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Avoiding the Ouch: Mastering Time-to-Pain Progression Analysis

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ABSTRACT

In Oncology studies, time to pain progression (TTPP) is an endpoint that measures the time from randomization or treatment start to a patient experience a significant worsening of their pain. While Progression Free Survival (PFS) and Overall Survival (OS) are the typical primary endpoints, TTPP can be selected as a secondary endpoint to assess disease progression and treatment efficacy. In this study, the worsening of pain is defined by an increase of 2 or more points on Brief Pain Inventory Short Form (BPI-SF) Question 3 (pain at its worst in the last 24 hours) or an initiation of new Opioid recorded in BPI-SF Question 7 (what treatment/medications are you receiving for pain) for at least two consecutive assessments.

In this paper, we report how we use patient reported outcome (PRO) from the BPI- SF information to assess TTPP endpoint. We describe how BPI-SF data is collected, mapped to SDTM and ADaM domains, and used to derive and analyze pain worsening. Additionally, we will discuss the challenges and solutions involved in identifying opioid use from the pain medication data collected in the PRO BPI-SF dataset.

INTRODUCTION

Time to Pain Progression (TTPP) is a critical clinical endpoint in oncology that measures the duration it takes for a cancer patient to experience an increase in pain intensity or the emergence of new pain. Pain is a prevalent and debilitating symptom in cancer, often significantly affecting a patient's quality of life. As survival rates improve with more effective treatments, patients are living longer with their disease while managing pain caused by both the cancer itself and its treatments, such as chemotherapy or radiation. Monitoring TTPP is essential for evaluating treatment effectiveness, understanding disease progression, and assessing the correlation between pain and tumor growth, particularly in metastatic cancers. This metric provides valuable insights into the impact of treatments on pain management, helping clinicians tailor interventions and optimize care (Cleeland et al., 2003; Cleeland & O'Mara, 2003).

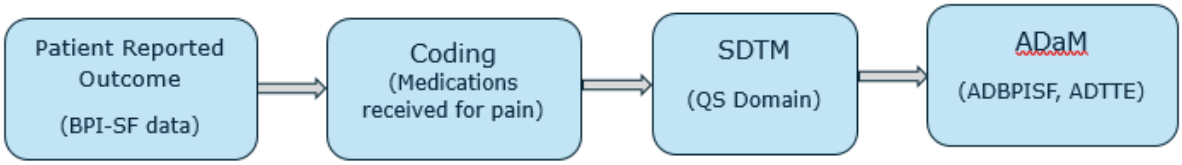
The Brief Pain Inventory Short Form (BPI-SF), a widely used and validated tool, is integral in assessing cancer-related pain and its interference with daily life. It measures pain intensity and evaluates how pain affects aspects such as mood, sleep, and social interactions, offering a comprehensive view of a patient's functioning. By assessing the worst, least, and average pain experienced over the last 24 hours, the BPI-SF helps clinicians track pain fluctuations and adjust treatment strategies accordingly. The tool’s reliability and cross-cultural validity have made it a preferred choice in clinical trials globally, allowing researchers to capture pain levels and their impact on quality of life across diverse populations (Cleeland et al., 1994; Atkinson et al., 2011). The integration of Electronic Patient Reported Outcomes (ePROs) further enhances the utility of the BPI-SF, enabling real-time tracking of pain levels and treatment outcomes, and providing essential insights into pain progression and the efficacy of treatment strategies (Cleeland, 1991).

In clinical trials, TTPP serves as a valuable endpoint for assessing treatment efficacy in managing pain progression, offering insights that complement traditional clinical endpoints like Progression-Free Survival (PFS) and Overall Survival (OS). TTPP provides a more patient-centered perspective on treatment effectiveness, capturing the subjective experience of pain. For example, pain worsening may be defined as a 2 or more-point increase on the BPI-SF's worst pain scale, or the initiation of a new opioid regimen, offering a measurable framework for assessing pain progression (Cleeland et al., 2003). This integration of

TTPP with tools like the BPI-SF helps clinicians and researchers understand the broader impacts of cancer pain and improve the management of symptoms throughout treatment.

