Paper AS19

Time-to-Event Analysis in Pain Management: A Case Study of the Double Stopwatch Method and ADaM Dataset Development in Relation to Rescue Medication

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Abstract

Pain assessment methodologies are critical in clinical trials evaluating analgesic efficacy. The double stopwatch technique represents an advanced approach for measuring both perceptible and meaningful pain relief. This methodology incorporates a crucial censoring mechanism when rescue medication is administered, addressing a significant methodological challenge in pain research.

The double stopwatch method employs two concurrent measurements: the time to first perceptible pain relief and the time to meaningful pain relief. This method provides complementary endpoints that capture both the onset and the clinical significance of analgesic effects.

In this paper, we will discuss in detail the concept of the double stopwatch method, explore all possible pain relief scenarios, and demonstrate how to create the time-to-event ADaM dataset for time to first perceptible pain relief and time to meaningful pain relief in relation to rescue medication intake, using a case study example.

1. Introduction

Timely and accurate assessment of pain relief is critical to evaluate the analgesic efficacy in clinical trials. The traditional scheduled assessments for pain relief occur at fixed post-dose intervals. These fixed assessments often miss the true onset of pain relief and rely on retrospective recall, which reduces measurement precision and introduces bias. The Double Stopwatch Method (DSM) overcomes these limitations. It allows participants to record both First Perceptible Relief (FPR) and Meaningful Pain Relief (MPR) in real time and provides a sensitive, patient-centered approach to capturing analgesic onset. By providing precise time-to-event data, DSM complements scheduled assessments, improves the accuracy of onset measurement, and strengthens pharmacodynamic and regulatory analyses.

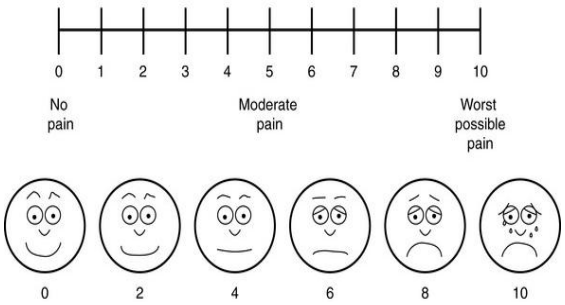
This paper consolidates the operational guidance, analytic strategies, and time-to-event ADaM dataset design considerations required for implementing DSM in pivotal pain studies. It also emphasizes the appropriate handling of rescue medication as an intercurrent event to ensure valid and interpretable endpoint estimation.

2. Background and Rationale

Pain assessments provide standardized and quantifiable evidence of drug effect, guide dose optimization, and support regulatory decision-making. Standardized assessments also ensure consistent comparison across different treatments and clinical trials.

Pain intensity is commonly measured using NUMERICAL RATING SCALE 11-POINT and/or VERBAL RATING SCALE 6-POINT.

NUMERICAL RATING SCALE 11-POINT



VERBAL RATING SCALE 6-POINT

NONE (0)
MILD (1)
MODERATE (2)
MODERATELY SEVERE (3)
SEVERE (4)
EXTREME (5)

Pain relief is typically assessed through scheduled evaluations using VERBAL RATING SCALE 5-POINT and/or binary measurements such as ‘Starting Pain at Least 1/2 Gone’ (No/Yes).

VERBAL RATING SCALE 6-POINT

NO RELIEF (0)
A LITTLE RELIEF (1)
SOME RELIEF (2)
A LOT OF RELIEF (3)
COMPLETE RELIEF (4)

These evaluations are typically collected at pre-specified timepoints such as pre-dose (for pain intensity only) and 0.5, 1, 2, …, 24 hours post-dose. This approach produces structured longitudinal data but can obscure individual variability in analgesic onset. Because pain relief may occur between scheduled assessments, fixed-interval approaches can miss the true onset of action. They can also introduce recall bias when patients retrospectively estimate when the relief began.

The DSM overcomes these limitations by allowing participants to record two granular, real-time onset milestones: FPR and MPR. FPR represents the earliest detectable analgesic effect (any initial

pain relief), while MPR reflects clinically meaningful improvement. Participants may also indicate immediately whether the initial FPR is itself meaningful. By allowing relief milestones to be captured as they occur rather than relying on retrospective recall, DSM substantially reduces bias and improves sensitivity for detecting treatment differences. It provides more accurate onset-of-action data than conventional scheduled assessments. This method offers a patient-centered framework that strengthens both clinical interpretation and pharmacodynamic modeling in pivotal pain trials.

