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

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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.
• **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 (sub-scales) 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)
• 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 = Σ [T(i) – T(i-1)] x 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 = Σ [T(i) – T(i-1)] x [(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 ± 2 mins
  • 2 weeks ± 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)

- Note that each method makes strong assumptions.
**Observed Cases: No Imputation**

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

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>End of Study Status</th>
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**Last Observation Carried Forward (LOCF)**

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

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Baseline Observation Carried Forward (BOCF)

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

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Worst Observation Carried Forward (WOCF)

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

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**Issue with LOCF Imputation**

- Recall Subject #3 – Dropout due to an AE

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<td>WOCF</td>
</tr>
</tbody>
</table>

- 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

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</table>

- 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).
• 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)
• 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.
• 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.
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.
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.
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

