are being completed correctly
Archive completed paper PRO measures
Patient Burden
Patient concerns with receiving packages
Puts the burden on patients to print and mail
Returning completed PRO measures to site may take longer than anticipated
*See expanded list on following decision-tree slides.
PRO data collection not attempted due to site burden, low endpoint positioning, or protocol put on hold for other reasons
PROS:
Low burden on sites and patients
CONS:
Missing data
Unable to complete analyses
Patients given access to web-based system to complete measures
PROS:
Similar interface to the tablet used at site, familiar to patients
Can maintain data integrity
Maintains many of the benefits of ePRO
CONS:
Timelines for set up can be very long and process can be complicated (vendor-dependent)
Data Integrity
Potential additional analyses due to introduction of mixed modes
Missing data from start of COVID-19 impact through development time
Privacy Concerns
Internet security (i.e., hacking)
Data security (i.e., encryption)
Site Burden
Managing setting patients up/access rights
Increased training time for patients
Increased technical support services to patients
Patient Burden
Increased patient anxiety to learn new process/system remotely
Patient may not have access to internet
Patients given access to an app on their own device to complete measures (i.e., Bring Your Own Device)
PROS:
Can maintain data integrity
Maintains many of the benefits of ePRO
CONS
Timelines for build can be very long and process can be complicated (vendor-dependent)
Data Integrity
Potential additional analyses due to introduction of mixed modes
Missing data from start of COVID-19 impact through development time
Privacy Concerns
Security of personal information on patient's device
Site Burden
Managing setting patients up/access rights
Increased training time for patients
Increased technical support services to patients
Patient Burden
Increased patient anxiety to learn new process/system remotely
Patient has to download the app
Patient may not have access to internet
Patient needs to have suitable device

Patients No Longer Going to Clinic: Telephone and Paper-based Approaches OR Data Collection Not Attempted

PATIENTS NO LONGER GOING TO CLINIC

Patients **called by sites and administered measures over the telephone**

PROS:
- Patient access to telephones is widespread

CONS:
- 100% confirmation of timing of administration of measure impossible
- Data Integrity
  - Potentially difficult to determine what is source data
  - Measures / items within the measures might not be possible to administer over the phone (e.g., visual analogue scale)
  - Different mode of administration (interview) may introduce variability in the data
    - Potential additional analyses due to introduction of mixed modes
    - Potential bias due to social desirability
    - Measure is completed on behalf of the patient; patient will not be able to verify answers
- Privacy Concerns
  - Release of patient's telephone number
  - Privacy for patient when communicating with the site
- Site Burden
  - Requires sites that are already under pressure to find more time to conduct telephone interviews to collect data
  - Process needs to be put in place to get data into the database, may require recording on paper and entering manually
  - Use of tablet device to enter data may require change of patient's PIN which is a privacy and quality concern
- Patient Burden
  - Patient may be under stress/distracted during the call
  - Patient may not have the items in front of them; the patient might experience increased anxiety when answering
  - Patient burden increased in case of a large number of PRO measures to complete

Patients sent or print and complete **paper measures** at home and return them to the site via mail or email

PROS:
- Paper generally accepted by sites and patients

CONS:
- Standard limitations of paper*
  - Missing data (entire measure or items within it)
  - No time/date of entry or controls around time of entry
  - Quality of data may be questionable
- Potential contamination of paper and shipping materials
- Data Integrity
  - Potential additional analyses due to introduction of mixed modes
  - Lack of date and time stamp for entry
  - Manual data entry by site; potential source data verification (SDV) to occur
- Privacy Concerns
  - Patient privacy concerns with shipping paper
- Site Burden
  - Logistics of getting paper (including shipping times) to patients when it is not available for study
  - Ensuring correct PRO measures are distributed
  - Increased follow-up with patients to ensure correct PRO measures were received and are being completed correctly
  - Archive completed paper PRO measures
- Patient Burden
  - Patient concerns with receiving packages
  - Puts the burden on patients to print and mail
  - Returning completed PRO measures to site may take longer than anticipated

