A journey towards estimand specification in pain: motivation and challenges

Francesca Callegari, PhD
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Quote

"We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time."
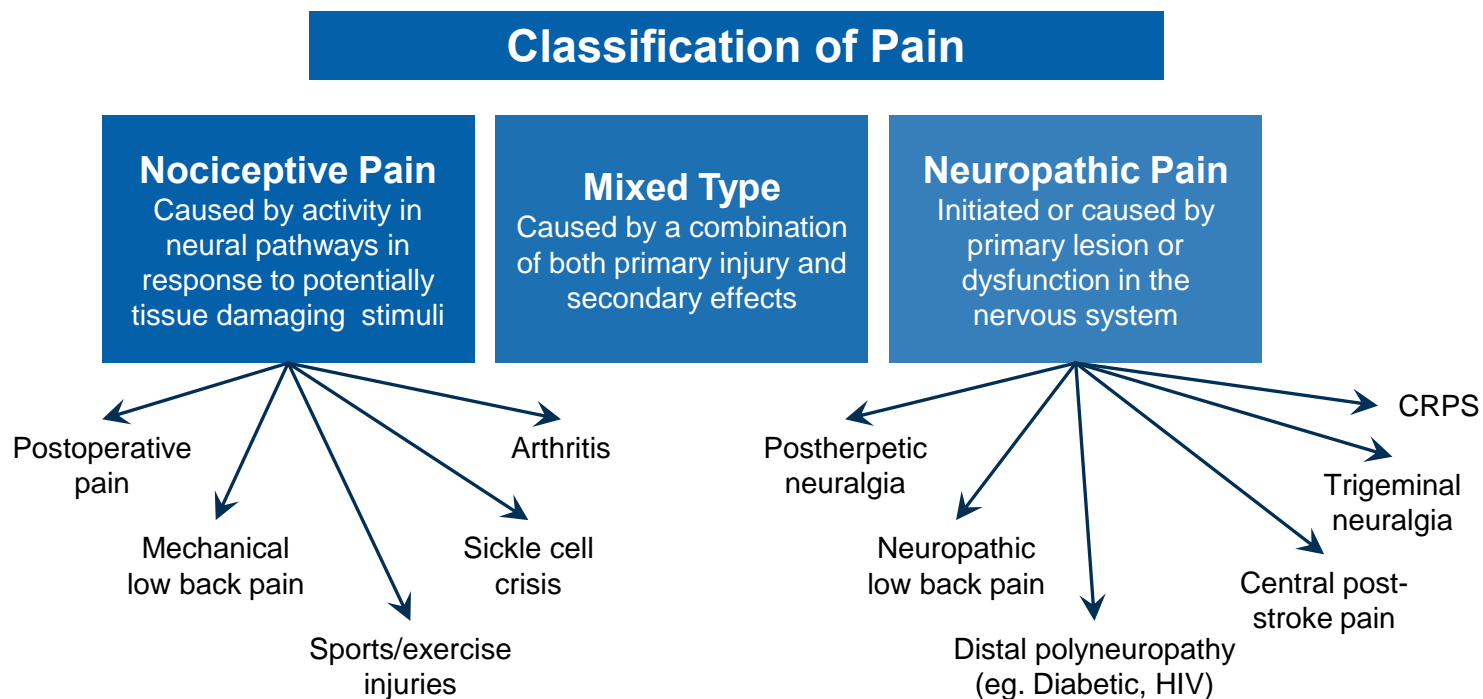
T.S. Eliot

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Agenda

1. What is pain?

2. How is pain measured?

3. Estimand specification: motivation and challenges

4. Estimand key attributes

5. Primary estimand: definition and rationale

6. Estimation of primary estimand

7. Supplementary estimands

8. Overcome challenges and opportunities

9. Conclusions/Q&A

What is pain?

