Assessing the impact of COVID-19 on oncology clinical trials – application of the estimand framework

Kaspar Rufibach
Methods, Collaboration & Outreach Group, Department of Biostatistics, Roche Basel
PSI Conference Webinar: Impact of COVID-19 to estimands
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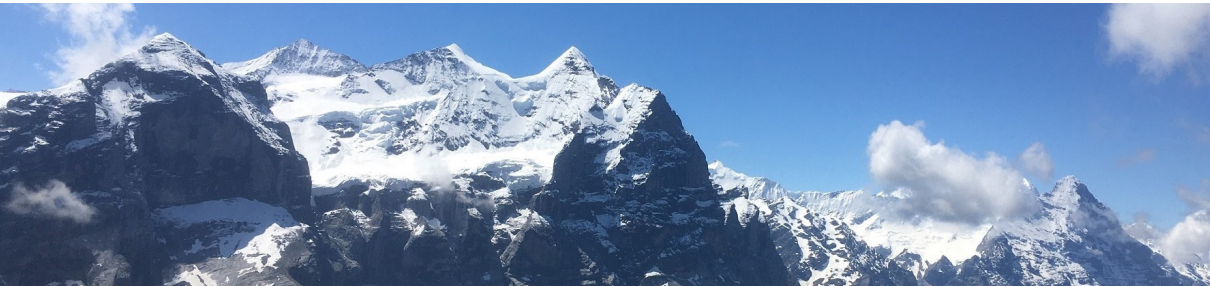

This talk

- Summarizes Degtyarev et al. (2020): *Assessing the impact of covid-19 on the objective and analysis of oncology clinical trials – application of the estimand framework*. https://arxiv.org/abs/2006.04480
- **Consensus opinion** of industry working group "estimands in oncology": **www.oncoestimand.org**.
- COVID-19 pandemic: new and evolving $\Rightarrow$ opinion may need refining over time.

Endpoint: **overall survival** in **superiority** trial.

How does COVID-19 change pre-pandemic clinical trial objective?

It does not!

Clinical trial objective

World without ongoing COVID-19 pandemic:

1. Disease **contained**:
   - Patients do not experience severe complications due to virus.
   - Spread of virus limited.
   - Therapy available.
2. **No disruption** of healthcare systems:
   - Patients access to routine standard of care.
   - Proper disease follow-up.

Key assumptions:

- Trials started before pandemic: designed to inform clinical practice in a world without pandemic.
- Pandemic will eventually end.

Clinical trial objective pre-pandemic = post-pandemic.

Data collected and trial results useful for informing clinical practice in a world without COVID-19 pandemic?

Estimate from initially planned analysis still provide answer to clinical trial objective?

If not:

- **Clarify primary estimand**.
- Modify **estimator**.
- Add **sensitivity** analyses.
- Introduce **supplementary** estimands.

If you update estimand:

- Effect size?
- Sample size?
- Missing data handling?

ESTIMAND

COVID-19 IMPACT ASSESSMENT

VARIABLE

The variable (or endpoint) to be obtained for each patient.

Q: Does the current endpoint reflect the treatment effect in the original scientific objective?

POPULATION

The population of patients targeted by the clinical question.

Q: Are the enrolled patients representative of the target population?

INTERCURRENT EVENTS (ICEs)

Other ICEs not already addressed by treatment, population and variable, and how they are handled.

Q: Can the original clinical trial objective be addressed without defining new strategies for ICEs related to COVID-19? (e.g. apply pre-specified rules for discontinuations to discontinuations due to COVID-19)

TREATMENT

The treatment condition of interest.

Q: Are the treatment conditions (e.g. non-compliance, drug discontinuation, subsequent therapy) representative of what would have been administered pre-COVID-19?

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison.

Q: Is the summary measure still interpretable?

Direct vs. indirect impact of pandemic

Direct:

- Treatment interruption or discontinuation due to **infection**.
- Additional therapies to treat COVID-19.
- Death due to COVID-19.