Originally developed within the dental pain model described by Desjardins (2002), DSM has been widely adopted and is recognized as a sensitive and reliable method for detecting analgesic onset, as noted by Cooper (2010).

3. Double Stopwatch Method: Concept and Operations

3.1 Core Concepts

- Two covered stopwatches are started at dosing - **Stopwatch A** for **FPR** and **Stopwatch B** for **MPR**. The faces of the stopwatches are covered to ensure that participants remain blinded to the exact time of pain relief.
- The participant stops Stopwatch A at FPR, and the elapsed time on Stopwatch A is recorded as the time to FPR.
- At the same time, the participant is asked whether the relief is meaningful.
- If the answer is **"Yes"**, MPR is confirmed at the same time as FPR and Stopwatch B is not used.
- If **"No"**, the participant uses Stopwatch B and stops it when meaningful relief occurs later. The elapsed time on Stopwatch B is recorded as the time to MPR.
- If relief is never achieved during the observation window, corresponding time variables remain missing and the subject is censored at end of observation period.

3.2 Participant Instructions (Example Wording)

For FPR: "Stop the Stopwatch A as soon as you begin to feel even the slightest pain-relieving effect."

For MPR: "Stop the Stopwatch B when you experience meaningful relief - that is, when the pain relief feels significant to you."

4. Handling Intercurrent Events: Rescue Medication

Rescue medication (RM) is an intercurrent event that can preclude the observation of FPR or MPR. Per endpoints, time-to-event is evaluated up to the earlier of (a) initiation of RM or (b) end of scheduled observation period (e.g., up to 24 hours post-dose). If FPR/MPR is not observed prior

to RM, the subject is censored at RM initiation time for that endpoint. If FPR/MPR is observed prior to RM, the event time is recorded as the elapsed time from dosing to the event.

5. Understanding the Data

5.1 Case Report Form

Stopwatch Assessment

Did the participant experience any level of pain relief start of the assessment?

☐ Yes ☐ No

Stopwatch A – First Perceptible Relief

Enter the time when the subject first perceived any pain relief.

Time: _____ (24-hour clock)

At this point, did the participant consider the initial be meaningful?

☐ Yes ☐ No

Did the subject experience what they would describe meaningful pain relief?

☐ Yes ☐ No

Stopwatch B – Meaningful Relief

Enter the time when the subject experienced pain relief.

Time: _____ (24-hour clock)

5.2 Scenario Mapping with an example

Scenario	Perceptible Relief	Time to First Perceptible Relief	Relief Confirmed as Meaningful	Meaningful Pain Relief	Time to Meaningful Pain Relief
No Relief	No	-	-	-	-
Immediate Meaningful	Yes	01:35	Yes	Yes	01:35
Delayed Meaningful	Yes	03:22	No	Yes	11:24
Perceptible Only	Yes	04:09	No	No	-

5.3 Mapping Raw Data to SDTM

In the DSM, key data required to derive time-to-event endpoints originate primarily from the SDTM QS domain, which captures both scheduled pain-relief assessments and stopwatch-based real-time responses. The standard questionnaire used in analgesic trials includes several core items mapped through standard QSTESTCD values as follows:

QSTESTCD	QSTEST
PR0108	PR01 - Was there Perceptible Pain Relief
PR0109	PR01 - Time to Perceptible Pain Relief
PR01010	PR01 - Was there Meaningful Pain Relief
PR01011	PR01 - Time to Meaningful Pain Relief
PR0101	PR01 - Pain Relief

In addition to these standard items, DSM requires an operationally important but non-standard question: **"At this point, did the participant consider the initial relief to be meaningful?"** This confirmation step, used to determine whether the FPR should also be classified as MPR, is not included in the standard pain-relief questionnaire. To preserve traceability and ensure consistent implementation across studies, this item is captured in the QS domain using the dedicated variable **QSTESTCD = 'PRCMPR'**. This enables analysts to correctly distinguish scenarios in which MPR occurs immediately at the moment of FPR from those in which meaningful relief is achieved later in time.