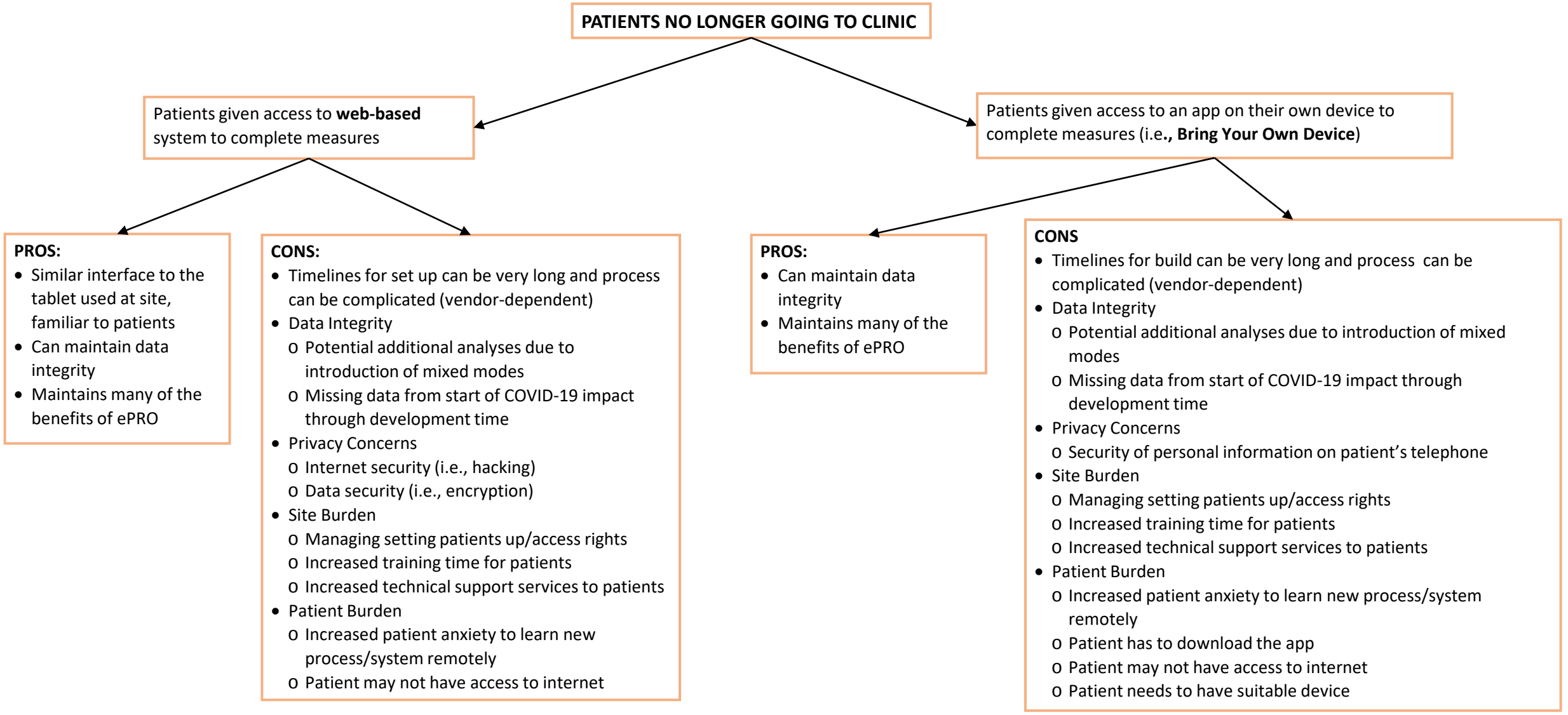
*See expanded list on following decision-tree slides.

