

BEST PRACTICES FOR IMPLEMENTATION AND ANALYSIS OF PAIN SCALE PATIENT REPORTED OUTCOMES IN CLINICAL TRIALS

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Outline

- During this presentation we will provide some insight on the use of pain scale Patient Reported Outcomes:
 - Introduction
 - Variables Measured
 - Derived Variables
 - Imputation Techniques
 - Analysis Techniques
 - Concluding Remarks
 - References Cited

Introduction

- From the FDA Guidance on Patient-Reported Outcomes (PRO): A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's response by a physician or anyone else).
- PRO variables are commonly utilized in acute and chronic pain studies.
- There is variation in the question 'prompt' in practice.

Common Acute (**A**) and Chronic (**C**) Pain PROs: Instruments applied for assessing Pain

- Pain Intensity (PI): VAS – (A & C)
- PI: Categorical – (A & C)
- PI: NPRS – (A & C)
- Pain Relief (PR) – (A only)
- Global Assessment of Study Medication – (A & C)
- Quality of Analgesia – (A & C)
- Patient Global Impression of Change (PGIC) – (A & C)
- Time to Perceptible (PPR) and Meaningful Pain Relief (MPR) – (A only)
- Brief Pain Inventory (BPI) – (A & C)
- SF QOL Questionnaires – (C only)
- WOMAC Osteoarthritis Index – (C only)
- McGill Pain Questionnaire – (A & C)

Pain Intensity (PI) - Visual Analogy Scale (VAS)

- Prompt:
 - How severe is your pain (either at rest or after aggravated movement [cough])?
- Response:
 - Pain Intensity will be measured on a horizontal 100-mm VAS scale labeled: No Pain (0 mm) as the left anchor and Worst Pain Imaginable (100 mm) as the right anchor. The patient will draw a vertical mark on the line to indicate his pain intensity.

PI – Categorical

- Prompt:
 - How severe is your pain (either at rest or after aggravated movement [cough])?
- Response:
 - Scored on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe)

PI - Numerical Pain Rating Scale (NPRS)

- Prompt:
 - How severe is your pain (either at rest or after aggravated movement [cough])?
- Response:
 - Scored on an 11-point numerical scale (0 = no pain and 10 = worst pain)

Pain Relief (PR)

- Prompt:
 - Compared to the time right before you took the study medication, rate the amount of pain relief you feel right now?
- Response:
 - Pain Relief category is recorded as:
 - None
 - A Little Relief
 - Some Relief
 - A Lot of Relief
 - Complete Relief

Global Assessment of Study Medication

- Prompt:
 - How would you rate the study medication you received during the past week?
- Response:
 - Global Assessment category is recorded as:
 - Poor
 - Fair
 - Good
 - Very Good
 - Excellent



Quality of Analgesia

- Prompt:
 - How would you rate the quality of your pain relief at this time?
- Response:
 - Quality of Analgesia category is recorded as:
 - Poor
 - Fair
 - Good
 - Very Good
 - Excellent

Patient Global Impression of Change (PGIC)

- Prompt:
 - Rate your overall status since the beginning of treatment?
- Response:
 - Patient Global Impression category is recorded as:
 - Very Much Improved
 - Much Improved
 - Minimally Improved
 - No Change
 - Minimally Worse
 - Much Worse
 - Very Much Worse

Time to Perceptible (PPR) and Meaningful Pain Relief (MPR)

- Prompt:
 - Patient does not provide a verbal assessment. Assessed after the first dose of study medication.
- Calculated using a two stopwatch method
 - Stop first stopwatch when subject experiences first perceptible pain relief.
 - Stop second stopwatch when subject experiences meaningful pain relief.

Brief Pain Inventory (BPI) - Short Form

- Consists of 9 questions (last question has 7 parts). No overall score is usually calculated.
- The questionnaire assesses the following:
 - Location of pain
 - Severity of pain (worst, least, average, right now)
 - Pain medications being taken
 - Amount of pain relief
 - Impact of pain on daily functions

Short Form (SF) QOL Questionnaires

- Multipurpose surveys that measure 8 domains of health (subscales) and yields two summary measures:
 - Vitality
 - Physical Functioning
 - Bodily Pain
 - General Health Perceptions
 - Physical Role Functioning
 - Emotional Role functioning
 - Social Role Functioning
 - Mental Health
 - Physical Component Summary (PCS)
 - Mental Component Summary (MCS)
- SF-36 and SF-12 are most common in clinical trials.
- Standard (4-week recall) and Acute (1-week recall) formats.
- Each scale transformed into 0-100 scale (higher scores indicate better health or functioning).