The date-time of each QS observation (QSDTC) can be derived by adding the elapsed time for FPR or MPR to the subject's dosing start date-time recorded in **DM.RFXSTDTC**. For example, if a participant receives the study drug on **16 December 2025** at **08:30** and experiences perceptible pain relief **2 hours and 15 minutes** later, the derived QSDTC for all corresponding QS records such as those with QSTESTCD = **PR0108**, **PR0109**, and **PRCMPR** would be **2025-12-16T10:45**, reflecting the precise onset time aligned with the dosing timestamp.

For QSTESTCD = PRCMPR, the derived QSDTC should always match the QSDTC values derived for PR0108 and PR0109, since the participant must confirm whether the relief is meaningful immediately when the FPR is observed, regardless of whether the participant responds "Yes" or "No".

RM plays a central role as an intercurrent event in DSM-based analyses, as it may censor or truncate the observation window for FPR and MPR endpoints. RM data are sourced from the SDTM CM domain, where administrations classified as rescue therapy are identified through **CMCAT = "RESCUE MEDICATION"**. These timestamps provide essential boundary conditions for time-to-event derivations in ADTTE, ensuring that event times are appropriately censored when FPR/MPR is not achieved before the first RM administration. Integrating QS-based onset measures with CM-based RM timing ensures consistent and regulatory-aligned treatment of intercurrent events within the DSM analytic framework.

5.4 ADaM: Time-to-Event Analysis Dataset (ADTTE)

Derivations of Key Variables

Variable (Label)	Algorithm / Derivation
PARAM / PARAMCD (Parameter / Parameter Code)	1. Time to First Perceptible Relief / TTFPR 2. Time to Meaningful Pain Relief / TTMPR 3. Time to First Perceptible Relief Confirmed as Meaningful Relief / TTFPCMPR
EVNTDESC (Event or Censoring Description)	1. If there is a record in SDTM.QS with QSORRES = 'Yes' for QSTESTCD = 'PR0108' and QSDTC < earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION', then set as 'First Perceptible Relief' 2. If there is a record in SDTM.QS with QSORRES = 'Yes' for QSTESTCD = 'PR01010' and QSDTC < earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION', then set as 'Meaningful Pain Relief' 3. If there is a record in SDTM.QS with QSORRES = 'Yes' for QSTESTCD = 'PRCMPR' and QSDTC < earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION', then set as 'First Perceptible Relief Confirmed as Meaningful Relief' If the event is not observed the set as 'No Event'
STARTDTM (Time-to-Event Origin Datetime)	ADSL.TRTSDTM
CNSR (Censor)	0 if the event is observed, 1 if event is not observed (EVNTDESC = 'No Event')
ADTM (Analysis Datetime)	If CNSR = 0, set to QS.QSDTC (in numeric format) for corresponding QSTESTCD, where QSDTC < earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION' If CNSR = 1 then set as Date/time of end of Observation in DB period: Minimum (earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION', latest QS.QSDTC where QSTESTCD = 'PR0101')
AVAL (Analysis Value)	ADTM – STARTDTM, rounded to the nearest minute
CNSDTDSC (Censor Date Description)	Populate if CNSR = 1: a. if ADTM comes from CM.CMSTDTC then set as 'Date/time of First Rescue Medication' b. if ADTM comes from QS.QSDTC where QSTESTCD = 'PR0101' then set as 'Date/time of Last Pain Relief Score Assessment through Verbal Rating Scale'

6. Statistical Analysis

- **Study Title as an Example:** A randomized, double-blind, single-dose, placebo-controlled Phase 3 study to evaluate the Analgesic Efficacy and Safety of the study treatment in patients with postsurgical pain

- **Secondary Objectives:**
    1. Onset of pain relief as determined by the time to first perceptible relief
    2. Onset of pain relief as determined by the time to meaningful pain relief

- **Secondary Endpoints:**
    1. Time to first perceptible relief
    2. Time to meaningful pain relief
    3. Time to first perceptible relief confirmed as meaningful relief

- **Treatment Condition:** Study Treatment will be compared to Placebo

- **Analysis Population:** As specified by protocol, usually Modified Intent-to-treat (mITT)

- **Observation Window:** From start of dosing to the last pain relief score assessment through Categorical Pain Relief Rating Scale, planned at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24 hours post-dose

- **Intercurrent Event:** Rescue Medication - the endpoints will be assessed up to initiation of RM; observation duration will be from the date/time of 1st double-blind IMP to date/time before initiation of RM

- **Population-level Summary:** P-value based on stratified log-rank test adjusted by randomization strata; Kaplan-Meier estimates and plots; Hazard ratio of study treatment vs placebo and its 95% CI based on Cox regression model

- **Censoring Rules:** Participants who do not have FPR/MPR will be censored at the end of observation period - at the time of last pain relief score assessment or at the initiation of rescue medication, whichever is earlier

7. Case Study Examples

To illustrate the derivation rules for time-to-event endpoints in acute pain studies, some representative participants scenario is used to demonstrate the handling of FPR, MPR, FPR confirmed as MPR and the impact of RM administration (if any) on censoring.

