Adelphi

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

Tuesday 22nd October Session 208.4

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defining value >> driving decisions >> delivering success

Objectives

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- 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?

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

ICH
harmonisation for better health

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ISOQOL 26th Annual Conference
20-23 October 2019
San Diego, California, USA

What is ICH E9 (R1) Addendum

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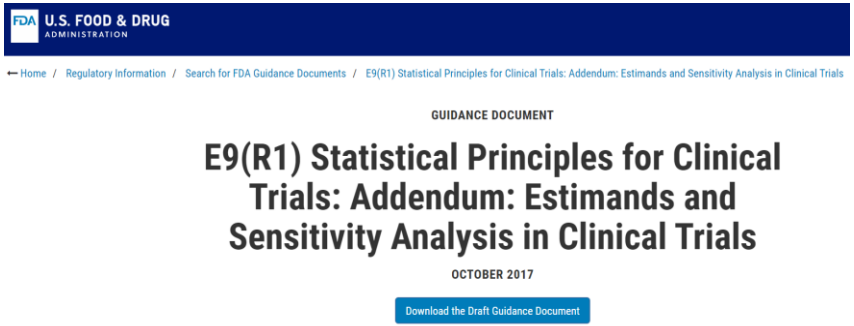
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998



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What is an estimand?

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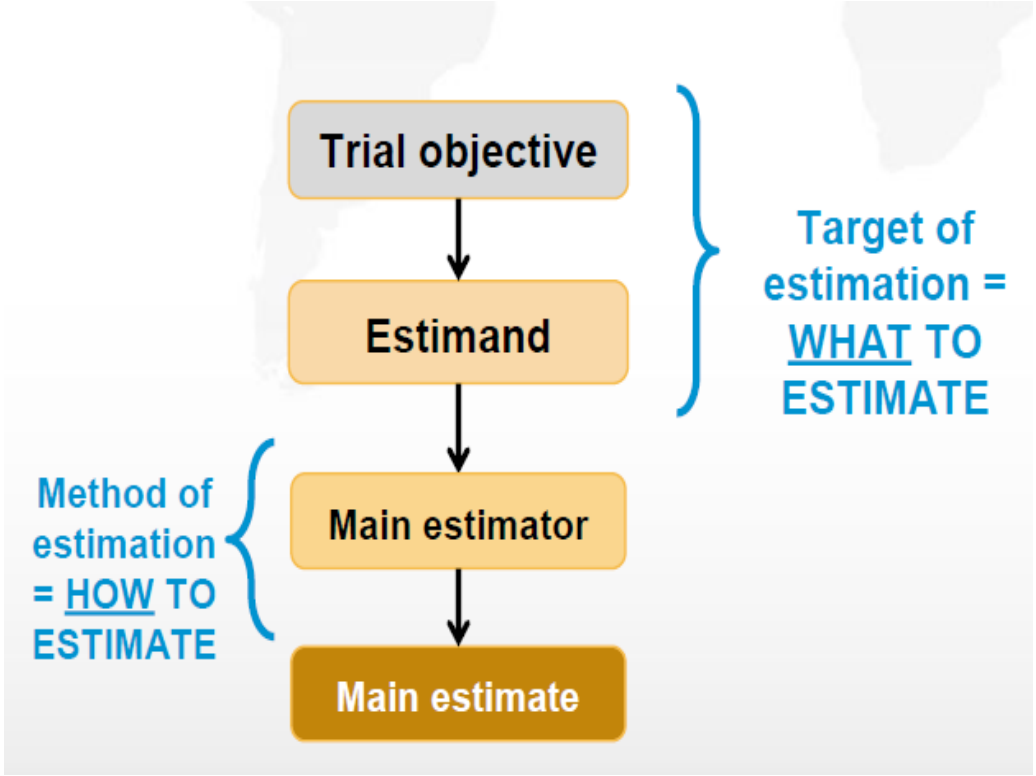