- *Pain* is an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both*

- Pain can be nociceptive or neuropathic

Classification of Pain

Nociceptive Pain
Caused by activity in neural pathways in response to potentially tissue damaging stimuli

Mixed Type
Caused by a combination of both primary injury and secondary effects

Neuropathic Pain
Initiated or caused by primary lesion or dysfunction in the nervous system

Postoperative pain

Arthritis

Postherpetic neuralgia

CRPS

Trigeminal neuralgia

Mechanical low back pain

Sickle cell crisis

Neuropathic low back pain

Central post-stroke pain

Sports/exercise injuries

Distal polyneuropathy (eg. Diabetic, HIV)

CRPS, complex regional pain syndrome; HIV, human immunodeficiency virus

As defined by International Association for the Study of Pain

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Chronic Pain vs. Acute Pain

- **Acute Pain**: pain with a warning function. It is of **short duration (less than 3-6 months)** and declines with the healing of the underlying injury or disease (e.g. post-surgical pain).

- **Chronic Pain**: pain that persists past normal healing time and hence lacks the acute warning function of physiological nociception. Usually it is regarded as chronic when it **lasts or recurs for more than 3-6 months** (ICD-11 classification).

  – Chronic pain includes chronic pain from different etiologies, such as chronic cancer pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain etc.

How is pain measured?

- The Numerical Rating Scale (NRS) is an 11–point scale for patient self-reporting of pain.

Numerical Rating Scale:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain

- Patients will evaluate their average pain during the past 24 hours based on NRS on an electronic diary device.

- Weekly mean of the 24h average pain score=average of seven daily pain intensity scores measured in that week.

- The primary efficacy variable is the change from baseline to the last week of study in the weekly mean of the 24-hour average pain score.

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Estimand: motivation and challenges

Motivation

- At the time of Phase 2 study design, interest to clearly understand the treatment effect of the study drug vs. placebo

- In previous interactions, HAs requested discussion on estimand

Challenges

- Estimand is a complex entity to be defined, due to a variety of factors (disease characteristic and multitude of possible confounders)

- To define it, discussion needed among multiple stakeholders (including clinicians, statisticians etc)

- Upcoming ICH E9 addendum in preparation during study design, however not yet released

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Estimand: key attributes

- **Target population**
  - Patients suffering from the chronic pain condition at a moderate to severe disease stage. Patients may or may not be already on a concomitant medication for pain.

- **Variable**
  - Change from baseline to last week of the study in weekly mean of the 24h average pain score measured by NRS

- **Intercurrent events**
  - Events happening post-randomization, which can be an expression of how well the treatment works, but also of its safety and tolerability

- **Summary measure**
  - Treatment difference of variable means between study drug and placebo.

We focus primarily on the **intercurrent events.**

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Intercurrent events

- **Events not leading to study treatment discontinuation, with potential confounding effect:**
  - E.g. Changes in doses of allowed concomitant medications for pain

- **Events leading to study treatment discontinuation:**
  - Adverse events (AEs)
  - Lack of efficacy (LoE)
  - Use of other concomitant medications leading to treatment discontinuation
  - Other reasons

Note: Patients are allowed to take short-acting pain relief medication during the study, however no confounding is expected.

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Primary estimand: definition

We are interested in the **treatment effect if patients**:

- would not change dose of allowed concomitant medications for pain

- are allowed to take short-acting pain relief medication

- would continue to be treated for the entire study duration unless forced to discontinue treatment due to

  - AE

  - lack of efficacy

  - use of other concomitant medications leading to treatment discontinuation

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Primary estimand: justification

- In Phase 2, the treatment effect of the drug is not yet fully elucidated.