PRO data collection not attempted due to site burden, low endpoint positioning, or protocol put on hold for other reasons

PROS:
- Low burden on sites and patients

CONS:
- Missing data
- Unable to complete analyses

Patients No Longer Going to Clinic: Web-based and BYOD Approaches



Patients Still Going to Clinic

- **Tablet** – have patients complete ePRO formats of measures
  - Increasingly mainstream and preferred method of capturing COAs
  - Possible disease transmission vector, but disinfection possible
- **Paper-based** - have patients complete paper formats of measures
  - Perceived as easily scalable
  - All the challenges of paper
  - Also possible transmission vector, disinfection challenging

Patients No Longer Going to Clinic

- **Telephone** – patients called by sites and answers collected over the phone
  - Most patients have phone access
  - Burden on sites, data security, introduces mixed modes and integrity challenges
- **Paper-based** – send patients paper measures
  - Perceived to be easily scalable, generally acceptable to patients
  - All the challenges of paper, logistics, data security, mixed modes, and integrity concerns
- **Data Collection Not Attempted or Study On Hold**
  - Poses a risk to the integrity of the trial

Patients No Longer Going to Clinic

- **Web-based Approach** – patients access a web-based format of measures
  - Maintains consistency and benefits of electronic data collection
  - Challenging to develop, introduces mixed modes, and can be burdensome on sites and patients to manage access
- **BYOD Approach** - patients access measures via an app on their own mobile device
  - Maintains consistency and benefits of electronic data collection
  - Challenging to develop, introduces mixed modes, and can be burdensome on sites and patients to manage access

Regulatory Considerations

- Ensuring patient safety is paramount
  - Consider each decision to modify trial procedures in terms of how it affects patient safety
  - Consult with investigators and IRBs
  - Inform patients of procedural changes
- COVID-19-related procedural changes must be documented in the Clinical Study Report, reported to IRB and updated in IND
  - Prospective reporting is preferred, but changes made immediately to ensure patient safety may be reported retrospectively:
    - Duration of those changes
    - Which patients were impacted
    - How those patients were impacted
- FDA has indicated that for a study-wide change in protocol conduct, protocol amendments that are necessary to prevent imminent hazards to patients can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND or IDE.

Considerations

- The right solutions will depend on the endpoint hierarchy, trial phase, and where in the course of the trial.
- The development timeline for some solutions may force certain decisions.
- Be mindful of what will work best for the specific patient population
- There is no perfect solution, all require the weighing of various pros and cons.

The full document is available on the ePRO Consortium's website under the "Best Practice Documents" category

(https://c-path.org/programs/eproc/)

Lessons Learned:
Janssen Global Services, LLC

Presenter

Patricia (Trish) Delong, MS
Manager, Patient-Reported Outcomes
Janssen Global Services, LLC

Janssen's Mitigation Approach

Engaged with Regulatory Consultant

Resulted in a memo that was distributed to the Janssen PRO Team and Janssen eCOA Operations Team

Yes

No

Site to contact the patient via phone to complete the PRO measures through an interview *(paper and electronic)*

Web-based back-up (additional time to setup) – *ePRO only*

Considerations for use:
- Only to be used during COVID-19 pandemic
- Study teams to choose one solution (if needed)
- Web-based back-up may not be available for every study
- Not all COAs can be completed remotely (example: joint assessments)

Result

Monitoring compliance across trials and portfolio level

- Are the solutions fit for long-term use?
- Do they meet the needs of sites and patients?
- Recommend contingency plans on all eCOA trials

Lessons Learned: GlaxoSmithKline

Presenter

Megan Turner
Senior Manager, COA Implementation
Value Evidence and Outcomes (VEO)
R&D Chief Medical Office
GlaxoSmithKline

Evaluation of alternate options

- Desire to avoid pen-and-paper back-up for eCOA trials
- Electronic back-up options available via eCOA providers
- Remote interviewer implementation of the PRO measures

Recommendations (assumes no telemedicine / home health)

Near-term Solutions (4 – 6 Weeks)

Primary Solution

If trial visits are being conducted on-site:

- Continue collecting PRO data on provided devices
- Clean devices between uses following provided guidance

If trial visits are being conducted off-site*:

- Reset participant PIN; site logs-in to device, then performs interview over-the-phone
  - Or access web back-up and complete interview
- Negates DCF/DCR completion; eCOA vendor report on PIN changes
- Site completes form indicating interview completed and files in patient record

Alternate Solution

If trial visits are being conducted on-site:

- If site will not accept devices on site, then print screenshots
- Participant completes PRO measures on paper
- Site enters data via Data Change Form (DCF) / Data Change Request (DCR)

If trial visits are being conducted off-site*:

- If site is not able to use the device, or web, then site prints screenshots and completes interview over-the-phone. *May consider external expert interview and DCF entry.*
- Site completes form indicating interview completed and files in patient record

***Mail a copy of printed screenshots or provide web link to screenshots to patients as a guide for the interview.**

Implementation Challenges

Local Regulations	Timing	Interviewer Considerations	Training
• External interview providers may not be able to perform interviews due to local regulations	• Set-up of external interview contracts, or eCOA web back-ups if not in place already • Programming of web back-ups	• External interview providers have broad, but not 100% coverage of study languages	• Site staff training on interview techniques • Educating participants if direct participant web entry back-up used

Lessons Learned

- More work to be done in terms of solid back-up options as the COVID-19 pandemic continues and looking beyond the pandemic
- Flexibility is key while keeping the safety of site staff and participants in mind and maintaining high quality data
- A strong partnership with open communication between functions to address site concerns is crucial
- Must have a plan for balancing missing data versus multiple formats of data collection

Lessons Learned: Clinical Ink

Presenter

Gena Gough, MBA, PMP
Senior Director, Outcomes Solutions
Clinical Ink

Tablet → BYOD Smartphone

- Originally onsite PRO measure completion on tablet at visits
- "Flipped the switch" to make PRO measures available on the same device used for the at-home diaries
- No re-programming
- No translation re-migration
- Same log-in and password
- Same site portal
- Copyright holder approved
- Download app and simple training
- Time to implement: 3 days (no contract updates)

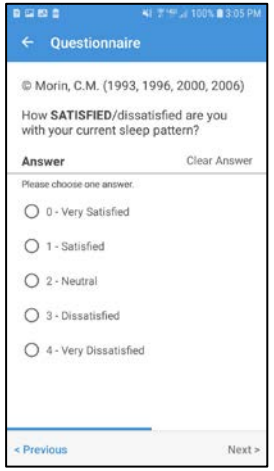
Samsung Galaxy Tab A 10"

4. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

Paper source

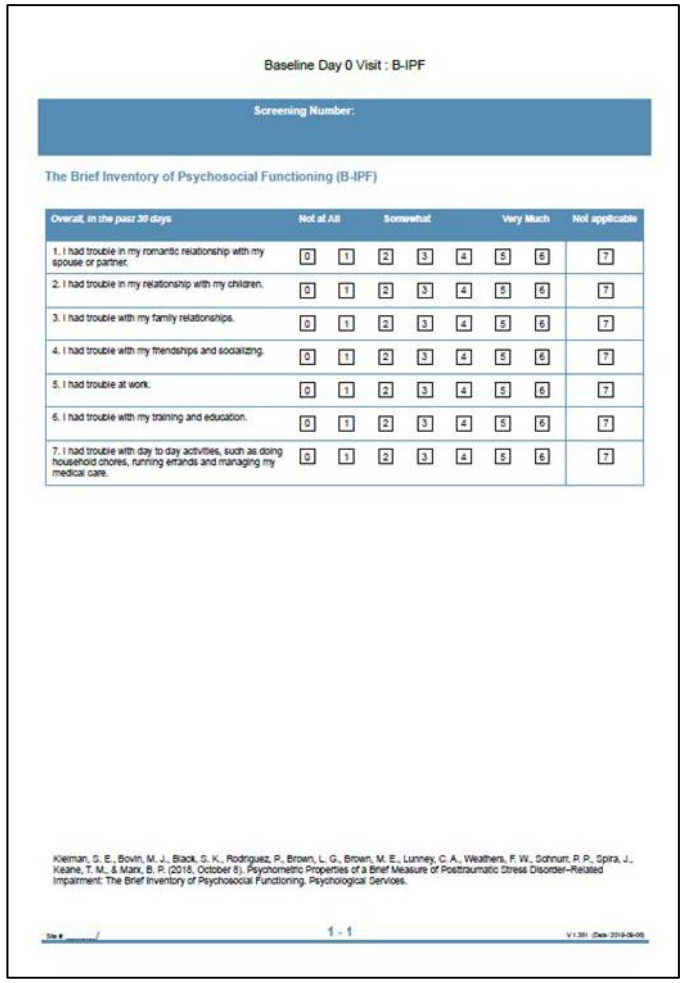
iOS iPhone XR



Samsung J3

Tablet → BYOD or Provisioned Smartphone

- Onsite PRO measure completion on eSource tablet at visits
- Re-developed for at home BYOD completion
- Developed detailed training and reference material
- Worked with copyright holder
- Initiated CD-UT for unique response scale to NRS
- New log-in and password
- New site portal
- Time to implement: 3 weeks, followed by 4 weeks for translation re-migration



Baseline Day 0 Visit : B-IPF

Screening Number:

The Brief Inventory of Psychosocial Functioning (B-IPF)

Overall, in the past 30 days	Not at All		Somewhat				Very Much	Not applicable
1. I had trouble in my romantic relationship with my spouse or partner.	0	1	2	3	4	5	6	7
2. I had trouble in my relationship with my children.	0	1	2	3	4	5	6	7
3. I had trouble with my family relationships.	0	1	2	3	4	5	6	7
4. I had trouble with my friendships and socializing.	0	1	2	3	4	5	6	7
5. I had trouble at work.	0	1	2	3	4	5	6	7
6. I had trouble with my training and education.	0	1	2	3	4	5	6	7
7. I had trouble with day to day activities, such as doing household chores, running errands and managing my medical care.	0	1	2	3	4	5	6	7

Kleiman, S. E., Bovin, M. J., Black, S. K., Rodriguez, P., Brown, L. G., Brown, M. E., Lunney, C. A., Weathers, F. W., Schnurr, P. P., Spira, J., Keane, T. M., & Marx, B. P. (2018, October 8). Psychometric Properties of a Brief Measure of Posttraumatic Stress Disorder–Related Impairment: The Brief Inventory of Psychosocial Functioning. Psychological Services.

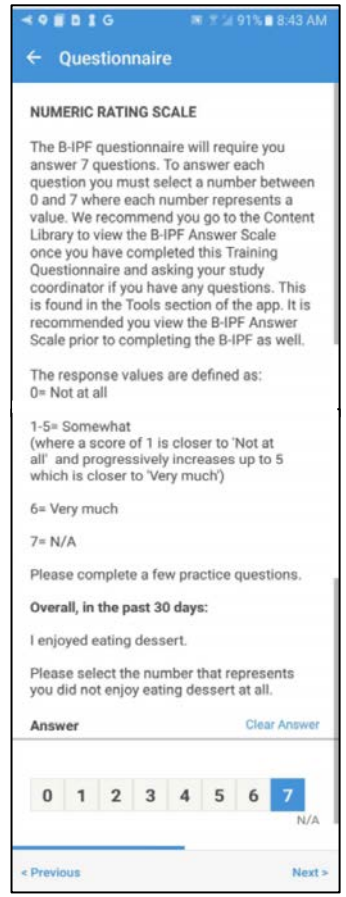
1 - 1

Dell Latitude 5290 2-in-1 tablet 12.3”

B-IPF

Overall, in the past 30 days:	Not at all	Somewhat					Very much	N/A
1. I had trouble in my romantic relationship with my spouse or partner.	0	1	2	3	4	5	6	7

Paper source



Questionnaire

NUMERIC RATING SCALE

The B-IPF questionnaire will require you answer 7 questions. To answer each question you must select a number between 0 and 7 where each number represents a value. We recommend you go to the Content Library to view the B-IPF Answer Scale once you have completed this Training Questionnaire and asking your study coordinator if you have any questions. This is found in the Tools section of the app. It is recommended you view the B-IPF Answer Scale prior to completing the B-IPF as well.