Five components of an estimand

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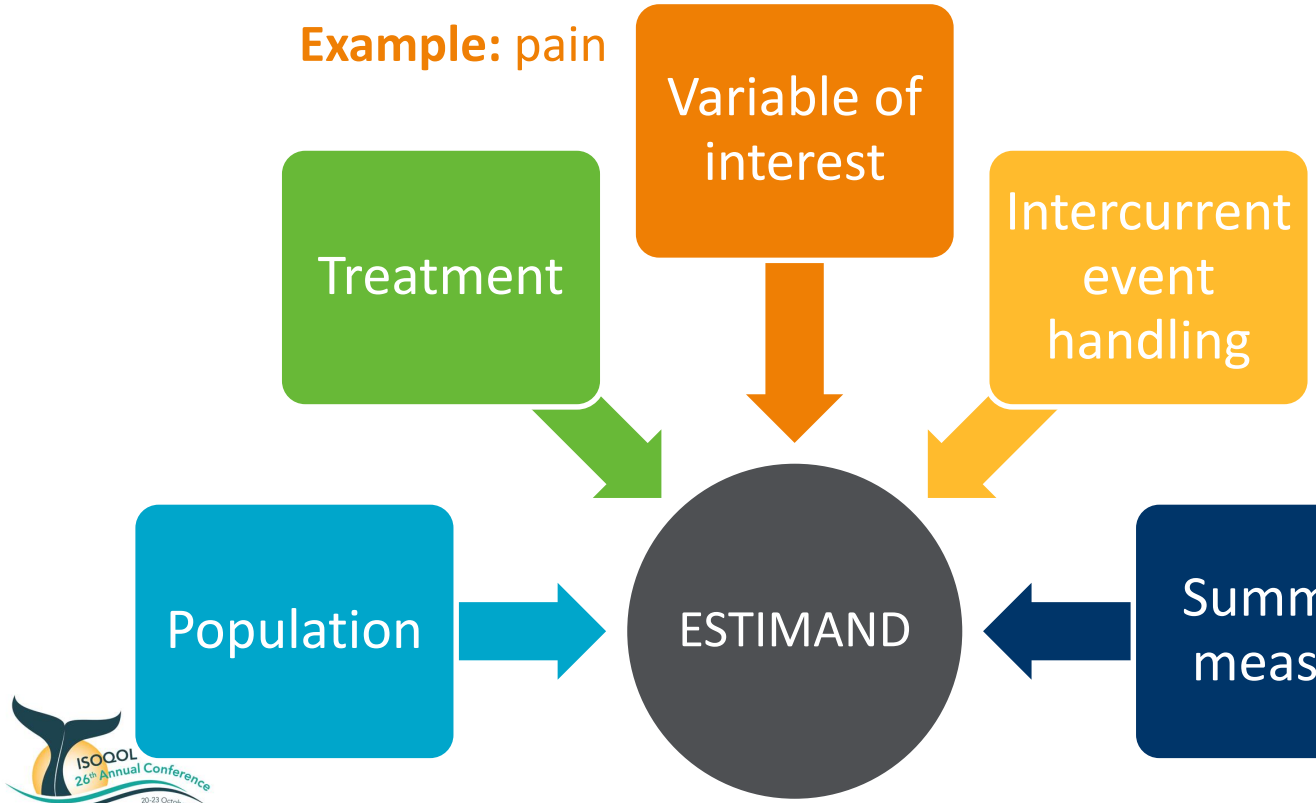

Something that prevents the observation of the endpoint in a clinical trial or affects its interpretation

Examples:

> stop treatment

> death

Patients' Journeys

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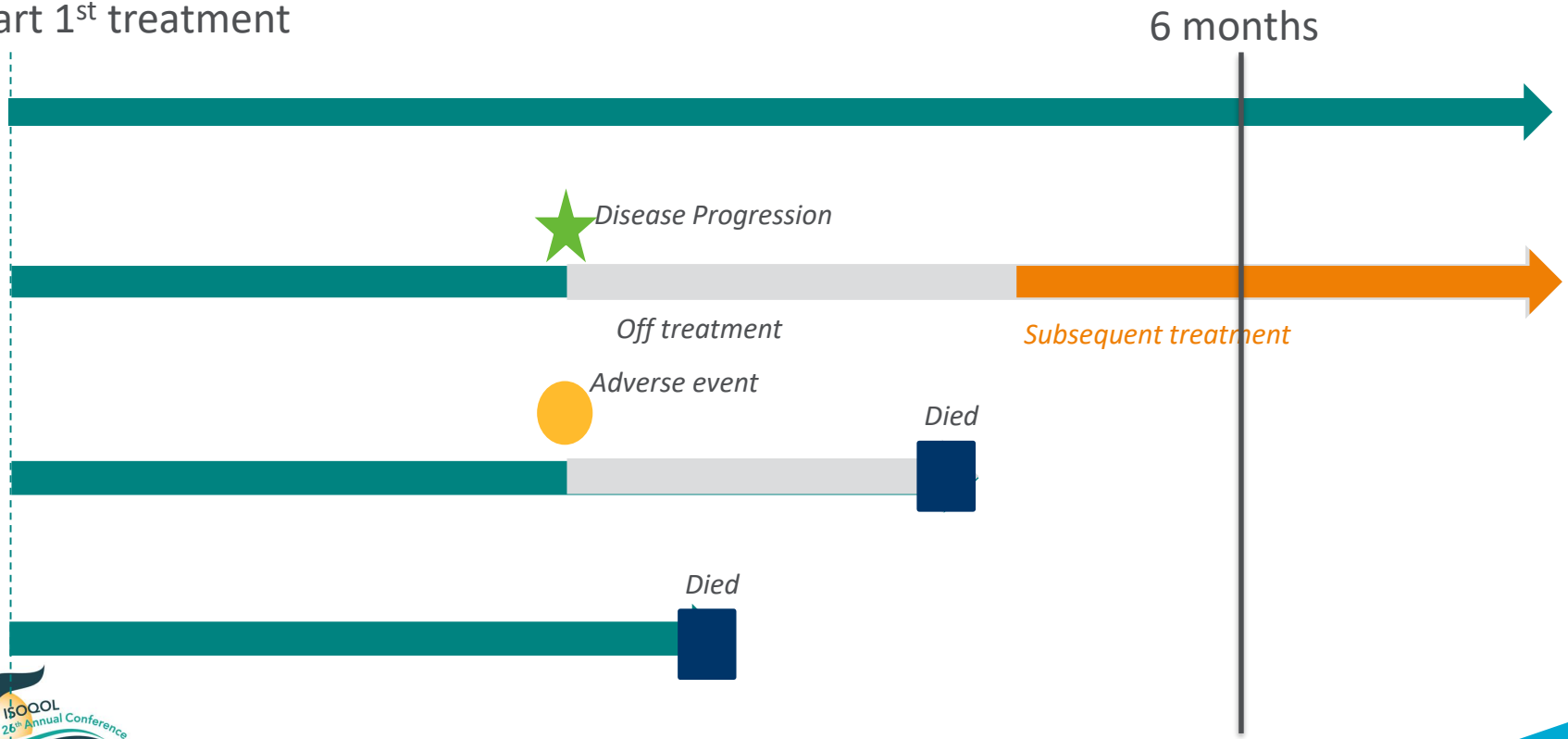
Randomisation
Start 1st treatment



Building an estimand

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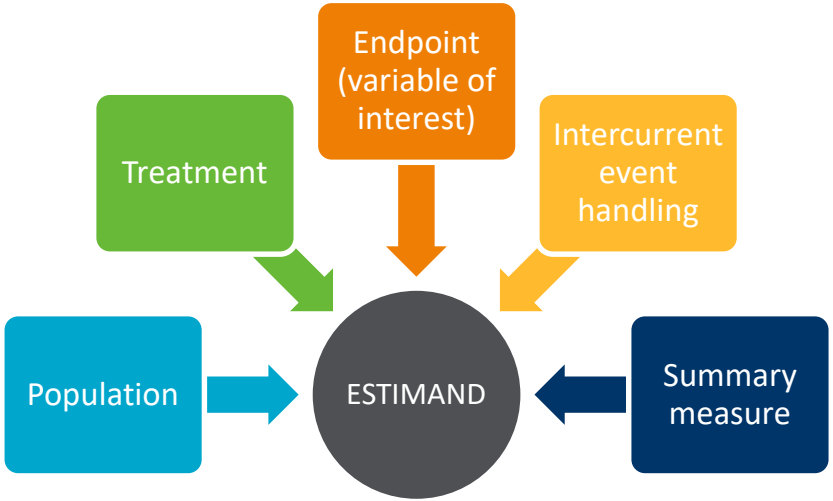
“What is the effect of drug X on PROs?”



