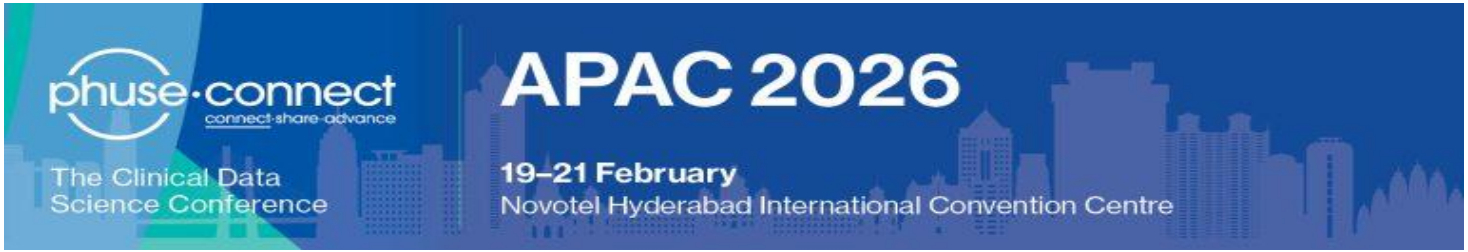
sanofi

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

Arnode Mukherjee, Senior Statistical Programmer

Abhishek Paul, Senior Statistical Programmer



6 March 2026

Disclaimer ⚠

The views and opinions expressed in this presentation are those of the presenters and do not necessarily reflect the official policy or position of their employer, affiliates, or partners.

Some parts of this presentation are taken from other sources within Sanofi and publicly available from internet which may or may not have copy right, it is solely used for this presentation purpose only.

Table of Contents

Background

Importance of Pain Assessments in Clinical Trials

Objective Measurement of Efficacy

Provide standardized and quantifiable data on pain intensity and pain relief, ensuring reliable evaluation of the drug's effectiveness

Safety and Dose Optimization

Understanding onset and duration of pain relief helps optimize dosing regimens and minimize adverse effects

Patient-Centric Outcomes

Capture real-time changes in pain, reflecting the patient's actual experience rather than relying on recall

Comparability Across Studies

Standardized assessments allow consistent comparison between different treatments and trials

Regulatory Compliance

Accurate pain assessment is required by regulatory agencies to demonstrate clinical benefit and support approval

Traditional Scheduled Pain Assessments

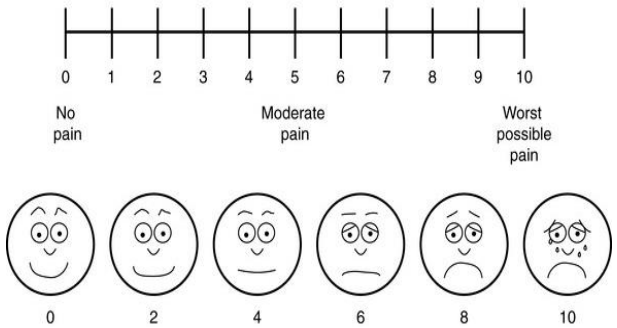
- Conducted at fixed intervals, such as pre-dose (for pain intensity only) and 0.5, 1, 2, ….., 24 hours post-dose using categorical and numerical rating scales

Pain Intensity

VERBAL RATING SCALE 6-POINT

- NONE
- MILD
- MODERATE
- MODERATELY SEVERE
- SEVERE
- EXTREME

NUMERICAL RATING SCALE 11-POINT



Pain Relief

VERBAL RATING SCALE 5-POINT

- NO RELIEF
- A LITTLE RELIEF
- SOME RELIEF
- A LOT OF RELIEF
- COMPLETE RELIEF

Starting Pain at Least 1/2 Gone

- No
- Yes

Limitations of the Scheduled Assessments for Pain Relief

Fixed Intervals

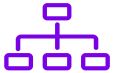
Fixed time points do not capture the dynamic and individual variations in pain relief experienced by patients

Challenges with Retrospective Reporting

Often miss the exact onset of pain relief, and patients' difficulty in recalling relief timings further reduces data accuracy