This paper presents hypothetical study data to show how BPI-SF can assess the TTPP endpoint. We will outline how BPI-SF data is collected, mapped to SDTM and ADaM domains, and analyzed to define pain progression. In this study, pain progression is defined as a 2+ point increase on worst pain or the initiation of a new opioid for at least two consecutive assessments.

FLOW OF DATA



MAP RAW BPISF data to SDTM

The Brief Pain Inventory Short Form typically contains questions to collect information like:

1. Location of Pain: Specific areas of the body affected by pain. (in Question 2).

2. Pain Severity: Includes how severe the pain is (e.g., "Worst pain," "Least pain," "Average pain," etc.). (in questions Q3, Q4, Q5, and Q6).

3. Treatments for Pain: Treatments/medications receiving for pain. (in question 7).

4. Percentage of pain relief. (in question 8).

5. Pain Interference: How much pain interferes with daily activities (e.g., mood, walking, sleep, work). (in question 9).

DECODE OPIOID MEDICATION

We used pain medication reported by patients in ePRO form BPI-SF Question #7: What treatment or medication are you receiving for pain. This is a free text field, therefore the medications need to be coded for analysis. Usually, the coding is done based on the Verbatim in the coding system. However, the ePRO data was not able to be imported to the Rave Coder system to code electronically, so the data is coded manually following a very strict guideline per SOP (The SOP is not Pfizer's and is from the legacy company which conducted the study), for coding data external to the Clinical Coding System. The manual coding follows the two rules: 1. Split out all multi-ingredient products to reflect each active ingredient and code that accordingly. 2. For opioid ingredients code only to base even if salt is reported (e.g., MORPHINE HCL or MORPHINE SULFATE would code to only the base MORPHINE). The table 1 below illustrates how ePRO entries are decoded to flag Opioid element following the two decoding rules. Q07 is the BPI-SF question #7 entry field. DURGNAME, PDN (Preferred Drug Name), PAINMED and OPIOID are fields added by the coder. Opioid usage is flagged when OPIOID=1.

Q07	MED	DRUGNAME	PDN	PAINMED	OPIOID
Optalgin, Lyrica and Targin	1	OPTALGIN	METAMIZOLE SODIUM	1	0
Optalgin, Lyrica and Targin	1	LYRICA	PREGABALIN	1	0
Optalgin, Lyrica and Targin	1	TARGIN	NALOXONE HYDROCHLORIDE	0	0
Optalgin, Lyrica and Targin	1	TARGIN	OXYCODONE	1	1

Table 1: how ePRO entry is decoded to flag Opioid usage

This coding is essential to identify when new opioid is added for patient's pain management. This table is merged with the BPI-SF Q07 to flag whether Opioid is used for each visit.

MAP DATA to QS DOMAIN

Here's a simple way to understand the mapping of the Brief Pain Inventory Short Form (BPI-SF) to the SDTM QS (Questionnaire/Survey) domain to facilitate regulatory submission and data analysis.

The QS (Questionnaires) domain is used to store data related to questionnaires or surveys, such as the BPI-SF, and contains the following key variables:

- USUBJID: Unique subject identifier (maps from BPISF's Subject ID).
- QSTEST: The test or measure (maps from questions and sub questions from in BPI-SF).
- QSTESTCD: A code for the test or measure.
- QSTRESN: Numeric result (maps from the numeric responses to the BPI-SF questions).
- QSSTRESC: Character result
- QSTRESU: Unit of measurement.
- QSEVLINT: Evaluation Interval (maps from the time frame BPI-SF question is referring to)
- VISIT: Visit during which the data was entered.

Annotated BPI-SF form:

QS = QUESTIONNAIRES | QSCAT=BPI SHORT FORM | QSEVAL=STUDY SUBJECT

STUDY ID#_____ HOSPITAL #_____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

Name: _____ _____ _____

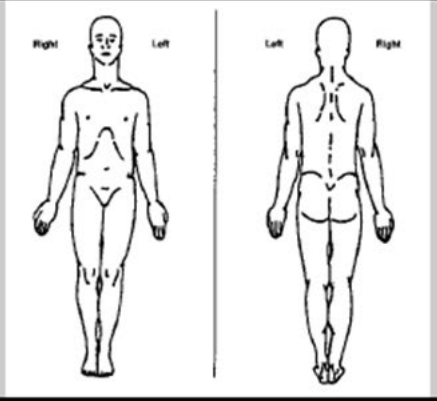
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today? QSORRES for QSTESTCD=BPI201

