

Panel Discussion #2:

Selection of Appropriate Recall Period

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Session Objectives

- Discuss some of the issues and considerations associated with selecting an appropriate “Recall Period”



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Choice of recall period for patient-reported outcome (PRO) measures: criteria for consideration

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- Discuss how the PRO Consortium Working Groups have addressed recall period in their development work

Session Participants



- Moderator
 - *Steven I. Blum, MBA*, Director, Health Economics, Forest Research Institute
- Presenter
 - *Sheri Fehnel, PhD*, Vice President of Patient-Reported Outcomes, RTI-Health Solutions
- Working Group Panelists
 - **Asthma:** *Linda Nelsen, MHS*, Senior Principal Scientist, Epidemiology, Merck Sharpe & Dohme Corporation
 - **Cognition:** *William Lenderking, PhD*, Senior Research Leader, United BioSource Corporation
 - **Depression:** *Nicholas Greco IV, MS, BCETS, CATSM*, Clinical Research Manager, Psychometrics and Assessment, AbbVie, Inc.
 - **Irritable Bowel Syndrome:** *Robyn T. Carson, MPH*, Associate Director, Health Economics & Outcomes Research, Forest Research Institute
- Audience Q&A

Choice of Recall Period for Patient-Reported Outcome (PRO)

Measures:

Criteria for Consideration

Sheri Fehnel, PhD

RTI-Health Solutions



Recall Period - Definition



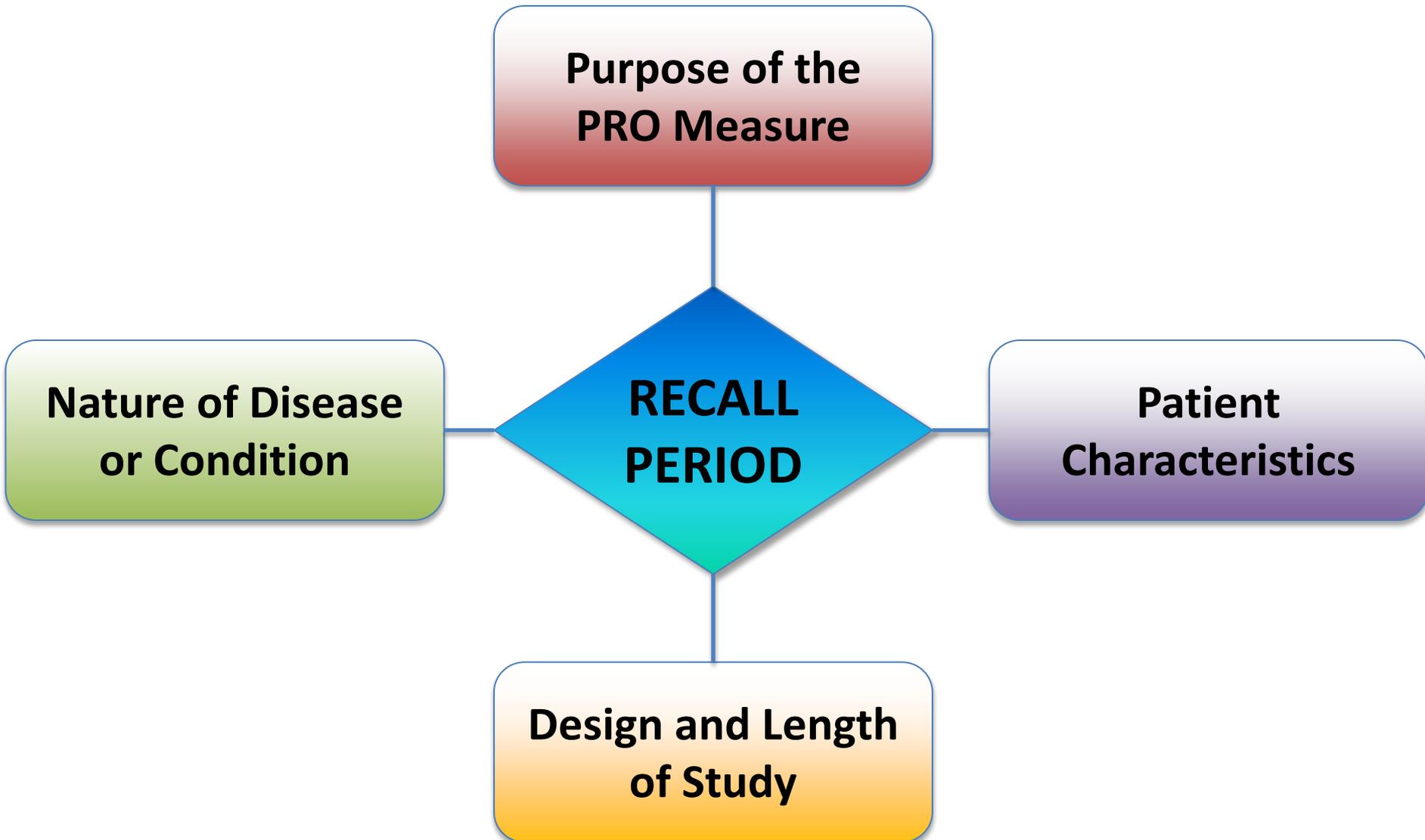
“The period of time patients are asked to consider in responding to a PRO item or question. Recall can be momentary (real time) or retrospective of varying lengths.”

