Some Thoughts on Estimands in a Chronic Pain Indication

1st EFSPI-Workshop on Regulatory Statistics

12 SEP 2016 / PD Dr. Christoph Gerlinger; Dr. Michael Kunz / Basel
Agenda

- Medical Background
- Problem Statement
- Physicians’ Wish List for the Label
- Options to Specify an Estimand
- Summary
Acknowledgements & disclaimer

This is work in progress and the talk represents the current thinking of the authors

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Medical background: endometriosis

Relieving pain

Endometrial tissues can migrate to various organs in the abdominal cavity and cause inflammation there. Women who are affected by this condition generally suffer extreme pain. Bayer scientists are now taking a two-fold approach to the disease: they are developing active substances that both inhibit inflammation and influence the onset of pain signals in the endometrial lesions and the peripheral nervous system.

A crisis in the abdomen: endometriosis causes extreme pain that can seriously restrict the sufferer’s daily life.

Sites of action of new active substances:

- Pain stimulus is suppressed
- Inflammation is prevented from spreading
Problem statement

Pain killers (rescue medication) can be taken in addition to study drug that might affect the primary outcome

- Study specific rescue medication provided (for standardization)
- Use of rescue pain medication
  - Is by itself an outcome
  - Needs to be accounted for
Problem statement – 2

Different from diabetes “toy example“

- Rescue medication is add-on not replacement of study drug
- Patient decides
  - Whether to take rescue medication
  - Dose of rescue medication
- Huge daily variations within patients
- Pain correlated with menstrual cycle (in a subset of patients)
Pain measurement (ePRO)

11-point Numerical Rating Scale (NRS) with **daily recall**:

Number of rescue tablets taken (daily)
Intake of other pain medication is also recorded
Two typical endometriosis pain patterns

Days with rescue medication

Days w/o rescue medication

Pain correlated with bleeding

Pain independent of bleeding
Physicians’ wish list for the label

I would be interested in the

- effect in patients not responding to drug class “X”
- effect attributable to the drug
- effect in all patients
- proportion of patients who discontinue due to AE or lack of efficacy

I would prefer to

- separate efficacy and non-adherence as much as possible
Recall: An **estimand** is that what is to be estimated to address the scientific question of interest

The choice of an estimand involves

- Population of interest
- Endpoint of interest
- Measure of intervention effect
Population with adequate disease severity

- Disease severity to exceed a certain threshold at baseline

Two populations of interest:

- Patients with the disease, non-responder to drug class “X”
  - Important for health technology assessment
- All patients with symptomatic disease
Need a summary measure over the female cycle (~28 days/4 weeks) due to periodicity of endometriosis pain in many patients

Mean (or AUC) not sensitive due to periodicity and/or huge daily variations

Proposal: Mean of worst 7 days in 28 days/4 weeks
Number of successful days (in 28 days/4 weeks), defined as

- pain below a certain threshold $c$ and
- no intake of pain medication

Discussion points:

Threshold $c$ as an element of a responder analysis

- Averaging over several values of $c$?
- $c$ chosen individually for each patient? E.g. 50% reduction from baseline?
- No pain medication too strict?
  - E.g. no more pain medication than at baseline?
Treatment difference (based on change from baseline)

- Taking rescue medication into account

Mean of worst 7 days:

- Hypothetical pain values are imputed on days with rescue
- Pain score treated as censored on days with rescue
- Bivariate analysis of pain and rescue
  (Röhmel et al. Biometrical Journal 2006;48(6):916-33.)
Number of successful days:

- Straightforward, given the threshold definitions

Proportion of patients not discontinuing due to AE or lack of efficacy:

- Data are (almost) complete by definition
- A non-inferiority setting
- Challenge: Defining the non-inferiority margin
Summary

• The estimands framework greatly facilitates the discussions between clinicians, statisticians, and other stakeholders

• Accounting for rescue medication (or other pain medication) in chronic pain not obvious

• Defining ‘successful days’ for the patient might be a solution
  • But, no generic definition of ‘successful days’
  • Not yet discussed with regulatory agencies

• Work in progress
Thank you!