
Outline of an estimand proposal in Migraine Prevention and *Neuropathic Pain Therapy*



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Overview

- Introduction *to Migraine and Neuropathic Pain*
- Study frame work/estimand components
- Intercurrent events
- Proposal for Migraine/Neuropathic pain
- Summary

Introduction to Migraine/Neuropathic pain

Migraine

- characterized by recurrent headaches, lasting 4-72 hours
- often accompanied by symptoms such as nausea, vomiting and hypersensitivity to light (photophobia) and sound (phonophobia).
- The headache attack itself is often preceded by non-specific prodromes, sensory warning symptoms immediately prior to the headache attack (aura)
- Due to these symptoms, patients report substantial impairment in their ability to perform daily or physical activities, attend school/work and function socially.

Neuropathic pain

- can be defined as a chronic pain condition initiated or caused by a primary lesion or dysfunction in the nervous system and includes pain generated at both peripheral or central nervous system.
- The conditions and the pathophysiological states that determine the onset of neuropathic pain are heterogeneous, such as metabolic disorders or neuropathy caused by viral infections.
- Neuropathic pain may be associated with mood changes, sleep disturbance, fatigue and may have an impact on physical and social functioning.

Study framework/estimand components

Migraine prevention

- For the estimand discussion we consider a typical study in migraine prevention as a double-blind, placebo-controlled trial
- 3 to 6 months trial duration for double-blind phase
- Treatment is typically given as monthly injections
- Primary variable is the number of migraine days during the last month of the trial.
- The summary measure is the treatment difference of the variable means between the active treatment group and placebo
- Alternatively, define a responder status such as response if decrease from baseline in monthly migraine days is greater than 50%
- Migraine days are assessed using an electronic diary where patients enter for each study day the (signs of) occurrence of migraine attacks, and information on migraine-specific medications and other pain medication taken.

Neuropathic pain

- For the estimand discussion we consider a typical study in neuropathic pain as a double-blind, placebo-controlled trial
- 3 months trial duration for double-blind phase
- Primary variable is the weekly mean of the 24-hour average pain score at week 12 assessed using an 11-point numerical rating scale.
- The summary measure is the treatment difference of the variable means between the active treatment group and placebo
- Alternatively, define a responder status such as response if decrease from baseline in weekly average pain level is greater than 50%
- Pain level are assessed using an electronic diary where patients enter for each study day their average and maximum pain levels and information on pain-specific medications taken.

Disease specific Intercurrent Events (ICE)

Migraine Prevention

- Intake of migraine-specific medication (e.g. Triptans, Ergotamines) to treat an acute attack or when a patient is sensing an attack is imminent – „rescue“
- Intake of other migraine-prevention medication not allowed during the trial
- Start of other preventive measures for migraine during the trial (e.g. acupuncture) not allowed during the study

Neuropathic pain

- Intake of medication to treat acute pain peaks on a study day (e.g. Paracetamol) – „rescue“
- Intake of other pain medication not allowed during the trial (e.g. opioids)
- Increase in level of allowed concomitant neuropathic pain medication

Intercurrent event handling at different steps of processing and analytics

Example 1: “Rescue” Medication – Handle ICE in data collection and/or variable definition process

Migraine Prevention (start of rescue before migraine attack)

- Treatment policy strategy:
If migraine day is defined as day with a migraine event, the evaluation would be solely based on the occurrence of an event or not, regardless if a rescue was taken or not.
- Hypothetical strategy:
A study day will count as a „migraine day“ if medication was taken, irrespective of the migraine attack occurred or not (what if rescue had not been taken)
- Composite strategy:
A study day will count as a „migraine day“ if acute migraine-specific medication was taken, irrespective of the migraine attack occurred or not („failure“ on that study day)

Neuropathic pain (intake of pain medication to treat acute pain „peaks“ on study day)

- Treatment policy strategy:
Report the pain level for the day as planned at the end of the day irrespective of intake of paracetamol
- Hypothetical strategy:
Patient to report average pain for the day level prior to the intake of paracetamol (what if paracetamol had not been taken)
- Composite strategy
For example report highest level of pain prior to intake of paracetamol („failure“ day)

Intercurrent event handling at different steps of processing and analytics

Example 2: “Intake of prohibited medication – Handle ICE in analysis process

Migraine Prevention

- Treatment policy strategy:
Ignore the fact that prohibited medication was taken and count migraine days if migraine occurred (or migraine specific medication was taken).
- Hypothetical strategy:
Depending on the duration of intake of prohibited medication, model expected number of migraine days during that period (e.g. prorate from remaining unaffected days during that month)
- Composite strategy:
Patient will count as not having obtained response, if prohibited preventive migraine medication has been initiated

Neuropathic pain

- Treatment policy strategy:
Report the pain level for the day irrespective of intake of prohibited medication
- Hypothetical strategy:
Replace reported data with modeled data during the time the prohibited medication was active („what if prohibited medication had not been given“)
- Composite strategy
For example, replace reported pain level for the days the prohibited medications were active by the highest level of pain possible (or by the highest level experienced during the past x weeks prior to the intake)
With repeated intake, classify patient as a non-responder in analysis.