- Therefore, desire to quantify the treatment effect of the study drug under the situation where:
    - any potential confounders are removed, since these could lead to an attenuation or a dilution of the treatment effect of interest
    - the drug is taken for the stipulated duration, however
    - we cannot ignore the situations when a patient can no longer tolerate or benefit from the treatment (e.g. occurrence of AE, LoE etc), from whom a continuation of treatment would not be conceivable
    - other patients who discontinued the drug due to other reasons could have theoretically continued to be treated without being put at undue risk

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Estimation

Primary estimator based on **ANCOVA model** applied **after multiple imputation.**

Changes in dose of allowed concomitant medications for pain accounted for as follows:

- Eliminate confounding effect by excluding "affected" observations and imputing them based on a *missing at random* assumption

- I.e. we assume that these patients could continue to be treated and derive a benefit from the study drug in a similar way to similar patients in the same treatment arm who did not have such change in dose

Note: Intake of short acting pain relief medication: use the observed efficacy data (no confounding expected)

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Estimation (cont'd)

- **Discontinuations due AE, LoE, use of other concomitant medications:**

  Test treatment arm:

  – Use data after treatment discontinuation if available

  – else, multiple imputation of missing data based on placebo arm data (*jump to reference*) from similar patients [Carpenter et al 2013].

  Placebo arm: Multiple imputation based on *missing at random assumption*

- **Discontinuations due to other reasons**:

  Both arms: Multiple imputation after study treatment discontinuation based on similar patients in the same treatment arm (*missing at random assumption*).

Sensitivity analyses have also been specified to assess the robustness of estimation for the primary estimand.

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Implied design features

The estimation method relies on the following **design features**:

- Information on changes in dose of allowed concomitant medications for pain

- Retrieved Dropout: data collected after study treatment discontinuation

Therefore, the estimand impacts study design and study conduct.

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Supplementary estimands

First supplementary estimand: Target the treatment effect if patients

- do not change dose of allowed concomitant medications for pain

- are allowed to take short-acting pain relief medication

- continue to be treated for 12 weeks, unless they are forced to discontinue study treatment for reasons that are not administrative

Justification: While the primary estimand is of highest clinical relevance, it cannot be completely ruled out that other reasons of study treatment discontinuation are associated with an unfavorable outcome.

Supplementary estimands (cont'd)

Second supplementary estimand: Target the treatment effect if patients

- do not change dose of allowed concomitant medications for pain

- are allowed to take short-acting pain relief medication

- continue to be treated for the entire study duration

Justification: Allows a comparison to historical trials that have traditionally targeted the effect in the investigational drug in the scenario where all patients adhere to the treatment for the full duration.

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Supplementary estimands (cont'd)

Third supplementary estimand (treatment-policy):

Targets the treatment effect regardless of presence of intercurrent events, e.g. regardless of adherence to study drug and regardless of intake of other medications

Justification: it may be of interest in later drug development stages and it is proactively included in Phase 2 to ensure comparability with target effect that may be estimated in later trials

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Challenges overcome

- In this indication, patient characteristic (e.g. elderly population) with co-morbid diseases and use of several concomitant medications created a complexity of intercurrent events

- It was difficult to **isolate the treatment effect** of **clinical relevance.**

- The specification of the scientific questions related to the trial objectives required **numerous discussions** among stakeholders.

- We were able to **successfully define** primary estimand based on highest clinical relevance and supplementary estimands

- We **successfully incorporated** these concepts in study protocol and further trial documentation

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Opportunities

- **Opportunity** to more transparently define the target treatment effect (based on highest clinical relevance) and propose suitable statistical methods to address it; also to define other possible target treatment effects

- The estimand specification directly **guided** the choice of the statistical analysis needed to quantify the primary treatment effect of interest.
  – Statistical analyses completely linked to trial objectives and scientific questions

- The estimand specification **guided** the **collection of additional data** necessary to address the scientific question of interest
  – e.g. data after study treatment discontinuation, data on changes in doses of allowed concomitant medications for pain

- More work will be needed as the knowledge evolves, but now we have the framework to continue it

Recommendations

- Adopting estimand framework will allow **alignment** between study objectives, scientific questions of interest and methods of analysis

- The complexity of the field may require **several discussions** to isolate the target treatment effect, thus it is **recommended to engage early in this discussion**

- HAs are adopting already the estimand framework, the proactive estimand specification will allow an **easier communication with HAs** on this theme

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Conclusion

We have not ceased from exploration

We have arrived where we started, but now we know the place much better

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