WOMAC Osteoarthritis Index

- Designed for patients with hip and/or knee osteoarthritis.
- Questionnaire contains 24 questions that are used to create 3 subscales and an overall composite index:
 - Pain
 - Stiffness
 - Physical Function
 - Total Score
- Lower scores correspond to better health or functioning.

McGill Pain Questionnaire

- Used in studies where patients are expected to experience “significant” pain.
- Questionnaire has 3 sections:
 - What does your pain feel like?
 - How does your pain change with time?
 - How strong is your pain?
- Total score ranges from 0 to 78 with higher scores indicating greater pain.

Derived Variables for Analysis

- Analysis variables are often derived from the various instruments to assess patient reported pain.
 - Average Pain Intensity (mostly C) – (mostly C)
 - Response to Treatment – (mostly C)
 - Pain Intensity Difference (PID) – (A & C)
 - Summed PID (SPID) – (A only)
 - Summed PI (SPI) – (A only)
 - Pain Relief and PID (PRID) – (A only)
 - Summed PRID (SPRID) – (A only)
 - Total Pain Relief (TOTPAR) – (A only)
 - Time to Perceptible Pain Relief (PPR) and Meaningful Pain Relief (MPR) – (A only)
 - Time to Onset of Analgesia – (A only)

Average Pain Intensity

- Some studies capture Pain Intensity values daily in a diary and weekly pain scores need to be calculated.
- These weekly scores are often calculated by averaging the daily Pain Intensity scores (last 2 days of a week, last 3 days of a week, or all 7 days in a week).

Response to Treatment

- Often referred to as a responder variable (0,1)
- Calculated:
 - Use percent change from baseline in Pain Intensity
 - Use cut-off values (30%, 50%, etc.)
 - Often use multiple cut-off values to assess response to treatment for sensitivity.



Pain Intensity Difference (PID)

- Differences in Pain Intensity reported:
 - Completed for VAS, Categorical, and NPRS instruments.
 - Calculated at each post-baseline time point
 - Post-Baseline minus Baseline: Lower is better
 - Baseline minus Post-Baseline: Higher is better (more common)

Summed Pain Intensity Difference (SPID)

- Use Pain Intensity Difference (PID) at each time point
- Completed for VAS, Categorical, and NPRS instruments.
- Calculated over different time periods (e.g., SPID-6 is calculated over first 6 hours)
- Can be calculated using Time Weighted or AUC – Trapezoidal formulas.
 - AUC is becoming more common.
 - Time Weighted: $SPID-6 = \sum [T(i) - T(i-1)] \times PID(i)$,
 - Where : $T(0) = 0$, $T(i)$ is the scheduled time, and $PID(i)$ is the PID score at time i .
 - AUC – Trapezoidal: $SPID-6 = \sum [T(i) - T(i-1)] \times [(PID(i-1) + PID(i))/2]$.

Summed Pain Intensity (SPI)

- SPI is similar to SPID: Utilizes Pain Intensity at each time point that is sampled.
- Completed for VAS, Categorical, and NPRS Instruments.
- Can be calculated using Time Weighted or AUC – Trapezoidal formulas. AUC is becoming more common.

Pain Relief and PID (PRID)

- Add Pain Relief (PR) and Pain Intensity Difference (PID: Categorical) together at each time point to derive this analysis variable.

Summed PRID (SPRID)

- Calculated like SPID: Utilize PRID at each time point sampled.
- Calculated:
 - Time Weighted
 - AUC – Trapezoidal formulas.
 - AUC is becoming more common.

Total Pain Relief (TOTPAR)

- Calculated like SPID: Utilize PR at each time point sampled.
- Calculated:
 - Time Weighted
 - AUC – Trapezoidal formulas.
 - AUC is becoming more common.

Time to Perceptible Pain Relief (PPR) and Meaningful Pain Relief (MPR)

- This derived variable is computed as a duration of time to the pain relief event.
- The censoring status of time-to-event variables needs to be assessed before analysis and clearly specified in the SAP.
- Typically, if a subject has any of the following three events prior to achieving PPR or MPR, the subject will be censored at the event time.
 - Takes rescue medication
 - Terminates from the study early
 - Completes study (or dosing interval)

Time to Onset of Analgesia

- Calculated using Time to MPR and PPR.
- Time to Onset of Analgesia is set to Time to PPR only if subject also achieves MPR.
- If subject achieves PPR but does not achieve MPR then they are censored.

Missing Data: Imputation Strategies

- Patient reported pain data are often missing when sampling over a period of time.
- Reasons include:
 - Missed visit
 - Diary not filled out
 - Early termination or dropped out of study
- As a general rule you will see an increase in the number of missing pain assessments with the longer duration of sampling (e.g. assessed over 10 days or 3 months).