Impact on Pharmacodynamic Profiles and Drug Evaluation

Delayed recording distorts pharmacodynamics, hinders dose optimization and treatment efficacy comparisons, and leads to flawed interpretations of clinical data



Reduced Sensitivity in Treatment Comparison

Missing onset times lower sensitivity for detecting subtle differences between analgesic treatments

Individual Variability

Differences in pain perception and drug response among patients are often obscured by rigid assessment intervals

Why Double Stopwatch Method

- Developed based on the dental pain model described by Desjardins (2002), the method has demonstrated strong sensitivity and reliability for detecting analgesic onset (Cooper, 2010)
- The Double Stopwatch Method uses two synchronized stopwatches to separately capture perceptible and meaningful pain relief, providing a precise, patient-reported measure of the onset of analgesic action

Real-Time Pain Relief Onset

Provides precise, real-time tracking of perceptible and meaningful pain relief onset, improving accuracy

Supports Pharmacodynamics

Delivers granular time-to-event data critical for understanding drug action and optimizing dosing regimens

Enhanced Sensitivity

Detects even small differences in treatment onset times with high sensitivity

Reduced Recall Bias

Patients record pain experience in real time, minimizing recall bias common in scheduled assessments

Integrated and Regulatory-Compliant Analysis

Integrating stopwatch and scheduled data clarifies onset speed, peak effect, and duration, enhancing regulatory interpretability through pain-score correlations

Double Stopwatch Method: Core Data Elements

Time to First Perceptible Relief

Indicates if the participant experiences any initial pain relief detected by the Stopwatch A

First Perceptible Relief Confirmed as Meaningful

Participant confirms whether the relief felt is clinically meaningful and significant