Building an estimand

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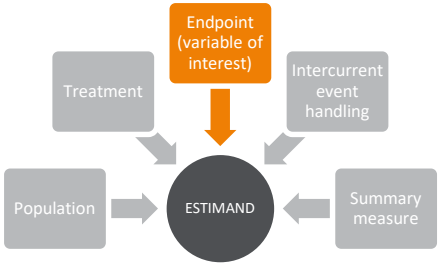

What is the effect of drug X on patient's perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation

Building an estimand

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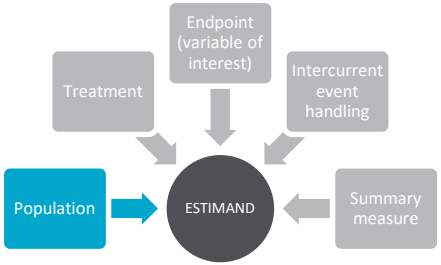

In advanced cancer patients, what is the effect of drug X on patient's perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation

Building an estimand

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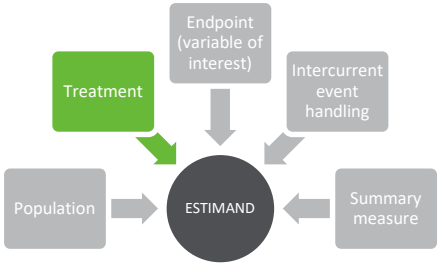

In advanced cancer patients, is there a difference between treatment with drug X compared to drug Y on patient's perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation

Building an estimand

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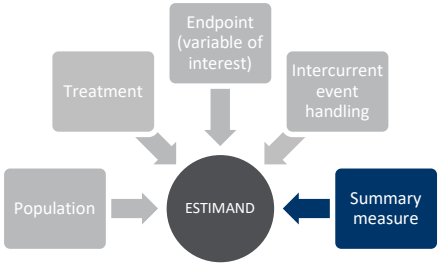

*In advanced cancer patients, is there a **meaningful difference in mean score (≥ 7-points)** between treatment with drug X compared to drug Y on patient's perceived pain, as measured on the EORTC QLQ-C30, after 6 months post randomisation*

Intercurrent Events

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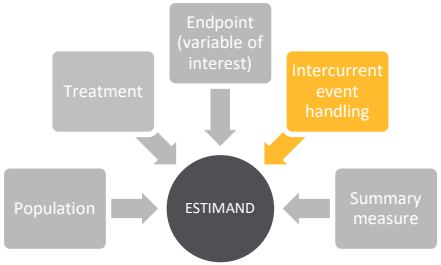

Define events:

> #1 Treatment discontinuation

> #2 Death

Agree a strategy to handle them

Intercurrent event: treatment discontinuation

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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***

While on treatment

…after 6 months post randomisation ***or at the time of treatment discontinuation***

Collect data until month 6 or treatment discontinuation, whichever comes 1st

Intercurrent event: death

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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***

Building an estimand

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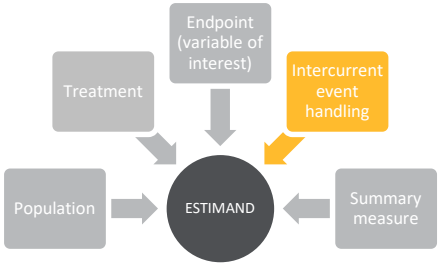

In advanced cancer patients, is there a meaningful difference in mean score (≥ 7-points) between treatment with drug X compared to drug Y in patient's perceived pain, as measured on the EORTC QLQ-C30, after 6-months post-randomisation or death (whichever occurs first), regardless of treatment discontinuation?

Proposed estimand

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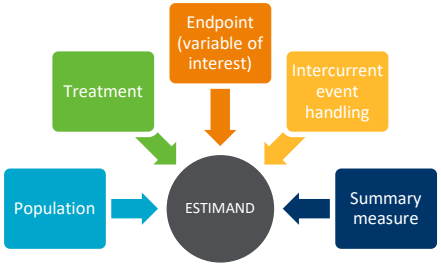

In advanced cancer patients, is there a meaningful difference in mean score (≥ 7-points) between treatment with drug X compared to drug Y in patient's perceived pain, as measured on the EORTC QLQ-C30, after 6-months post-randomisation or death (whichever occurs first), regardless of treatment discontinuation?

Implications

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- 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

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- 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 – lets ensure that objectives relating to patient's perspective are at the heart of this

Thank you – Any Questions?

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