How can the estimand framework support decentralized trials?

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on behalf of the oncology estimand working group

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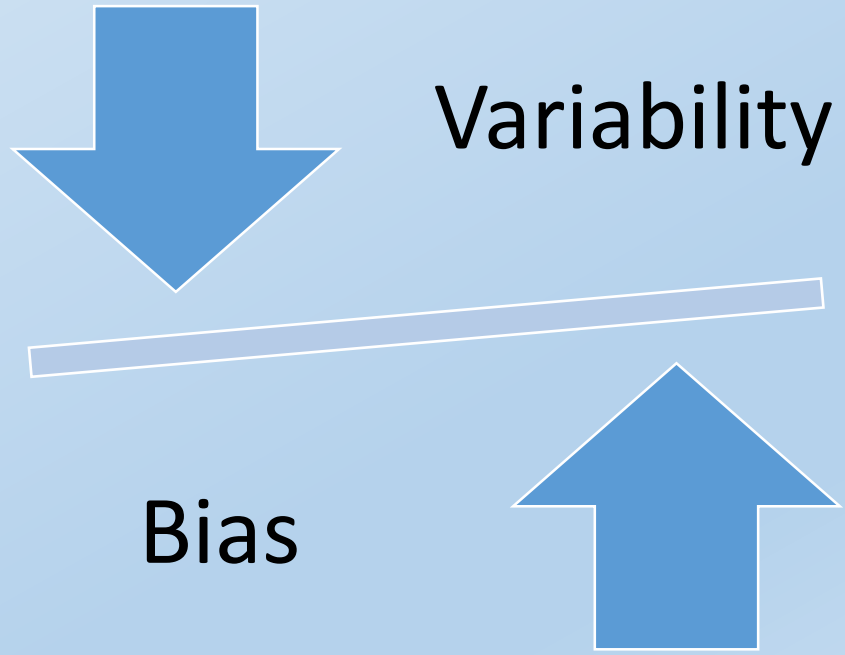
- www.oncoestimand.org

«Traditional» clinical trial

- Scientific experiment designed to **assess effect of new treatment**:
  - Precisely and
  - Unbiased.

- Pandemic experience in Decentralizing:

  option for future trials?



What changes if we decentralize trials? Bias might be reduced

- Decentralized trials offer potential to be **more inclusive**:
  - geographically,
  - minorities,
  - etc.

→ Reduce **bias** generated through narrow in- and exclusion criteria in «traditional» clinical trials.

What changes if we decentralize trials? Variability might increase

- Potential **increase in variability**:
  - endpoint measurements (e.g. local vs. central assessments),
  - treatment scheduling,
  - adherence,
  - etc.

- If variability increases:
  - Might miss potentially effective treatment.
  - Missed opportunity & **potential risk for patients**.

Implications

- Need data to understand **bias – variance tradeoff**!
- «Decentralized» vs. «traditional» false dichotomy: first decentralize «simple» assessments → low hanging fruits.
- **How do decentralized trials need to look like to generate scientific evidence we need for new drugs?**

The estimand framework – tool to get clarity on the research question

- Dec 2019: final version of ICH E9 estimand addendum published.
- **Broadly implemented** in industry. More and more requested and appreciated by stakeholders: trial sponsors, regulators, payers, ...
- Various **X-industry working groups** supporting implementation.
- Facilitates precise definition of the research question accounting for different **patient journeys**.

How can estimand framework support decentralized trials?

- Goal of estimand framework: **Systematic alignment** of
  - trial objectives,
  - design,
  - data collection,
  - conduct,
  - analysis and inference.

- Beneficial for **every type of trial**.

- «Traditional» vs. «decentralized» trials:
  - No change in question of interest expected.
  - But different patient journeys may be observed.

Early treatment discontinuation → initiation of new anticancer treatment

- Risk of **more** new anticancer treatments?
  - IMP delivered at home instead of the clinic.
  - «Less skin in the trial game» of local HCP providers.
  - Unexpected safety events: have to be managed at local HCP level.
- Potential of **fewer** new anticancer treatments?
  - «Burden of trial» may be lower → patients may stay longer on treatment.
- Impact on EFS, PFS, OS: depends on type, timing, and frequency of new anticancer treatment.

Conclusions

- Decentralized trials:
  - We appreciate their potential for being more **inclusive**.
  - **Precisely answering scientific question** remains paramount. We want to do it well!
  - Appreciate regulatory guidance.

- Estimand framework:
  - Very **useful to structure thinking for every type of trial**.
  - Useful to **assess impact of Covid-19 on ongoing trials**.
  - Useful to think about differences between «traditional» and decentralized trials.

- Key: Generate sufficiently precise evidence that we can bring drugs to even more patients.

- **Opportunity for collaboration** between patients + regulators + payers + industry.

Backup

The estimand framework and Covid-19: case for hypothetical estimand strategies?

- Patient Journey's → E. Zuber's talk LUNGevity - FDA Webinar about COVID-19 impact (4th August):
  - Assessment of benefit in clinical trial: needs to account for anticipated patient journeys.
  - Impact of pandemic on patient journeys neither foreseen nor addressed at trial design stage.

- Ongoing trials: Designed assuming
  - **No major disruption of healthcare systems**.
  - **No highly infectious disease** with severe complications
  - for which **no effective therapy** available.

- Intercurrent events (indirect impact): independently of disease or treatment
  - primarily caused by disruption of healthcare system or
  - patients' desire to minimize traveling.
  - **Hypothetical strategy potentially reasonable**.
  - Caveat: estimand needs to be estimable under plausible assumptions.

- Estimand framework: very useful to assess impact of pandemic on trial objectives, estimand, and estimation.

Potential impact of decentralization on PFS

- Effect in **world where no new anticancer treatments** would be given?
  - Estimated through censoring at new anticancer treatment.
  - Hypothetical strategy.

- Effect understanding **new anticancer treatment as part of treatment strategy**?
  - Estimated based on observed PFS time irrespective of new anticancer treatment.
  - Treatment policy strategy.

- Estimand framework can bring clarity on the question we are asking.

Potential impact of decentralization on PFS

- Hematology:
  - Bone marrow: key in response assessments.
  - Local HCP able to perform an aspirate / biopsy?

- Radiological assessments for determination of (absence of) PD:
  - Adds another layer: local imaging center - local investigator (country-specific PI) – central assessment.
  - Clarity needed who decides on treatment based on radiological assessment.

Potential impact of decentralization on EFS and OS

- EFS:
  - New anticancer treatment typically counted as event.
  - Subjectivity in initiation of new anticancer treatment might have even bigger impact than for «traditional» endpoints.

- OS:
  - Intercurrent event of new anticancer treatment typically absorbed in **treatment attribute** (treatment policy strategy).
  - Change in frequency and timing of new anticancer treatment → impact on duration of experimental treatment.

Further comments

- Implications of DCTs may vary dependent on the setting.
- Useful to identify settings with little impact of decentralization and settings requiring a bit more time to understand potential impact on the generated evidence.
- Estimand framework could facilitate structured comparison of different indications:
  - Rare *populations* may be less suitable as large sites have more experience in diagnosis, treatment and disease assessment.
  - Knowledge about *treatment*: if it's first indication, likely more early discontinuations than if it's the fifth indication and safety profile is well established; complexity of treatment also relevant – double-blind trials likely less impacted.
  - *Endpoint*: different response criteria – settings with more complex response criteria may require more pre-work.