Using PROs in clinical trials: what should I know about “estimands”? 

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*Presented by: Rachael Lawrance* 

*Co-authors: Philip Griffiths, Evgeny Degtyarev, Kaspar Rufibach, Kim Cocks* 

defining value >> driving decisions >> delivering success
Objectives

> What is an “estimand”?  
  – ICH, E9 (R1) addendum & estimand framework

> How do I develop a good estimand for a PRO objective in a clinical trial?  
  – Step by step example

> Why is this topic important to me?  
  – Key take-away message
What is ICH?

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

MEMBERS

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Founding Regulatory Members
  - EC, Europe
  - FDA, United States
  - MHLW/PMDA, Japan

Founding Industry Members
  - EFPIA
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  - PhRMA
What is ICH E9 (R1) Addendum
What is an estimand?

Trial objective → Estimand → Main estimator → Main estimate

Target of estimation = WHAT TO ESTIMATE

Method of estimation = HOW TO ESTIMATE
Five components of an estimand

- **Population**
- **Treatment**
- **Variable of interest**
- **Intercurrent event handling**
- **Summary measure**

**Example:** pain

**Variable of interest**

**Intercurrent event handling**

**Example:** mean

Something that prevents the observation of the endpoint in a clinical trial or affects its interpretation.

**Examples:**
- stop treatment
- death
Patients’ Journeys

Randomisation
Start 1st treatment

6 months

Disease Progression

Off treatment

Adverse event

Subsequent treatment

Died

Died
Building an estimand

“What is the effect of drug X on PROs?”

- Population
- Treatment
- Endpoint (variable of interest)
- Intercurrent event handling
- Summary measure

ESTIMAND
Building an estimand

What is the effect of drug X on patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation
In advanced cancer patients, what is the effect of drug X on patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation.
In advanced cancer patients, is there a difference between treatment with drug X compared to drug Y on patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation.
In advanced cancer patients, is there a **meaningful difference in mean score** (> 7-points) between treatment with drug X compared to drug Y on patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation.
Defining events:
> #1 Treatment discontinuation
> #2 Death

Agree a strategy to handle them
Intercurrent event: treatment discontinuation

What is meant by “after 6 months post randomisation”? .... Is it after 6 months of treatment or regardless of treatment discontinuation?

- Treatment policy: ...after 6 months post randomisation regardless of treatment discontinuation
  - Collect data until month 6 (including beyond disease progression)

- Hypothetical: ...after 6 months post randomisation in the absence of treatment discontinuation
  - Collect data until month 6 or treatment discontinuation, whichever comes 1st

- While on treatment: ...after 6 months post randomisation or at the time of treatment discontinuation
Intercurrent event: death

What is meant by “after 6 months post randomisation”? ..... and what if patient dies before 6 months?

Treatment policy

...after 6 months post randomisation regardless of death

While on treatment

...after 6 months post randomisation or until the time of death
In advanced cancer patients, is there a meaningful difference in mean score (> 7-points) between treatment with drug X compared to drug Y in patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6-months post-randomisation or death (whichever occurs first), regardless of treatment discontinuation?
In advanced cancer patients, is there a meaningful difference in mean score (> 7-points) between treatment with drug X compared to drug Y in patient’s perceived pain, as measured on the EORTC QLQ-C30, after 6-months post-randomisation or death (whichever occurs first), regardless of treatment discontinuation?
Implications

> Different stakeholders (patients, physicians, regulators, payers) may prefer different estimands and this framework facilitates discussions between all of them
  - also helps to understand whether current typical PRO analyses actually address relevant questions for patients

> Choice of estimand may need to influence protocol design e.g. maybe PRO data has to be collected after treatment is stopped

> A very precise estimand will enable statisticians to think about exactly how to analyze the data

> A clearer estimand will enable much clearer interpretation
Take-Away messages

> Understanding the new estimand framework developed by ICH is essential for designing good clinical trials containing PROs

> A good estimand for a PRO objective in a clinical trial has five components to consider
  - In particular intercurrent events need thought and discussion; may need a number of different estimands

> This is an example of how to think about building an estimand – please apply it to your clinical studies!

> The estimand framework is not just a new language – it will change the way clinical trials are designed, analyzed & interpreted – let’s ensure that objectives relating to patient’s perspective are at the heart of this
Thank you – Any Questions?