Optimal Recall Period



- Reduces measurement error by facilitating accurate response but without placing undue burden on the patients
- *“...items with short recall periods or items that ask patients to describe their current or recent state are usually preferable.”*

Issues to Consider in Selecting Recall Periods



- Purpose of the PRO measure
 - What is the concept being addressed?
 - Symptom severity or frequency, functional status, global impression
 - How high are the stakes?
 - Support of labeling vs. publication strategy
- Nature of the disease or condition
 - Is the condition acute, episodic, or chronic?
 - What is the temporal pattern of symptom presentation?
 - To what extent and how rapidly do symptoms fluctuate?
 - How salient are symptom (or functional) fluctuations to patients?

Issues for Consideration (continued)



- Patient characteristics
 - Are patients very young or very old?
 - Does the condition under study (or common co-morbid conditions) impact cognitive function?
 - Could patients' health or environment/daily activities limit the practicality of frequent assessment?
- Design and length of the study
 - What is the duration of the clinical trial after randomization?
 - What is the schedule for clinic visits?
 - How many (other) PRO measures are being used?
 - When and how are these to be administered?

Consequences of Insufficiently Frequent Assessment



- Measurement error attributable to:
 - Recall bias
 - Response influenced by current state rather than assessment across the entire recall period
 - Recall errors
- Limitations in responsiveness and sensitivity to treatment differences
 - Note that reliability limitations will not make an ineffective treatment appear effective

Consequences of Too Frequent Assessment



- Needlessly burdening patients
- Missing data
 - Non-compliance due to fatigue or frustration
 - Inability to complete PRO measure at every relevant timepoint (e.g., based on environment, activities)
- Early withdrawal from study
- Inflated cost of data collection, management, and analysis

- Gather patient input
 - How quickly do changes that are salient to patients (in the concept to be measured) occur?
 - What recall period allows patients to be confident in their responses?
 - How often can patients reasonably complete the PRO measure?
 - How long would they be willing to complete the PRO measure at this frequency?

- Facilitate accurate recall and reporting
 - If fluctuations occur rapidly, focus assessment on a salient point in time (e.g., pain at its “worst”)
 - Make data recording/entry as quick and convenient as possible
- Balance the need for precision with practical considerations

Asthma Working Group

Linda Nelsen, MHS

Merck Sharpe & Dohme Corporation



Recall: Nature of Disease

- Asthma is a heterogeneous condition with
 - Acute episodic deterioration (exacerbations)
 - Background of chronic persistent airway inflammation
- Asthma symptoms are episodic and fluctuate within a day and between days
 - By time of day (often worse in early morning)
 - Based on triggers such as exercise, allergen exposure or upper respiratory infections
 - By season
- Perception and impact of symptoms vary based on day (interference with activities) or night (awakenings with asthma symptoms)

Maximize asthma control:

- Optimize Lung Function
 - Not well correlated with symptoms
- Minimize symptoms
 - Important from patient perspective
 - Guidelines emphasize control of daytime and night-time symptoms
- Prevent exacerbations
 - Change in patient's status requiring change in treatment
 - Range from change from usual range of day-to-day asthma variation to events requiring healthcare