Example 1

Scenario Overview

A participant (Subject A-100-001) received the study drug on **18 December 2025** at **08:05**. All subsequent questionnaire (QS) assessments and rescue medication (CM) records were aligned to this dosing timestamp to derive event or censoring times for the ADaM time-to-event (ADTTE) dataset.

Assessment of Perceptible Pain Relief

FPR was reported corresponding to a latency of **3 hours and 47 minutes** from dosing. The associated QS evaluations (QSTESTCD = PR0108 and PR0109) confirmed both the occurrence of FPR and the elapsed time to its onset. As per dataset conventions, the derived datetime of the FPR event (QSDTC) was anchored at **2025-12-18T11:52** for all relevant QS records. The participant was also asked whether the FPR was meaningful (QSTESTCD = PRCMPR). Although the response was "No", the QSDTC for PRCMPR was derived using the same timestamp **(11:52)** because the meaningfulness confirmation question is administered at the moment FPR is observed.

Per the study's derivation rules, the time to first perceptible relief (TTFPR) was defined as the interval between the dosing start time and the QSDTC for PR0108/PR0109. As the event occurred prior to any rescue medication use, TTFPR was classified as an observed event.

Assessment of Meaningful Pain Relief

MPR was subsequently reported with an elapsed time of **13 hours and 21 minutes** from dosing (QSTESTCD = PR01010 and PR01011). However, the participant had taken RM prior to this time, with administrations recorded at the times **14:56** and **20:50** on **18 December 2025**. Because MPR occurred after the intake of RM, the time to meaningful pain relief (TTMPR) was censored at the time of first RM, i.e., the elapsed time of RM initiation from dosing **(6 hours 51 minutes)**.

Similarly, the derived endpoint 'Time to first perceptible relief confirmed as meaningful relief' (TTFPCMPR) was also censored at the same time, as MPR confirmation did not occur at the time of FPR. In both cases, censoring was applied in accordance with prespecified study procedures to avoid attributing post-rescue medication improvements to the investigational treatment.

ADTTE Derivations

Final ADTTE derivations reflected the following:

- **TTFPR:** 227 minutes; event observed (First Perceptible Relief)
- **TTMPR:** 411 minutes; censored at 14:56 (First Rescue Medication)
- **TTFPCMPR:** 411 minutes; censored at 14:56 (First Rescue Medication)

Endpoint	STARTDTM	ADTM	AVAL (min)	CNSR	EVNTDESC	CNSDTDSC
Time to First Perceptible Relief (TTFPR)	18DEC2025: 08:05	18DEC2025: 11:52	227	0	First Perceptible Relief	
Time to Meaningful Pain Relief (TTMPR)	18DEC2025: 08:05	18DEC2025: 14:56	411	1	No Event	Date/time of First Rescue Medication
Time to First Perceptible Relief	18DEC2025: 08:05	18DEC2025: 14:56	411	1	No Event	Date/time of First

Confirmed as Meaningful Relief (TTFPCMPR)						Rescue Medication

Example 2

Scenario Overview

This case study illustrates the derivation of time-to-event endpoints when FPR and MPR occurred at the same time. Also, no RM was taken during the assessments. The scenario reflects a participant (Subject A-100-002) who received the study treatment on **24 December 2025 at 10:30**, after which all questionnaire (QS) timestamps were aligned to derive event times for ADaM time-to-event (ADTTE) variables.

Assessment of Perceptible and Meaningful Pain Relief

The participant reported FPR corresponding to **7 hours and 15 minutes** after dosing. At this same assessment, the participant confirmed that the FPR was meaningful. As a result, all related QS records (QSTESTCD = PR0108, PR0109, PRCMPR, PR01010, PR01011) shared the identical derived datetime value of **2025-12-24T17:45**.