Imputation Methods

- Analyzing only observed data can introduce bias. This is typically referred to as Observed Cases.
- Imputation has been historical way of dealing with this introduced bias (there are other ways though).

Windowing

- Before applying an imputation method, a common practice is to create windows around visits.
- For instance:
 - 10 mins \pm 2 mins
 - 2 weeks \pm 3 days
- Values falling in windows are analyzed at the visit or time point. Visits or time points without data are missing.
- Windows allow early termination visit values to be placed at the closest visit or time point.

Common Imputation Methods

- Last Observation Carried Forward (LOCF)
 - Baseline Observation Carried Forward (BOCF)
 - Worst Observation Carried Forward (WOCF)
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- Note that each method makes strong assumptions.

Observed Cases: No Imputation

- Example – Pain Intensity (measured in 0-10 NPRS)– Observed Cases

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | End of Study Status |
|---------|----------|--------|--------|--------|--------|---------------------|
| 1 | 9 | 8 | 6 | 5 | 3 | Completed |
| 2 | 8 | 9 | 8 | . | . | Lack of Efficacy |
| 3 | 8 | 3 | . | . | . | AE |
| 4 | 7 | 5 | 4 | 2 | . | Lost to FU |

Last Observation Carried Forward (LOCF)

- Example – Pain Intensity (measured in 0-10 NPRS)– LOCF

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | End of Study Status |
|---------|----------|--------|--------|--------|--------|---------------------|
| 1 | 9 | 8 | 6 | 5 | 3 | Completed |
| 2 | 8 | 9 | 8 | 8 | 8 | Lack of Efficacy |
| 3 | 8 | 3 | 3 | 3 | 3 | AE |
| 4 | 7 | 5 | 4 | 2 | 2 | Lost to FU |

Baseline Observation Carried Forward (BOCF)

- Example – Pain Intensity (measured in 0-10 NPRS)–
BOCF

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | End of Study Status |
|---------|----------|--------|--------|--------|--------|---------------------|
| 1 | 9 | 8 | 6 | 5 | 3 | Completed |
| 2 | 8 | 9 | 8 | 8 | 8 | Lack of Efficacy |
| 3 | 8 | 3 | 8 | 8 | 8 | AE |
| 4 | 7 | 5 | 4 | 2 | 7 | Lost to FU |

Worst Observation Carried Forward (WOCF)

- Example – Pain Intensity (measured in 0-10 NPRS)– WOCF

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | End of Study Status |
|---------|----------|--------|--------|--------|--------|---------------------|
| 1 | 9 | 8 | 6 | 5 | 3 | Completed |
| 2 | 8 | 9 | 8 | 9 | 9 | Lack of Efficacy |
| 3 | 8 | 3 | 8 | 8 | 8 | AE |
| 4 | 7 | 5 | 4 | 2 | 7 | Lost to FU |

Issue with LOCF Imputation

- Recall Subject #3 – Dropout due to an AE

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | Imputation Method |
|---------|----------|--------|----------|----------|----------|-------------------|
| 3 | 8 | 3 | . | . | . | Observed Cases |
| 3 | 8 | 3 | 3 | 3 | 3 | LOCF |
| 3 | 8 | 3 | 8 | 8 | 8 | BOCF |
| 3 | 8 | 3 | 8 | 8 | 8 | WOCF |

- Notice for LOCF that a low pain score (good response) is being carried forward for a bad event (AE).
- FDA has issues with this scenario.

Modified BOCF (mBOCF)

- Recall Subject #3 – Dropout due to an AE

| Subject | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | Imputation Method |
|---------|----------|--------|--------|--------|--------|-------------------|
| 3 | 8 | 3 | . | . | . | Observed Cases |
| 3 | 8 | 3 | 8 | 8 | 8 | mBOCF |
| 3 | 8 | 3 | 8 | 8 | 8 | BOCF |
| 3 | 8 | 3 | 8 | 8 | 8 | WOCF |

- Dropout due to AE → impute BOCF instead of LOCF
- Dropout due to other reasons, including lack of efficacy → impute LOCF
- Note that mWOCF is a similar approach

Imputation Methods

- Intermittent missing data can be imputed via linear interpolation or previously described methods.
- Often need to impute after subject takes rescue medication, regardless of availability of subject reported values.
 - WOCF for remainder of study
 - Use therapeutic window (e.g., impute up to 6 hours after dose)

Imputation

- No best imputation method, need to try different methods as sensitivity analyses depending upon the study.
- Other Imputation methodologies include:
 - mean
 - regression
 - Multiple Imputation
- Some analysis models do not need imputation prior to analysis (MMRM).