Purpose: Link Measurement Concepts to Product Labeling Claims



- **Key symptom measurement concepts for labeling**
 - Daily symptom experience (daytime and night-time symptoms)
 - To calculate symptom-free days
 - Daily symptom severity (daytime and night-time symptoms)
 - To assess improvements/worsening in symptoms overtime
 - Night-time awakenings
 - To calculate frequency of night-time awakenings
 - Relief medication use (daytime and night-time)
 - To understand if changes in symptom frequency or severity are due to changes in relief medication use.
 - To assess relief-free days

Asthma: Qualitative Research

Supporting Twice Daily Reports



- Difference in timing (day vs. night) of individual or collective asthma symptoms
 - Described as periods when symptoms were “worse” or “more often” or “only” during a specific time during the day or night
 - “Usually when I wake up in the morning it’s worse, and when I’m starting to go to bed at night it’s worse. During the regular portion of the day, it’s less severe”
- No specific daily pattern but fluctuations related to general well-being
 - “The time of the day doesn’t’ seem to have anything to do with it, but when I’m more tired, ...that seems to have more of an effect on it.”
- Frequency of individual and collective symptoms varied from multiple times per day to a few days a month
 - “Oh, how often? Now, almost every day because – almost.”
 - “Uh, probably maybe three times every – three, four – four or five months. A few times every few months.”

Cognition Working Group

William Lenderking, PhD
United BioSource Corporation



Recall Period in MCI



- In MCI, memory itself is a central challenge. At what point do patients begin to lose insight?
 - Some evidence for heightened insight into early symptoms and functional deficits relative to caregivers and clinicians (Lenderking et al., 2011, CTAD)
 - Are there deficits in temporal perception as well?
- There are relatively few instruments which have been previously validated in patients with mild cognitive impairment, most are Clinical Assessments for patients with Alzheimer's
 - ADAS-Cog, Behav-AD, BPRS, BRSD, CDR, DS have no set recall period
 - Bristol ADL, Cohen-Mansfield Agitation Inventory, DAD have 2 week recall period
 - Cornell SDD, FACT-Cog have 1 week recall period
 - Blessed has 6 month recall period

Regarding time perception



- Rueda et al (2009) investigated the role of episodic memory impairment in temporal perception using a prospective verbal time estimation paradigm.
 - In Experiment 1, the verbal time estimates of 24 individuals with mild cognitive impairment (MCI) were comparable with those of age-matched controls at both short and long (i.e., >30 s) intervals.
 - The verbal time estimates of both older adult groups, however, deviated more significantly from true time when compared with younger adult controls.
 - In Experiment 2, 17 individuals with Alzheimer's disease (AD) demonstrated greater error and variability in their time estimates, but no disproportionate differences emerged between short- and long-duration estimates when compared with age-matched controls.
 - The findings did not support a noteworthy role for episodic memory impairment in temporal perception but rather elucidated a significant effect of normal aging, as well as a detrimental effect of AD on temporal perception. Rueda et al 2009. *Neuropsychology*, Vol 23(2), Mar 2009, 178-188

Recall Period



- At 1st Expert Panel (prior to affiliating with C-Path), experts recommended evaluating a 4 week recall period in the focus groups
- During the qualitative item reduction phase, the WG considered both a 1-week recall period and a 1-month recall period for selected items based on UBC recommendation
 - Decided to use a single recall period for simplicity given the subject population
 - Recall period was unspecified
- At 3rd Expert Panel meeting (Jan 2012), clinical experts cautioned against having an unspecified recall period due to variability in the way patients could respond, and this might be an issue for FDA

- Participants used a variety of different time frames when answering the questions, but most preferred the past few days or a week to a month
- The measure describes aspects of higher level functioning, which may not be tested on a daily basis.
- Participants used a variety of different time frames in order to identify the most recent example that illustrated their functioning
- The WG was comfortable with keeping the unspecified timeframe in spite of the experts' recommendations (two recommended 6 months to a year, one was OK with unspecified period)
 - Unspecified timeframe is close to present state recall
 - Assessing function requires assessing abilities which are present but may not be needed every day—thus no single specific recall period would be appropriate for all tasks