The response values are defined as:
0= Not at all

1-5= Somewhat
(where a score of 1 is closer to 'Not at all' and progressively increases up to 5 which is closer to 'Very much')

6= Very much

7= N/A

Please complete a few practice questions.

Overall, in the past 30 days:

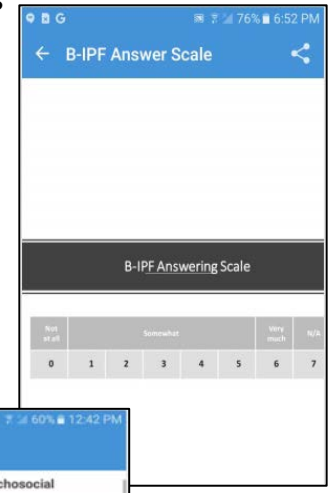
I enjoyed eating dessert.

Please select the number that represents you did not enjoy eating dessert at all.

Answer Clear Answer

0 1 2 3 4 5 6 7 N/A

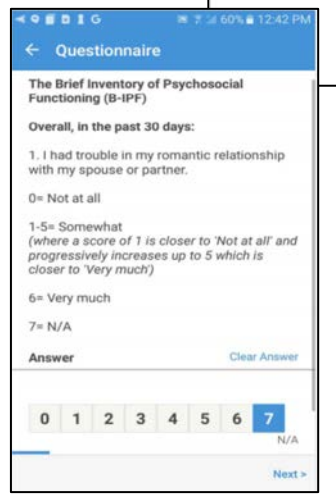
< Previous Next >



B-IPF Answer Scale

B-IPF Answering Scale

Samsung J3



Questionnaire

The Brief Inventory of Psychosocial Functioning (B-IPF)

Overall, in the past 30 days:

1. I had trouble in my romantic relationship with my spouse or partner.

0= Not at all

1-5= Somewhat
(where a score of 1 is closer to 'Not at all' and progressively increases up to 5 which is closer to 'Very much')

6= Very much

7= N/A

Answer Clear Answer

0 1 2 3 4 5 6 7 N/A

Next >

Key Takeaway: Support Clients with More Flexibility

- **Create one seamless platform purpose built to support all study modalities**
  - Single database
  - Single authoring tool: extend configuration beyond ePRO to ClinRO measures, PerfO measures, and Direct Data Capture (DDC)
  - Single view of all data: patient- and clinician-reported
- **Provide options for execution: deploy study based on *need* not technology**
  - ePRO: phone, tablet, web, or all
  - ClinRO measures and DDC: tablet, web, or both
  - BYOD, provisioned, or both for patients *and* sites
  - Virtual sites, physical sites, or both
- **Innovate and streamline the translation process**
  - Allow vendor to view screens side-by-side and update in real-time
  - Facilitate copyright holder review across multiple devices

Lessons Learned: .assisTek

Presenter

Cindy Howry, MS
CEO
.assisTek

Web-based Solution

Advantages

- Similar interface to the tablet used at site, familiar to patients
- Can maintain data integrity
- Maintains many of the benefits of ePRO device-based approach

- Originally, subjects completing site-based assessments at clinic prior to COVID-19
- Decision: Develop a web-based solution to allow data entry by subjects on web outside of clinic.
- Process
  - Site staff generate a code on .assisTek Portal.
  - Web-entry code sent to subject vial email (template) with link to web-based system
  - Subject enters entry code on web site and uses his/her same password to log in and authenticate.
  - Assessments presented to subject in same format as site-based tablet for selected visit (determined by site coordinator when generating the web-entry code).
- Implementation
  - Development, testing, and release took 3 weeks.
- Results
  - Site very happy with the ease of use

Panel Discussion and Questions

Electronic Patient-Reported Outcome (ePRO) Consortium Webinars

Thank you for attending this webinar!

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