Introduction to estimands

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Cabazitaxel for QoL

• Cabazitaxel *improves QoL* (EQ-5D) by *0.08* (95% CI 0.02 to 0.14) in patients with metastatic prostate cancer
Cabazitaxel for QoL

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- ... so if we give participants cabazitaxel, it will improve their QoL on average by 0.08?
Cabazitaxel for QoL

- Cabazitaxel **improves QoL** (EQ-5D) by **0.08** (95% CI 0.02 to 0.14) in patients with metastatic prostate cancer.

- ...so if we give participants cabazitaxel, it will improve their QoL on average by 0.08?
Cabazitaxel for QoL

- **0.08** is an estimate of what the treatment effect *would be in the hypothetical setting where men with metastatic prostate cancer never experience disease progression or death.*
Statistical methods

QoL data collected up to point of disease progression

Mixed-model for repeated-measures used for analysis

Treatment effect

?
Statistical methods

QoL data collected up to point of disease progression

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Treatment effect
**Statistical methods**

QoL data collected up to point of disease progression

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**Estimand**

Difference in means of EQ-5D between cabazitaxel vs. control in the hypothetical setting where adult men with metastatic prostate cancer never experience disease progression or death
Estimand

• Structured approach to defining the treatment effect, to make clear **what** is being estimated
  – Ensure everyone understands what’s being estimated
  – Ensure what’s being estimated is relevant
  – Ensure study design/data collection/analysis are aligned with the question
Estimands – ICH E9 (R1) Addendum (2019)

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY
ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR
CLINICAL TRIALS
E9(R1)

Final version
Adopted on 20 November 2019

ICH E9(R1) Addendum reaches Step 4 of the ICH Process

4 December 2019

The ICH E9(R1) Addendum to Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses reached Step 4 of the ICH Process at the ICH meeting in Singapore on 20 November 2019.

The ICH E9(R1) Addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address.

The ICH E9(R1) Addendum is available for download on the ICH website here.
Population

Treatment conditions

Summary measure

Intercurrent events

Endpoint
Intercurrent events

• Post-randomisation events which affect the **interpretation** or **occurrence** of outcome data

• Examples
  – Treatment discontinuation
  – Failure to initiate treatment
  – Treatment switching
  – Wrong dose of treatment
  – Use of rescue medication
  – Death
Intercurrent events

• Post-randomisation events which affect the **interpretation** or **occurrence** of outcome data

• Examples
  – Treatment discontinuation
  – Failure to initiate treatment
  – Treatment switching
  – Wrong dose of treatment
  – Use of rescue medication
  – Death

<table>
<thead>
<tr>
<th>Participant</th>
<th>Day 5 QoL score</th>
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<tbody>
<tr>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
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</table>
Strategies to address intercurrent events

- Treatment policy
- Hypothetical
- Principal stratum
- Composite
- While on treatment/while alive
Example

• Daily drug tablet vs. matching placebo to prevent disease recurrence within 12 weeks
  – Some participants discontinue treatment early (treatment discontinuation)
Treatment policy strategy

• Intercurrent event is considered part of treatment

• Effect of intervention, regardless of discontinuation
Hypothetical strategy

• We consider a hypothetical setting where intercurrent event would not occur

• Effect of intervention in hypothetical setting where participants don’t discontinued
Principal stratum strategy

- We are interested in the treatment effect in the principal stratum in which the intercurrent event would not occur.

- Effect of intervention in the set of participants who would not discontinue treatment.
Composite strategy

- The intercurrent event is incorporated into the endpoint definition (e.g. the endpoint is changed from “recurrence” to “recurrence or discontinuation”)

- Effect of intervention on recurrence or discontinuation
While on treatment/while alive strategy

- The endpoint prior to the occurrence of the intercurrent event is of interest

- Effect of intervention on recurrence up to 12 weeks or discontinuation
Intercurrent events

• We can use different strategies for different intercurrent events

• We can subdivide intercurrent events:
  – Discontinuation due to adverse events
  – Discontinuation for reasons other than adverse events
Example: Advanced cancer trials

Experimental

Control

Overall survival
Example: Advanced cancer trials

- **Experimental**
  - + SoC

- **Control**
  - + SoC

### Diagram

- Disease progression
- Overall survival

**SoC**

MRC CTU at UCL
Example: Advanced cancer trials

Experimental + SoC

Control + Experimental

Overall survival

Disease progression
Example: Advanced cancer trials

• Treatment policy strategy:
  – Experimental + SoC vs. Control + Experimental
  – Experimental as 1\textsuperscript{st} vs. 2\textsuperscript{nd} line treatment
Example: Advanced cancer trials

• Treatment policy strategy:
  – Experimental + SoC vs. Control + Experimental
  – Experimental as 1st vs. 2nd line treatment

• Hypothetical strategy:
  – Experimental + SoC vs. Control + SoC
  – Experimental as 1st line treatment as used in usual practice
## Results

<table>
<thead>
<tr>
<th></th>
<th>Treatment policy estimand</th>
<th>Hypothetical estimand</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>No. patients</td>
<td>115</td>
<td>108</td>
</tr>
<tr>
<td>No. switching</td>
<td>49</td>
<td>-</td>
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<tr>
<td>Hazard ratio</td>
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<td>0.79</td>
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<tr>
<td>95% CI</td>
<td>0.60 to 1.04</td>
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</tr>
</tbody>
</table>

*Clark TP, Kahan BC, Phillips A, et al*  *Estimands: bringing clarity and focus to research questions in clinical trials*  *BMJ Open*  2022;12:e052953. doi: 10.1136/bmjopen-2021-052953
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Difference in means of EQ-5D between cabazitaxel vs. control in the hypothetical setting where adult men with metastatic prostate cancer never experience disease progression or death

Clarity

Relevance

Alignment