EORTC
European Organisation for Research and Treatment of Cancer

Analysing clinical trial data collected during the pandemic

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Approaches to clinical data analysis

Real world - like

Clinical trial - like

- Description, information
- Situation ‘as is’, less a priori selection
- Can focus on many outcomes
- Potentially underestimating

- Causality
- Strong boundaries, curation, compliance
- Focus on treatment comparison
- Potentially overestimating

In this concept think about

- Where bias can originate
- How external validity can be gained or lost
  - And what “external” refers to in your mind

Concept of estimands

- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

What is an estimand ?

- A **treatment effect** describes the difference in outcome between taking and not taking a treatment
- What is this difference? Need to agree what treatment effect we are trying to estimate
- Before designing and analysing a clinical trial it should be clearly defined which treatment effects are of interest

Slide courtesy of Dan O' Connor (MHRA) for SISAQOL

Value in this way of looking

- Estimands is not revolutionary, but can give us insight
- Contribution: Transparency on decisions made that lead to estimation of treatment effect
- Industry, HTA, regulators are moving into this framework
- Estimand framework can be helpful in dealing with data messed up by COVID-19 in our clinical data analyses

What makes an estimand?

What (5 attributes):

- Targeted population
- The variable (or endpoint) to be obtained for each patient
- Treatments
- Specify and handling of intercurrent events (IE)
- Population level summary

Estimand attributes are NOT independent of each other.

Decision on one estimand attribute (e.g., intercurrent events) can impact another estimand attribute (e.g., population)

Specify Intercurrent Events

- "Things happen" in a clinical trial

- Specify intercurrent events upfront
  - Q: Will this event distort the interpretation or prevent the estimation of my treatment effect?
  - Depending on how intercurrent event is handled:

    uncollected observations after IE ≠ missing data.

- Example: endpoint = response at end of treatment. If patient stops early due to toxicity (IE):
  - failure by definition → uncollected observations are NOT missing data.
  - response assessment required → uncollected observations are missing data.

- Allow for planning on **which data need to be collected** and hence which data (when not collected) present a missing data problem to be addressed

Intercurrent Events Strategies

The 5 proposed strategies (ICH E9R1) can be condensed as:

- Treatment policy
  - IGNORE AS MUCH AS POSSIBLE

That's life.
I don't care

- Composite
  - IE = COMPONENT OF ENDPOINT

Looks like part of the event to me

- Hypothetical
  - WHAT IF IE DID NOT EXIST?

If we assume that the intercurrent event had not occurred, the assessments would be …