Depression Working Group

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Prior Instruments



- The Depression Working Group did an in-depth review of 13 existing Depression Scales
- Recall Periods of existing Depression instruments vary greatly:
 - Present time: Beck Depression Inventory-II (BDI-II), Hamilton Rating Scale for Depression (HAM-D)
 - Last few weeks: General Health Questionnaire
- 7-day recall period was the most utilized recall period (50% of instruments reviewed).
- Recall periods may also vary between different versions of the same instrument:
 - MADRS-Clinician: Uses no specific recall period
 - MADRS-Self-Report: 3 day recall period

Working Group Concerns



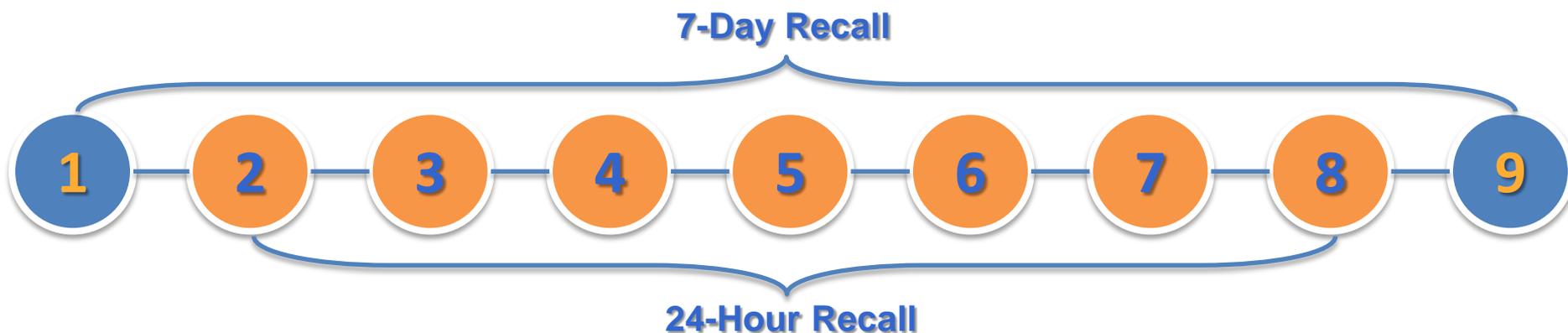
- Use of a daily diary would add another layer of complexity to already challenging clinical studies from an operational standpoint
 - High patient burden likely to increased patient drop-outs
- Due to the instrument length (number of concepts and items being measured), the practicality of a daily diary is not feasible
- While some symptoms may vary from day-to-day, patients do not seem to have difficulty using a longer recall period
 - Many patients expressed a preference for a weekly recall period
- Too short of a recall period may make it difficult for patients to perceive a change in their symptoms

- The working group explicitly explored recall periods during our cognitive interviews
- Examples of Probes:
 - For the symptoms that you experienced during the past 7 days, which ones did you have on a daily basis? For those that you don't experience daily, how often do you experience that symptom?
 - Were there any items in this section that would be easier for you to answer for the "last 24 hours" rather than the "last 7 days"? (Are there any symptoms that change within a 24-hour period?) Please identify those items.
 - If I had asked you to give me an answer for only the last 24 hours, with these same response options, what would it have been? (would you have answered any differently?)

- While patients indicated that there are some symptoms that vary from day-to-day, most did not have a problem with – and preferred the weekly recall period
 - **CT03-3054:** *I'm thinking you know the way you have got it written out, a week is good*
 - **CT03-3052:** *I think seven days would be like a fair, a good thing you know*
 - **CT03-3052:** *I don't know I think a week is a fair amount. I think from day-to-day you're not getting, I would think, enough information. So at least seven days sort of shows how we live you know*
 - **IL08-8053:** *No, I think the weekly basis was pretty clear.*
 - **IL08-8054:** *Seven days is good for remembering symptoms. Anger, confusion, sleepiness, sleeplessness, frustration.*

Future Evaluation

- The Depression Working Group plans to assess daily versus weekly recall in our upcoming pilot quantitative study
 - The proposed study will use longitudinal web-based survey data collection with samples of respondents drawn from existing panels of patients with major depressive disorder.
 - The main study period is 9 days. On days 1 and 9, all subjects will complete the 7-Day (retrospective) SMDDS, which asks about their symptom experience over the past 7 days. Subjects will also complete the 24-Hour SMDDS during days 2 through 8 of the study period.