Because the confirmation of MPR was provided immediately at the time FPR was experienced, no additional timing assessments were required. Accordingly, the stopwatch dedicated to tracking the elapsed time to MPR (Stopwatch B) was not used further for this participant.

Alignment of QSDTC Timestamps

Per study rules, the date-time of FPR (QSDTC for PR0108/PR0109) serves as the anchor for related assessments. In this scenario, the confirmation of meaningful relief (PRCMPR) was prompted in response to the perceptible relief event and therefore received the same QSDTC timestamp. Similarly, the MPR assessments (PR01010/PR01011) reflected identical timing because MPR was declared at the same moment FPR occurred.

Impact of Rescue Medication

No RM was recorded for this participant during the pain relief assessments. As such, no censoring was applied to any of the derived time-to-event endpoints due to RM. Every endpoint was classified as an observed event.

ADTTE Derivations

The following ADTTE parameters were derived:

- **TTFPR:** 435 minutes; event observed (First Perceptible Relief)
- **TTMPR:** 435 minutes; event observed (Meaningful Pain Relief)

- **TTFPCMPR:** 435 minutes; event observed (First Perceptible Relief Confirmed as Meaningful Relief)

Endpoint	STARTDTM	ADTM	AVAL (min)	CNSR	EVNTDESC
Time to First Perceptible Relief (TTFPR)	24DEC2025:10:30	24DEC2025:17:45	435	0	First Perceptible Relief
Time to Meaningful Pain Relief (TTMPR)	24DEC2025:10:30	24DEC2025:17:45	435	0	Meaningful Relief
Time to First Perceptible Relief Confirmed as Meaningful Relief (TTFPCMPR)	24DEC2025:10:30	24DEC2025:17:45	435	0	First Perceptible Relief Confirmed as Meaningful Relief

8. Implementation Considerations for Programmers

- **Timestamp precision:** ensure consistent parsing/rounding to the nearest minute across QS and CM sources.
- **Event ordering:** enforce logical consistency (e.g., FPR must occur on/after dosing; MPR cannot precede FPR if confirmed later).
- **Missingness:** explicitly allow missing times where relief not achieved; avoid imputations that bias time-to-event.
- **Censoring reasons:** populate CNSDTDSC with precise, auditable reasons (e.g., first RM vs last scheduled pain relief assessment).
- **Traceability:** maintain lineage from ADTTE back to SDTM (PARAMCD-level specify source variables and rules).
- **Quality control:** dual programming or independent review; spot-checks with subject profiles; validate at least the edge-case scenarios in this paper.

9. Conclusion

The DSM provides precise, real-time measurement of analgesic onset and substantially enhances sensitivity for detecting treatment differences by capturing the FPR and MPR events directly from patient input. Its ability to generate granular onset information supports the development of robust time-to-event analysis datasets. It also aligns naturally with regulatory expectations for endpoints that reflect patient-centric, clinically meaningful outcomes. DSM integrates effectively

with intercurrent event strategies, particularly the handling of RM, allowing clear and interpretable censoring rules within the ADaM time-to-event framework. When combined with scheduled time-point pain assessments, the method offers a comprehensive characterization of onset, trajectory, and duration of relief, thereby strengthening the clinical interpretation of analgesic efficacy. Collectively, the precision, alignment with regulatory principles, and compatibility with time-to-event methodology offered by DSM improve analytical clarity and enhance the interpretability of results in regulatory submissions.

Acronyms

Abbreviation	Description
ADaM	Analysis Data Model
ADTTE	Analysis Time-to-event Dataset
CI	Confidence Interval
CM	Concomitant Medications
DSM	Double Stopwatch Method
FPR	First Perceptible Relief
mITT	Modified Intent-to-Treat
MPR	Meaningful Pain Relief
QS	Questionnaires
RM	Rescue Medication
SDTM	Study Data Tabulation Model
TTFPCMPR	Time to First Perceptible Relief Confirmed as Meaningful Relief
TTFPR	Time to First Perceptible Relief
TTMPR	Time to Meaningful Pain Relief

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Recommended Reading

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ClinicalTrials.gov Protocol example NCT05317312

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The Value of the Dental Impaction Pain Model in Drug Development - Stephen A. Cooper and Paul J. Desjardins

www.fda.gov/media/156063/download Development of Non Opioid Analgesics for Acute Pain Guidance for Industry

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