General concept

- Handling of data collected after an ICE or handling of missing values can happen on different levels of the data processing if a PRO is used to collect the data on a frequent basis (such as daily)
 - During the data collection process (e.g. ask patient to record the relevant value before the ICE)
 - During dimension reduction process (e.g. only use a subset of values or modeled values for averaging when determining the weekly/monthly outcome variable)
 - During the derivation of the primary endpoint (e.g. assign failure status for patients who start prohibited medication irrespective of timing or patients who discontinue treatment prematurely)
- This provides a flexible approach also for indications beyond migraine prevention and chronic neuropathic pain.

Proposal for estimands for ICE in migraine prevention

Intercurrent event	Estimand strategy	Comments
Use of “rescue” medication (e.g. Triptans)	Composite strategy on assessment level , define “failure” for respective study day, i.e. count a migraine day irrespective of occurrence of a migraine attack	Failure on a study day basis
Use of prohibited medications for migraine	Composite strategy, i.e. define patient as a treatment failure for responder analysis	Failure on a patient level basis or failure on a study day basis used in counting of migraine days.

Clinical question of interest (regulatory)

- **Composite variable strategy:**

Estimand: The effect of treatment on the chance of seeing a 50% reduction in days with migraine or use of rescue medication, without use of prohibited preventive migraine medication, while remaining in the study

Proposal for estimands for ICE in chronic neuropathic pain

Intercurrent event	Estimand strategy	Comments
Use of short term acute “rescue” medication (e.g. Paracetamol)	Hypothetical strategy by collecting the value prior to intake as representative for that day (what if no rescue would have been taken)	Handling on a study day basis
Use of prohibited medications for neuropathic pain	Composite strategy, i.e. define patient as a treatment failure for responder analysis	Failure on a patient level basis

Clinical question of interest (regulatory)

- **Composite variable strategy:**

Estimand: The effect of treatment on the chance of seeing a 50% improvement in average weekly pain levels without starting prohibited pain medication. Patients are required to enter pain levels prior to intake of short acting pain medication on a study day.

Summary

- In indications where PROs are collected on a frequent (daily/weekly) basis we can deal with intercurrent events at different stages of data collection, handling, and analysis.
- Estimand thinking is important already at the data collection stage dictating how and what data should be collected when an ICE occurs.
- Estimands involving mixtures of hypothetical, composite, and treatment policy strategies might seem complicated to interpret, but could be useful when transparently documented.
- The strategies presented for migraine prevention and chronic neuropathic pain can easily be adopted in trials studying symptomatic treatments in other non-progressing neurological diseases.
- The NS estimand subteam is currently working on an integrated approach across such indications.

Backup

Strategies for handling ICE

- **Following a treatment policy strategy:**
We ignore the intercurrent event and use the data observed after the intercurrent event (assuming no future missing data problem)
- **Following a hypothetical strategy:**
We try to estimate quantities of interest assuming the ICE would not occur
- **Following a composite variable strategy:**
We make the intercurrent event part of the primary endpoint event, i.e. define response as “failure” if the intercurrent event occurs irrespective of the result of the clinical endpoint.

Intercurrent event handling at different steps of processing and analytics

Example 3: Treatment discontinuation due to adverse events or lack of efficacy

Migraine Prevention

Generally ask patient to continue recording migraine and specific medication information in the diary for the rest of the study irrespective of treatment discontinuation

- Treatment policy strategy:
Use the recorded values after the treatment discontinuation and determine the value of the primary variable based on all available values.
- Hypothetical strategy:
Replace the recorded values with modeled values assuming patient had continued treatment until the planned end of the study*
- Composite strategy:
Assign „failure“ status in a responder analysis of treatment effect

Chronic neuropathic pain

Generally ask patient to continue recording pain levels and pain specific medication information in the diary for the rest of the study irrespective of treatment discontinuation

- Treatment policy strategy:
Use the recorded values after the treatment discontinuation and determine the value of the primary variable based on all available values.
- Hypothetical strategy:
Replace the recorded values with modeled values assuming patient had continued treatment until the planned end of the study
- Composite strategy:
Assign „failure“ status in a responder analysis of treatment effect

* modeling may take into account the nature of application e.g. a monthly injection and the fact that efficacy activity can persist for more than a month after last intake