Analysis

- There are three basic types of PRO variables in pain studies.
 - Continuous (PI-VAS, SPID)
 - Categorical (response [yes/no], global evaluation)
 - Time-to-Event (PPR)
- Will look at some common analyses for these types of Patient Reported pain scores and analysis variables.

Continuous Analysis Variables

- Usually begin by summarizing actual, change, and possibly percent change from baseline values descriptively over all visits or time points.
- Common descriptive statistics include: n, mean, standard deviation (SD), minimum, median, and maximum.
- Also may see the following:
 - Coefficient of variation
 - Other quartiles (25th and 75th percentiles)
 - Interquartile range (IQR) (75th percentile – 25th percentile)
 - Standard error

Continuous Analysis Variables (Continued)

- Often have multiple treatments (active vs. placebo) and want to compare treatments.
 - Linear models (ANOVA or ANCOVA) are the most commonly used.
 - The effects included in the models (independent variables) usually are study dependent.

Continuous Analysis Variables (Continued)

- An example is an ANCOVA model for PID at Week 12. This is often referred to as a landmark analysis.
- PID at Week 12 would be the outcome variable.
- Independent variables would include treatment and baseline PI.
- Separate model usually tests for treatment-by-baseline PI interaction.

Continuous Analysis Variables (Continued)

- Additional baseline/demographic variables (age, gender, etc.) and site can be added to the linear models.
- Interactions are included in some models (treatment-by-site).
- P-values, model adjusted means (LS means), standard errors (SEM), and confidence intervals are often presented.

Continuous Analysis Variables (Continued)

- An additional model becoming more popular (not a new model though) is called a Mixed Model for Repeated Measures (MMRM).
- Actually a special case of a mixed effects model that contains both fixed and random effects.
- The MMRM model includes all visits or time points in the model and accounts for the intra-subject correlation (a subject's measurements are correlated).

Continuous Analysis Variables (Continued)

- The MMRM model can yield more powerful tests and does not need to have data imputed before analysis.
- There are still strong assumptions that need to be made (missing data assumptions, etc.).
- Mallinckrodt et al (DIJ 2008) has a nice summary of this model.

Categorical Analysis Variables

- Usually begin by summarizing each variable descriptively over all visits or time points using the frequency (n) and percentage (%) of each category (level).
- Treatments can be compared using tests designed for the type of variable. Two types include:
 - Nominal: binary response to treatment (yes/no)
 - Ordinal: global assessment (Poor, Fair, Good, Very Good, Excellent)

Categorical Analysis Variables (Continued)

- For nominal variables:
 - Most common test is Pearson's chi-square.
 - Small samples: Fisher's exact test is recommended.
- Adjustment (or stratification) variables (e.g., site)
 - Cochran-Mantel-Haenszel (CMH) test is often used.
- One can adjust for more variables by using a logistic regression model. Mostly done for dichotomous (yes/no) variables. This is a generalized linear model.

Categorical Analysis Variables (Continued)

- Ordinal variables give more information than nominal variables.
- The outcome can be ordered.
- A CMH mean score test takes this ordering into account. Can be thought of as being like an ANOVA analysis.

Categorical Analysis Variables (Continued)

- There are models available that model categorical variables over time by including all responses into the model (e.g. GEE model).
- These are not used as much as comparing treatments at certain time points individually.

Time to Event Analysis Variables

- The analysis of Time-to-Event (TTE) variables is unique.
 - It has to take into account subjects who are censored (have not achieved the event yet for one reason or another [ET, end of study, etc.])
- TTE variables are summarized by survival curves (Kaplan-Meier method is the most common).
- Usually present the survival estimates at various time points, quantiles (25th, 50th, and 75th percentiles), and corresponding confidence intervals.

Time to Event Analysis Variables (Continued)

- Nonparametric Tests are most common way of comparing treatments:
 - Log rank test (compares entire survival curves)
 - Wilcoxon test (more weight on earlier time points)
- Semi-Parametric Models
 - Cox proportional hazards model (used to estimate hazard ratios or adjust for covariates)
- Parametric models are available (Weibull, Exponential, etc.), but rarely used in pain studies

Concluding Remarks

- PROs are an important element for assessing efficacy in pain clinical trials.
- Hopefully this presentation has shed some light on:
 - Pain variables,
 - Imputation methods,
 - Analysis techniques commonly used in these trials.

Some References

- Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Draft). February 2006. <http://www.fda.gov/cder/guidance/5460dft.pdf>
- Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. *DIJ* 2008(42): 303-319.

Questions

