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 <u>A</u>cute (**A**) and <u>C</u>hronic (**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)

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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

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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.

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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

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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.

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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)

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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 = 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].

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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)

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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).

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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.

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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

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

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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.

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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

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Imputation Methods

- Intermittent missing data can be imputed via linear interpolation or previously described methods.

- Often need to impute after subject takes <u>rescue medication</u>, 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 <u>landmark analysis</u>.

- 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)

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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

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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.

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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