Federal Institute
for Drugs
and Medical Devices

Regulatory considerations on estimands in pain studies

1st EFSPI-Workshop on Regulatory Statistics

Ann-Kristin Leuchs / 12.09.2016 / Basel

Disclaimer

Views expressed in this presentation are the author's personal views and not necessarily the views of BfArM.

This presentation is work in progress and contains the author’s current thinking on the subject.

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    - Symptomatic versus “disease-modifying”
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Introduction

Introduction

- Pain often categorised as mild/moderate/severe
- Difficult/impossible to objectively measure pain
- Endpoints in pain studies: patient self-reported outcomes
    - VAS (visual analogue scale, 0-100)
    - NRS (numeric rating scale, 0-10)
    - multidimensional scales (e.g. NPS, NPSI)

- Most common types of post-randomisation events in pain studies
    - **Use of rescue medication as add-on** to study medication
    - Treatment discontinuation
        - Stopping treatment completely
        - Switching to alternative treatment

Estimands in pain studies

Estimands in pain studies

- Phase III trial to compare new analgesic to a control for the treatment of pain
- Randomised, controlled, double-blind, parallel-group
- 12 weeks duration
- Endpoint: 11-point numeric rating scale averaged over the last week

- Rescue medication allowed
- Patients may not adhere to treatment (due to AEs, LoE, or other reasons)
    - Treatment discontinuation
    - …

- Superiority over placebo or non-inferiority compared to active control
- No restriction to specific pain severity

Estimands in pain studies

	Treatment policy estimand	Attributable estimand	De jure estimand "if all patients had adhered and not taken rescue medication"
Population			
Endpoint			
Measure of intervention effect			

Estimands in pain studies

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Population	Intended post-approval population of patients with pain as defined in the study protocol	Intended post-approval population of patients with pain as defined in the study protocol	Intended post-approval population of patients with pain as defined in the study protocol
Endpoint	Change from baseline to week 12 in the average weekly pain intensity measured on an 11-point NRS scale	Change from baseline to week 12 in the average weekly pain intensity measured on an 11-point NRS scale	Change from baseline to week 12 in the average weekly pain intensity measured on an 11-point NRS scale
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Estimands in pain studies

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Measure of intervention effect	Subject-specific effect regardless of the intake of rescue medication and regardless of the treatment actually received → 'treatment + rescue' versus 'control + rescue'	Subject-specific effect of the initially randomised treatment assuming that the effect of treatment disappears if patients discontinue treatment or take rescue medication (i.e. no mean difference to control after discontinuation or rescue intake)	Subject-specific effect of the initially randomised treatment had all patients adhered to treatment and not taken rescue medication

Estimands in pain studies

- Treatment policy estimand
- Attributable estimand

Potentially reduced assay sensitivity

↓

Discouraged in non-inferiority studies

- De jure estimand

Tend to be more sensitive in non-inferiority settings
("pure pharmacological effect")

Rescue medication
Add-on versus switch (superiority)

- In general, distinction between:
  - Rescue medication as add-on to study treatment
  - Switching from study treatment to rescue medication

Add-on Rescue medication

- Rescue medication will also be available and taken in practice
- Combined effect of rescue and study treatment of highest relevance

→ Treatment policy estimand

Switching to rescue medication

- Distinction between
  - Symptomatic treatment settings
  - "Disease-modifying setting"
    → medication affects the cause of the disease/symptoms and not only the symptoms

Pain **Other indications**

Switching to rescue: Symptomatic versus “disease-modifying” (superiority)

Symptomatic treatment setting

- Symptoms will return after discontinuation of treatment
- Medications (study medication and rescue/switch) should be evaluated on their own

→ De jure estimand

“Disease-modifying setting”

- Chronology of treatments is important
- (Immediate) return to baseline not likely

→ De facto estimands

Mild versus severe pain

Mild pain

- Low rescue medication rates
- Depending on previous considerations one of
  - Treatment policy estimand
  - Attributable estimand
  - De jure estimand

Severe pain

- Intake of rescue medication in most patients
- De jure estimand not evaluable
- De facto estimands insensitive

- Estimands for alternative endpoints should be considered

Estimands in pain studies

	De facto: rescue medication estimand
Population	Intended post-approval population of patients with pain as defined in the study protocol
Endpoint	1. Amount of rescue medication needed during the 12-week study period **or** 2. Time to first intake of rescue medication
Measure of intervention effect	Subject-specific effect in the amount of rescue medication or time to first intake of rescue medication during the whole study period irrespective of adherence to the initial treatment

Estimands in pain studies

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	De facto: rescue medication estimand
Comments	• Assumes that pain is regulated by rescue medication to a given level
Analysis	ANCOVA or log-rank test / Cox regression • Follow-up of all patients with respect to rescue medication required

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Other options:

- Rank-based estimand
  → ranking according to (1.) time to rescue and (2.) pain intensity
- …

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Example

Combining aspects of different estimands

Example
Combining aspects of different estimands

- Phase III trial to compare new analgesic to placebo for the treatment of mild to moderate pain
- 12-weeks, randomised, double-blind, parallel-group, placebo-controlled
- Primary endpoint: NRS (weekly average pain intensity score at week 12)

- Superiority of active treatment over placebo
- Add-on rescue medication permitted
- Patients may discontinue study treatment

Proposed estimand

	Estimand
Population	Intended post-approval population of patients with pain as defined in the study protocol
Endpoint	Change from baseline to week 12 in the average weekly pain intensity measured on an 11-point Numeric Rating Scale (NRS)
Measure of intervention effect	• Treatment effect regardless of rescue medication (as add-on to study medication) • It is assumed that the effect of treatment disappears after **treatment-related** discontinuation of study medication (jump to reference) • Patients discontinuing treatment due to **non-treatment-related** reasons are assumed to behave like similar patients (i.e. same baseline covariates and measurement history) that remained in the study

Example
Combining aspects of different estimands

Considering the different post-randomisation events

- Treatment discontinuation
- Rescue medication (added to study medication)

a combination of aspects of different estimand is considered:

- **Treatment policy aspect** for the intake of recue medication on top of study treatment
- **Attributable aspects** for treatment-related discontinuation of study medication, i.e. assuming a disappearing effect of treatment after discontinuation
- **De jure aspects** (“if all had adhered and not discontinued treatment”) for non-treatment-related discontinuation of study medication

Example
Combining aspects of different estimands

- Combining these different aspects seems reasonable

- Treatment-related discontinuation of study medication is an unfavourable outcome and should be accounted for
- **However**: difficult to be sure that non-treatment-related discontinuations of study medication are really non-treatment related

Hence, considering the confirmatory nature of phase III trials a combination of

- Treatment policy aspect for added rescue usage
- Attributable aspect for treatment discontinuation due to **any** reason

might be a more appropriate choice from a regulatory perspective.

↳ **attributable estimand for 'active + rescue' vs. 'pbo + rescue'**

Thank you very much for your attention!

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