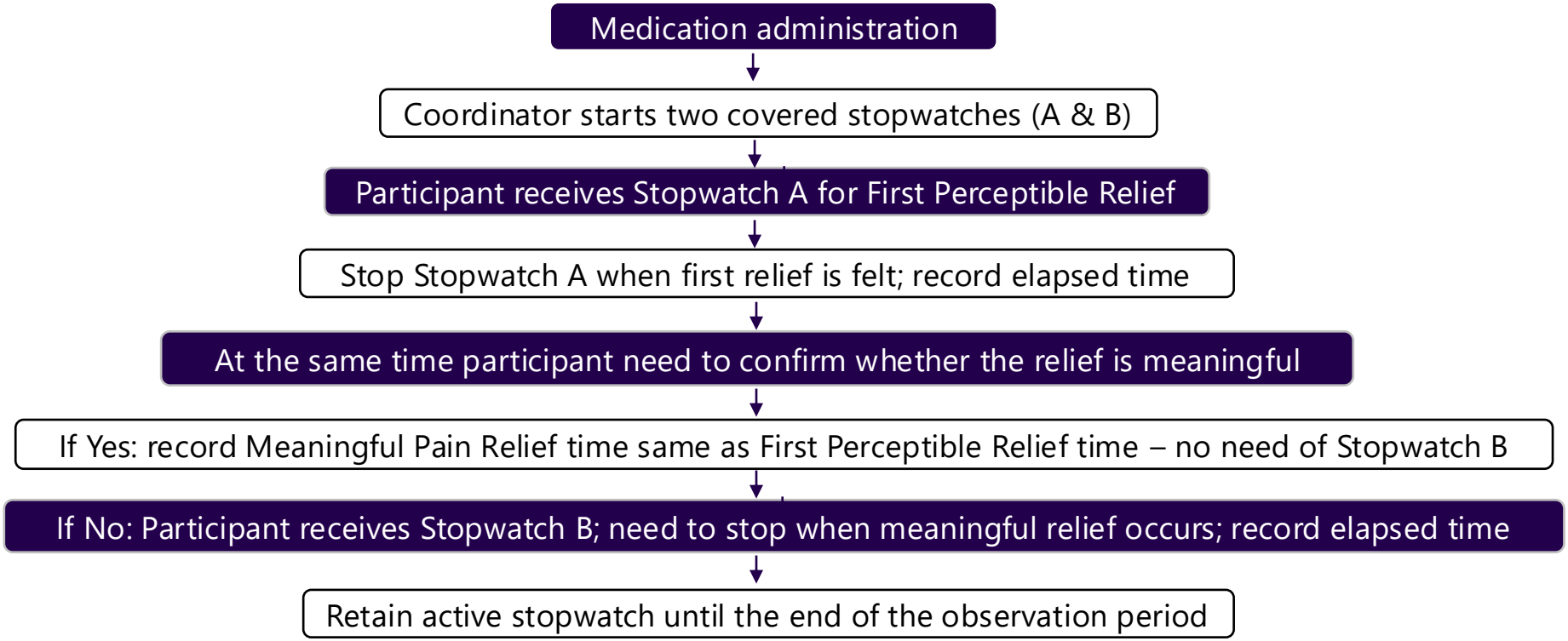
Time to Meaningful Pain Relief

Measured by Stopwatch B, this records the time until clinically significant relief occurs after initial relief

Data Integrity and Analysis

Missing time values are expected when relief does not occur till the observation period, ensuring dataset accuracy for analysis

Operational Workflow and Instructions for Participants



The faces of the stopwatches are covered to ensure that participants remain blinded to the exact time of pain relief

Scenario Mapping with Example

Case Report Form

Stopwatch Assessment

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

☐ Yes ☐ No

Stopwatch A – First Perceptible Relief

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

Time: _____ (24-hour clock)

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

☐ Yes ☐ No

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

☐ Yes ☐ No

Stopwatch B – Meaningful Relief

Enter the time when the subject experienced meaningful pain relief.

Time: _____ (24-hour clock)

Scenario	Perceptible Pain 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	-

Each scenario reflects a unique combination of perceptible relief, meaningful relief, and the timing of these events, enabling consistent interpretation across subjects

Analytical Approach

Attribute	Description
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 Duration	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 rescue medication; observation duration will be from the date/time of 1st double-blind IMP to date/time before initiation of rescue medication
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 perceptible or meaningful pain relief 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

Metadata – Time-to-event Analysis Dataset (ADTTE)

Variable	Algorithm
PARAM	Time to First Perceptible Relief
EVNTDESC	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' Else set to 'No Event'
STARTDTM	ADSL.TRTSDTM
CNSR	If EVNTDESC = 'First Perceptible Relief' then populate CNSR = 0 Otherwise, populate CNSR = 1
ADTM	If CNSR = 0 then set to QS.QSDTC in numeric format when QSORRES = 'Yes' for QSTESTCD = 'PR0108' and QSDTC < earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION' If CNSR = 1 then set as Date of end of Observation in DB period: Minimum (earliest CM.CMSTDTC where CMCAT = 'RESCUE MEDICATION', latest QS.QSDTC where QSTESTCD = 'PR0101')
AVAL	ADTM – STARTDTM, displayed in nearest minute
CNSDTDSC	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'

PR0108: QSTESTCD for the test 'Was there Perceptible Pain Relief'
PR0101: QSTESTCD for scheduled pain relief assessments through verbal rating scale

Case Study – Example 1

Scenario: Perceptible Relief ✓

Relief Confirmed as Meaningful ✗

Meaningful Relief Later ✓

Rescue Medication Taken ✓

CM

USUBJID	CMTRT	CMCAT	CMSTDTC
A-100-001	Treatment X	RESCUE MEDICATION	2025-12-18T14:56
A-100-001	Treatment X	RESCUE MEDICATION	2025-12-18T20:50

QS

USUBJID	QSTESTCD	QSTEST	QSORRES	QSDTC
A-100-001	PR0108	PR01 - Was there Perceptible Pain Relief	Yes	2025-12-18T11:52
A-100-001	PR0109	PR01 - Time to Perceptible Pain Relief	03:47	2025-12-18T11:52
A-100-001	PRCMPR	Perceptible Relief Confirmed as Meaningful	No	2025-12-18T11:52
A-100-001	PR01010	PR01 - Was there Meaningful Pain Relief	Yes	2025-12-18T21:26
A-100-001	PR01011	PR01 - Time to Meaningful Pain Relief	13:21	2025-12-18T21:26

