Estimands in oncology

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What is specific to oncology?
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Time-to-event endpoints.
What is specific to oncology?

Time-to-event endpoints.

Inertia?
### “DFS” in adjuvant trials

**Table 1. Example of Inconsistent Definitions of Disease-Free Survival**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Local/Regional Recurrence</th>
<th>Distant Metastasis</th>
<th>Death From Any Cause</th>
<th>Invasive Contralateral Breast Cancer</th>
<th>Second Primary Invasive Cancer (nonbreast)</th>
<th>Ipsilateral DCIS</th>
<th>Contralateral DCIS</th>
<th>Ipsilateral LCIS</th>
<th>Contralateral LCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIG 1-98</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>MA-17</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ATAC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>IES</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARNO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Event-free survival used by ARNO.

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; BIG, Breast International Group; MA, National Cancer Institute of Canada Clinical Trials Group MA-17; ATAC, Arimidex, Tamoxifen Alone, or in Combination; IES, Intergroup Exemestane 031; ARNO, Arimidex, Nolvadex 95 Study.

Hudis et al. (2007)
Treatment switching

RECORD-1: Motzer et al. (2010).

- Some trials **X-over** from control to experimental arm upon PD.
- Switching from control to drugs with same MoA in **other trial** ⇒ I/O therapies.
Randomized but not treated

- **Blinding** often infeasible.

  - Checkmate-37:
    - 20% vs 1.5%.

  - Quantum-R:
    - 23% vs 1.6%.
    - Cortes et al. (2019).
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(Rick Pazdur on Quantum-R)
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“ITT” effect really what we are interested in?
What do these findings have in common?
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They can all be anticipated!
What do these findings have in common?

They can all be anticipated!

Clear formulation of clinical trial objective is key.
Impact
Pre-addendum:

- “ITT” primary.
- Attempts to “rescue” failed OS with ad-hoc treatment switching analyses.
- Likely not all data collected that “proper modelling” requires.
- Post-hoc.
Pre-addendum:

- “ITT” primary.
- Attempts to “rescue” failed OS with ad-hoc treatment switching analyses.
- Likely not all data collected that “proper modelling” requires.
- Post-hoc.

Post-addendum:

- Estimand of interest: hypothetical.
- EMA Q&A document that opens door to such analyses IF:
  - Preplan.
  - Ensure quality throughout protocol, proper data collection, and analysis.
- Assumptions transparent.

Degtyarev et al. (2020): *Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials - application of the estimand framework*, available online.
“ITT” not always effect of interest.

Time invested at design stage *pays off* later.

Estimand framework = *opportunity*

- for better designed trials,
- transparent assumptions,
- *leadership of statisticians.*
“ITT” not always effect of interest.

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Also in oncology.
Industry working group on estimands in oncology:

- Founded November 2018.
- European special interest group “Estimands in oncology”, sponsored by PSI and EFSPi.
- ASA scientific working group of ASA biopharmaceutical section.
- 37 members representing 22 companies.
- Regularly interacts with 7 health authorities.

www.oncoestimand.org
Thank you for your attention.

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http://www.kasparrufibach.ch

twitter
numbersman77
github
numbersman77
References I


Backup slides
General implications of the addendum
Broader impact

Aligning drug developers and regulatory bodies’ expectations for target treatment effect *upfront* has potential to give:

- More *meaningful* descriptions of treatment effects for licensing and prescribing decisions.
- Clinical trials with designs that are *aligned to agreed objectives*.
- Increased *transparency* with respect to data analysis and inference.
- More *predictable* regulatory assessment procedures.
- More *flexibility* from regulators.
- *Reduction in total number of analyses* (primary + secondary + sensitivity).
- Clear language to describe and discuss different estimands required by different stakeholders.
- *Shift of resources* from analysis / filing to design.
Framework and language

- Promote alignment between trial objectives, design, data collection, conduct, analysis and inference.
- Promote understanding that trial objectives cannot be translated into estimands without reflecting how potential intercurrent events are addressed in scientific question of interest.
- Promote discussion of different strategies to handle intercurrent events to identify and describe treatment effects that reflect scientific questions of interest.
- Define treatment effect of interest - before a trial is designed and conducted - that is relevant in clinical practice.
- Highlight importance of considering whether main analysis provides estimate which is reliable for inference.
- Re-define missing data.
- Re-define sensitivity analysis and regulatory assessment of robustness.
- Introduce supplementary analysis as any other analysis to fully investigate and understand trial data.
<table>
<thead>
<tr>
<th>Protocols</th>
<th>Study population</th>
<th>Derive population from estimand definition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study intervention</td>
<td>Derive intervention from estimand definition, including rescue medicine</td>
</tr>
<tr>
<td></td>
<td>Discontinuation</td>
<td>Derive discontinuation actions from intercurrent event strategies in estimand definition</td>
</tr>
<tr>
<td></td>
<td>Statistical considerations</td>
<td>Hypothesis, analysis sets, sample size, endpoints follow from estimand definition Separate sensitivity from supplementary analyses.</td>
</tr>
<tr>
<td>Additional for SAPs</td>
<td>Sample Size</td>
<td>Optionally provide (even) more details how intercurrent events are taken into account in sample size computation</td>
</tr>
<tr>
<td>Additional for CSRs</td>
<td>Discontinuation</td>
<td>Tabulate observed intercurrent events.</td>
</tr>
<tr>
<td></td>
<td>Changes in Planned Analyses Prior to Unblinding or DB lock</td>
<td>Discuss how intercurrent events that were not foreseen at the design stage, or identified during the conduct of the trial, were handled. Discuss not only the choices made for the analysis, but the effect on the estimand.</td>
</tr>
</tbody>
</table>
Antidrug antibodies in I/O: Intercurrent event that may impact PFS / OS.
Antidrug antibodies in I/O: Intercurrent event that may impact PFS / OS.

**Pre-addendum:** Simple analyses conditioning on occurrence of ADA $\Rightarrow$ only valid under unrealistic assumption.
Antidrug antibodies in I/O: Intercurrent event that may impact PFS / OS.

**Pre-addendum:** Simple analyses conditioning on occurrence of ADA ⇒ only valid under unrealistic assumption.

**Post-addendum:** **Principal stratum** estimand ⇒ meaningful estimand, assumptions transparent.
Doing now what patients need next