1. Yes 2. No QSEVINTX=TODAY

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

QSORRES for QSTESTCD=BPI202A



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours. QSEVLINT=-P24H

0 1 2 3 4 5 6 7 8 9 10

No Pain — QSORRES for QSTESTCD=BPI203 — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours. QSEVLINT=-P24H

0 1 2 3 4 5 6 7 8 9 10

No Pain — QSORRES for QSTESTCD=BPI204 — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No Pain — QSORRES for QSTESTCD=BPI205 — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain — QSORRES for QSTESTCD=BPI206 — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

QSORRES for QSTESTCD=BPI207

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received. QSEVLINT=-P24H

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief			QSORRES for QSTESTCD=BPI208							Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your: QSEVLINT=-P24H

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209A							Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209B							Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209C							Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209D							Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209E							Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209F							Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere			QSORRES for QSTESTCD=BPI209G							Completely Interferes

QSTESTCD	QSTEST	QSSTRESN possible values	QSSTRESC possible values
BPI201	BPI2-Pain Other Than Everyday Kinds	0 1	No Yes
BPI202A BPI202B	BPI2-Areas of Pain BPI2-Area Hurts Most	1 2 3 4 5 6 7 8 9 10 11 12 13 14	Front Right Leg Front Left Leg Front Right Arm Front Left Arm Front Abdomen Front Chest Front Head Back Right Leg Back Left Leg Back Right Arm Back Left Arm Back Lower Back Upper Back Head
BPI203 BPI204 BPI205 BPI206	BPI2-Pain at its Worst in Last 24 Hours BPI2-Pain at its Least in Last 24 Hours BPI2-Pain on the Average BPI2-Pain Right Now	0 1 2 3 4 5 6 7 8 9 10	No Pain 1 2 3 4 5 6 7 8 9 Pain as bad as you can imagine
BPI207	BPI2-Treatments Receiving for Pain		Free text field
BPI208	BPI2-Relief Pain Treatments Provided	0 10 20 30 40 50 60 70 80 90 100	0 10 20 30 40 50 60 70 80 90 100
BPI209A BPI209B BPI209C BPI209D BPI209E BPI209F BPI209G	BPI2-Pain Interfered General Activity BPI2-Pain Interfered with Mood BPI2-Pain Interfered Walking Ability BPI2-Pain Interfered with Normal Work BPI2-Pain Interfered with Relations BPI2-Pain Interfered with Sleep BPI2-Pain Interfered Enjoyment of Life	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10

Table 2: Possible SDTM value level data for BPI-SF form.

Multiple entries are possible for BPI202A as the subject can shade multiple areas for pain at each completion of the form, resulting in multiple responses on the same study day.

The treatments reported on BPI207 are coded (as described in DECODE OPIOID MEDICATION section) and individual medications and their coded names are mapped to SUPPQS.

Set QSEVLINT to "-PT24H" (controlled terminology for past 24 hours) when QSTESTCD = "BPI203", "BPI204", "BPI208", "BPI209A", "BPI209B", "BPI209C", "BPI209D", "BPI209E", "BPI209F", or "BPI209G".

Set QSORRESU= "%" when QSSTRESU="BPI208".

In this study BPI-SF questionnaire is administered at Cycle 1 Day 1 before study treatment, once weekly for the first 12 weeks and once every 3 weeks for the remainder of the study. This schedule is different from regular study visits and for these records set VISIT=ePRO Week 0, ePRO Week 1 etc.

DERIVE ADAM VARIABLES AND PARAMETERS

Analysis dataset ADBPISF is created as an intermediate analysis dataset with various population flag and analysis date variables. These variables are used in ADTTE to derive Time to Pain Progression.

ADBPISF:

AVISIT is derived per analysis windowing specified in Statistical Analysis Plan.

ANL01FL: According to SAP, ANL01FL selects the unique record for each AVISIT.