As the subject experienced meaningful pain relief after rescue medication intake, the meaningful relief time is censored at the time to first rescue medication

ADTTE

USUBJID	PARAM	PARAMCD	STARTDTM	ADTM	AVAL	CNSR	EVNTDESC	CNSDTDSC
A-100-001	Time to First Perceptible Relief	TTFPR	18DEC2025:08:05	18DEC2025:11:52	227	0	First Perceptible Relief	
A-100-001	Time to Meaningful Pain Relief	TTMPR	18DEC2025:08:05	18DEC2025:14:56	411	1	No Event	Date/time of First Rescue Medication
A-100-001	Time to First Perceptible Relief Confirmed as Meaningful Relief	TTFPCMPR	18DEC2025:08:05	18DEC2025:14:56	411	1	No Event	Date/time of First Rescue Medication

Case Study – Example 2

Scenario: Perceptible Relief ✓

Relief Confirmed as Meaningful ✓

Rescue Medication Taken ✗

As the subject confirmed the perceptible relief as meaningful, Stopwatch B was not required further

QS

USUBJID	QSTESTCD	QSTEST	QSORRES	QSDTC
A-100-002	PR0108	PR01 - Was there Perceptible Pain Relief	Yes	2025-12-24T17:45
A-100-002	PR0109	PR01 - Time to Perceptible Pain Relief	07:15	2025-12-24T17:45
A-100-002	PRCMPR	Perceptible Relief Confirmed as Meaningful	Yes	2025-12-24T17:45
A-100-002	PR01010	PR01 - Was there Meaningful Pain Relief	Yes	2025-12-24T17:45
A-100-002	PR01011	PR01 - Time to Meaningful Pain Relief	07:15	2025-12-24T17:45

Event Observed for all the pain relief assessment scenarios at the same time

ADTTE

USUBJID	PARAM	PARAMCD	STARTDTM	ADTM	AVAL	CNSR	EVNTDESC	CNSDTDSC
A-100-002	Time to First Perceptible Relief	TTFPR	24DEC2025:10:30	24DEC2025:17:45	435	0	First Perceptible Relief	
A-100-002	Time to Meaningful Pain Relief	TTMPR	24DEC2025:10:30	24DEC2025:17:45	435	0	Meaningful Pain Relief	
A-100-002	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	

Key Takeaways 

- ✓ Double Stopwatch Method provides precise, real-time onset measurement and enhances sensitivity for detecting analgesic treatment differences
- ✓ Supports robust time-to-event analysis dataset development
- ✓ Time-to-event endpoints align with regulatory demands and patient-centric meaningful outcomes in trials
- ✓ Integrates well with intercurrent events (for e.g., rescue medication handling) and censoring logic
- ✓ Combining this method with scheduled time-point assessments offers a comprehensive view, supporting better clinical decisions
- ✓ Improves interpretability in regulatory submissions

References

- www.cdisc.org/standards
- pubmed.ncbi.nlm.nih.gov/21770716
- www.clinicaltrials.gov/study/NCT05485805
- pmc.ncbi.nlm.nih.gov/articles/PMC6194974
- ClinicalTrials.gov Protocol example NCT05317312
- www.tandfonline.com/doi/full/10.1080/03007995.2023.2294946
- www.iosrjournals.org/iosr-jdms/papers/Vol21-issue6/Ser-8/A2106080109.pdf
- 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
- Analgesic onset and efficacy of a fast-acting formulation of acetaminophen in a postoperative dental impaction pain model – PubMed
- Full article: Clinical validation of a fast-acting acetaminophen: a randomized, active and placebo controlled dental pain study
- Onset of analgesia by a topically administered flurbiprofen lozenge: a randomised controlled trial using the double stopwatch method. - Abstract - Europe PMC

Thank *you*

sanofi