- Principal stratum
  - LIMIT TO PATIENTS WO INTERCURRENT EVENT

I don't like people with IEs

- While on treatment
  - LIMIT TO PERIOD WO INTERCURRENT EVENT

As long as I have my teddy…

In the COVID situation

Real world - like

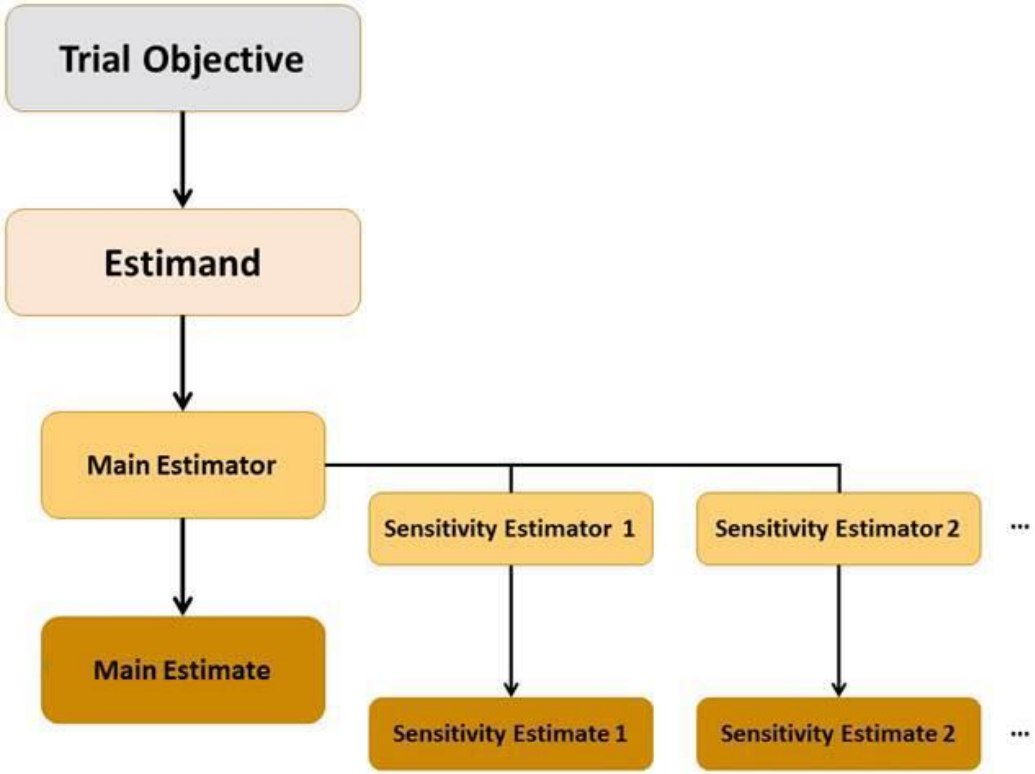
Clinical trial - like

- "Ignore"
- In this case, straightforward

- "Hypothetical" – the counterfactual question
- In this case, complex
- -> higher need for sensitivity analyses

Note: in general, I feel real world like analyses are more messy, and require more sensitivity analyses

Illustration out of EMA guidance



- **Sensitivity Analysis:**
- A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Think of the following

- Evocate how far COVID affected the data:
  - Involved hospitals, countries
  - (Calendar) timing
  - Capability to cope / comply with the protocol, treatment
  - Try to summarize deviations
- Make a clear assessment of the extent of data available (relating to COVID impact)
- Generally assess to what extent the above meant a deviation from normal pre-COVID practice

Identify Intercurrent Event

Endpoint: Tumor response at end of treatment

Examples of identified intercurrent events

- Death
- Treatment switching (new treatment initiated due to toxicity)

Handling treatment switching (due to toxicity)

Endpoint: Tumor response at end of treatment

Handling IE	Statistical	Clinical interpretation
Treatment policy	Continue observations (ignoring the intercurrent event)	Treatment switching in case of toxicity is part of treatment strategy
Composite	Treatment switching = tumour progression (event)	Treatment switching is the same as treatment failure
Hypothetical	Censoring • Values will be modelled based on observed data from patients who did not switch • Assumption: patients who are censored (due to treatment switching) are NOT different than patients who stayed on treatment	What will the estimate be *if patient did not switch treatment due to toxicity?*
Principal stratum	Eligibility criteria: Patients who will not switch treatments	Not ethical/ feasible
While on treatment	Competing risk	Tumor response before treatment switching

What makes an estimand?

What:

- **Specification and handling of intercurrent events**
- Population
- The variable (or endpoint) to be obtained for each patient
- Treatment
- Population level summary

In general, these other estimand attributes will remain unchanged unless intercurrent events will impact decisions on these other four variables

Note: These are not necessarily answers but points for discussion to see if there can be an appropriate general response for COVID-19 in our trials

Why is COVID-19 an issue?

- COVID-19 has a systematic impact on all our clinical trials. It has a potential impact on:
  - Outcome (e.g., death because of COVID-19)
  - Treatment (e.g., treatment delay because of COVID-19)
  - Assessment (e.g., missed lab assessment)
  - Toxicity (e.g. COVID-19 infection)

How problematic is the COVID-19 impact on our treatment estimates?

COVID-19 impacted data

	Definition	Advantage	Disadvantage
Time window – general	All patients with data collected within a specific time frame	Simple; captures also unobserved events	Many patients classified as affected
Time window – specific	Time frame dependent on eg. country	More precise; captures also unobserved events	Specific time definitions; Many patients classified as affected
Event based	Patient affected if at least one COVID19 related event reported	Simple; captured all observed events	Miss unobserved events; irrelevant events
Relevance based	**Data** affected considered meaningfully affected by COIVD19	Accurate; specification on data level	Intensive: Miss unobserved events

Note: Intercurrent events work on data level; not on patient level.

COVID-19 impacted data: statistician headaches

- COVID-19 subgroups
  - COVID-19 related to prognostic factors such as age, smoking, obesity, … → confounding with site/country possible.
- Efficacy outcomes (eg. survival curves) from patients without COVID19 issues should not be considered as representative of the trial population!
- AE: “COVID-19 related” similar to “treatment related”
- Is vaccination another intercurrent event? Does it bring a case back to ‘pre-COVID’?

Other issues

- Impact of recruitment suspension/reduction
  - Increase in trial recruitment duration
  - More events from earlier patients
  - Timing of interim analyses?
- Unblinding due to COVID-19
- Impact on HRQoL
  - Patient perspective affected

In summary

- Carefully consider what it is you would like to extract out of the dataset
  - Estimand framework
- Consider what kind of information and details you have access to
  - This will define the limits of what you can try to do
- Report qualitatively and quantitatively on the impact of COVID in your dataset
- Choose analysis strategies (and report them)
  - May very well be endpoint dependent
- The more complicated the analysis, the higher the need to embed the strategy in some sensitivity analyses
  - For example the ‘raw’ analysis could be a useful sensitivity analysis to report

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