Baseline Flag: This flag is set to the most recent non-missing measurement for each parameter taken before the first dose of study treatment, or randomization date for subjects who have not received any study treatment

Date of First Greater-than-2 Increase in Worst Pain: This flag, applied per subject, is set to the analysis date of the first visit record where the change from baseline in 'pain at its worst' (BPI203) is >= 2 for two or more consecutive AVISITs, considering all protocol-specified visits.

Flags Specific to Medication Received for Pain (BPI207): To derive these flags consider the medications taken before any subsequent anticancer therapy.

- **Baseline Opioid Flag**: This flag, applied per subject, marks the baseline "BPI207" record if the medication is identified as an opioid and the preferred drug name is not missing.
- **Opioid Medication Flag**: This flag, applied per record, marks both baseline and post-baseline records if the medication is an opioid (marked by coding group) and the preferred drug name is not missing.
- **New Post-Baseline Opioid Flag**: This flag, applied per record, marks post-baseline records where the preferred drug name does not match the one from the baseline record.
- **Date of First New Opioid Initiation**: This flag, applied per subject, is set to the analysis date of the first visit record where new opioid medications are detected in two or more consecutive AVISITs, considering all protocol-specified visits.

ADTTE:

TTPP is defined as the time from the date of randomization to the date when pain progression occurs.

The value for **AVAL** in TTPP is calculated as **Event/Censor date – start date + 1.**

- **Start Date**: The randomization date.
- **Event Date**: The event date is the earlier of the date of the first new opioid initiation or the date of the first recorded increase of 2 or more in worst pain. In the case of event, the **CNSR** = 0.
- **Censor Date and Censoring Reasons**:

a. If the BPI-SF Question 3 score is 9 or 10 at baseline or if no post-baseline BPI-SF assessments are recorded, the censor date is the randomization date.

b. If the subject dies before pain progression occurs or if no pain progression is recorded and no subsequent anticancer treatment is given, the censor date is the date of the last BPI-SF assessment.

c. If subsequent anticancer treatment begins before pain progression is observed, the censor date is the date of the last BPI-SF assessment that occurred on or prior to the start of the anticancer treatment.

If there is no event, **CNSR** = 1.

KAPLAN-MEIER (KM) ANALYSIS

Time to pain progression (how long it takes for pain to get worse) can be analyzed using Kaplan-Meier (KM) method. The data from KM analysis can be plotted to show the probability of staying pain free at different points in time. This method allows estimation and comparison of median time to progression between groups. Log-rank test can be used to see if the difference in curves between the groups is significant. Stratification factors can be used to split subjects into different groups for comparison.

```
proc lifetest data=ADTTE method=km outsurv=km plots=survival;
      by TRT;
      time AVAL*CNSR(1);
run;
```

Program 1. Lifetest to generate the probability of staying pain free at each time point and median time to pain.

```
proc lifetest data=ADTTE method=km conftype=loglog alpha=0.05;
      time AVAL*CNSR(1);
      strata STRAT1 STRAT2 …/group=TRT test=logrank;
run;
```

Program 2. Lifetest to generate P value and Confidence Intervals.

The Supporting variables list:

ADTTE: input dataset
TRT: Treatment group
AVAL: Time to pain progression
CNSR: censoring indicator
STRAT1, START2 etc…: Stratification factors

CONCLUSION

The BPI-SF's use in measuring Time to Pain Progression (TTPP) provides additional insights into the

effects of pain management and treatment efficacy beyond traditional clinical endpoints. By analyzing opioid use, researchers can better understand pain progression and management strategies. This paper highlights the importance of BPI-SF in clinical trials, offering a simple way to map the data to CDISC standards to help the use of patient-reported outcomes to contribute to patient-centered care.

While BPI-SF provides great value to analyze TTPP. It also brings some challenges. For example, we had to manually code for opioid flag because BPI-SF medication data (Question 7) is a free text field entered by patients. If the WHODrug version is updated, the impact of the up-versioning on opioid coding should be evaluated. If the ePRO data is collected in a language that is not English, we would have to translate the Q07 into English before we can code for Opioid flag.

If all the medications are collected in the Concomitant medications (Conmed) dataset, where coding can be done in the automatic coding system, some studies choose to use Conmed datasets instead of ePRO BPI-SF Question 7. This approach works if the study SAP does not request ePRO as source data.

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