- For each item, the relationship between the average of the repeated daily assessments of depression symptoms (of 7 days) and 7-day retrospective assessment will be assessed.
 - Several analyses will be performed including evaluating the correlation between the two measurements and assessing the difference between the two measurements.
 - In addition, regression analyses will be conducted to include participant demographic characteristics, participant health status as covariates.
- Findings from this analysis will be used to support the final selection of recall period for the measure along with other data

Irritable Bowel Syndrome (IBS) Working Group

Robyn T. Carson, MPH
Forest Research Institute, Inc.



Recall Period: Historical Perspective in IBS



| Drug and Indication | Primary Endpoint | Questions Used to Assess Efficacy | Recall Period |
|----------------------|---|--|---|
| Alosetron - IBS-D | Adequate relief | In the past 7 days, have you had adequate relief of your IBS pain or discomfort? | 7 days |
| Tegaserod - IBS-C | Satisfactory relief | Did you have satisfactory relief of your overall IBS symptoms during the last week? Did you have satisfactory relief of your abdominal discomfort or pain during the last week? | Last week |
| Tegaserod - IBS-C | Subject Global Assessment of Relief (SGA) | Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week? | The last week to before entering the trial (exact recall period variable dependent on trial length) |
| Lubiprostone - IBS-C | Modified version of the SGA | How would you rate your relief of your IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the trial? | The past week to before entering the trial (exact recall period variable dependent on trial length) |

Source: Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment, May 2012, FDA.

Provisional Endpoints and Trial Design for IBS Clinical Trials



- “Sponsors should choose a format for daily sign or symptom assessment (e.g., interactive voice response or personal digital assistant) so that patients can evaluate their IBS signs or symptoms **on a daily basis** throughout the trial.”

| Indication | Primary Endpoints | Entry Criteria | Responder Definition |
|------------|---|---|--|
| IBS-C | Abdominal Pain Intensity <i>(worst abdominal pain in the past 24 hours)...</i> ...AND Stool Frequency <i>(number of complete spontaneous bowel movements)</i> | Weekly average of worst pain score of ≥ 3.0 on a 0-10 point scale... ...AND < 3 CSBMs per week | Decrease of at least 30% compared with baseline... ...AND an Increase of 1 or more CSBM per week compared with baseline |
| IBS-D | Abdominal Pain Intensity <i>(worst abdominal pain in the past 24 hours)...</i> ...AND Stool Consistency <i>(stool form type as measured by the Bristol Stool Form Scale)</i> | Weekly average of worst pain score of ≥ 3.0 on a 0-10 point scale... ...AND ≥ 2 days/week with at least one stool that has a consistency of Type 6 or Type 7 | <u>Weekly or Daily</u> : decrease of at least 30% compared with baseline... <u>Weekly</u> : ...AND decrease at least 50% in # days/week with ≥ 1 stool that has a consistency of Type 6 or Type 7 compared with baseline. <u>Daily</u> : ...AND a patient whose stool consistency is less than Type 5 for all bowel movements on that day or no bowel movement. |

IBS WG – Recall Period: Results from Qualitative Research



- Recall period is not one size fits all...across sub-types or symptoms
- Differences across IBS sub-types:
 - Frequent, recurrent bowel movements (BMs) (IBS-D) vs. low frequency of BMs (IBS-C)
 - IBS-D participants reported that real-time data capture throughout the day would be helpful in improving accuracy of data reporting for the bowel symptoms
 - IBS-C patients reported that they could easily remember the number of bowel movements they had over the past 24 hours; however, over the course of a clinical trial, this bowel frequency should improve (for at least part of the population) and real-time data capture could assist in accurate recall.
 - The majority of participants reported that they could comply with real-time data capture

IBS WG – Recall Period: Results from Qualitative Research



- Differences across types of symptoms
 - Abdominal symptoms (24 hr) vs. BM frequency (event-driven)
 - Characteristics of BMs – per bowel movement
 - Stool consistency, straining, completeness (IBS-C, IBS-M)
 - Stool consistency, urgency (IBS-D, IBS-M)
- ePRO migration considerations:
 - Allowing BM reporting during end of day diary, in addition to event-driven reporting
 - Appropriate time window for missed BMs and missed diaries