Indirect:

- Overwhelmed healthcare system.
- Lock-down.
- Treatment interruption or discontinuation due to **logistic reasons, patient or physician decision**.

Death due to COVID-19

Direct impact

Death due to COVID-19

- **Composite**: count as death.
- **Hypothetical**: do not expect COVID-19 related deaths in a post-pandemic world.

Discontinuation from treatment not related to COVID-19 infection

Indirect impact

Non-related discontinuation

Oncology trials: **any** discontinuation $\Rightarrow$ **treatment policy**, because difficult to exclude relatedness to disease and/or treatment.

Unrelated discontinuation:

- Patients' or physicians' decision.
- Unable to travel.
- Avoid hospital.

Data after discontinuation:

- Start of new anticancer therapy: event in many settings.
- Unlikely to reflect **patient's journey** in world without COVID-19 pandemic.

Hypothetical strategy.

Estimation

- COVID-19 death **competing risk**? Meyer et al. (2020): patients not at risk for that cause from randomization on.
- Estimation of hypothetical estimand: often not obvious, but feasible.
- Estimating effect in patients infected by COVID-19 vs. patients not infected by COVID-19:
  - **Infection = ICE** $\Rightarrow$ simple subsetting breaks randomization $\Rightarrow$ validity of causal statements unclear.
  - Estimate via **principal stratification**.

Additional considerations in paper

- **Non-proportional** hazards.
- **Missing data**: capture reasons of missingness.
- **iDMC**:
  - Primary purpose: issue recommendations on safety of patients and interim analyses for trials $\Rightarrow$ unchanged by pandemic.
  - Impact assessment of pandemic feasible using **blinded** data $\Rightarrow$ iDMC not needed.
- Response, duration of response.
- **Non-inferiority**: usual considerations apply, nothing specific to pandemic situation.

Wrap-up

- **Estimand framework ideal to assess impact of pandemic**. Allows for **structured** assessment of impact.
- **Pragmatism**: We document changes to consider. But:
  - Estimate from initially planned analysis may still provide "right" answer.
  - **Nothing** relating to estimand and estimation necessarily needs to change!
- Key factors to consider choosing the strategy:
  - **Relationship** of intercurrent event to disease or treatment.
  - **Interpretability** of data after intercurrent event.
- Hypothetical strategy: reasonable for events caused by healthcare system disruption.
- Principal stratification: potentially valuable to assess treatment effect in patients who would not experience severe complications of COVID-19 infections.

Paper illustrates power of purpose-built networks.

Joint EFSPI / BBS Seminar: Estimands addendum is final: Anything new for oncology?

Basel Biometrics Section webinar
Basel, 29th June 2020

Kaspar Rufibach (Roche, member of BBS board)
Welcome and scene setting

Regulator's view (Anja Schiel, Norwegian Medicines Agency)
Experience with the estimand framework in oncology

Renaud Capdeville (Novartis), Tina Nielsen (Roche)
Challenges and open questions in hematology: RATIFY and GALLIUM

Break

Hannes Buchner (Staburo) & Ingolf Griebsch (Boehringer Ingelheim)
Treatment switching: challenges, estimands, and estimators

Stefan Englert (AbbVie)
Commentary on previous talks taking COVID-19 into account

Break

Panel discussion
(all speakers + Rob Hemmings from Consilium, Michael Wenger from Novartis)
Estimands – after first experiences anything new for oncology? If at all, what does it add?

Industry working group on estimands in oncology:

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

www.oncoestimand.org

Thank you for your attention.

kaspar.rufibach@roche.com
http://www.kasparrufibach.ch
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References I

- Degtyarev, E., Rufibach, K., Shentu, Y., Yung, G., Casey, M., Liu, F., Liu, Y., Sailer, O., Siegel, J., Sun, S., Tang, R. and Zhou, J. (2020). Assessing the impact of covid-19 on the objective and analysis of oncology clinical trials – application of the estimand framework (2020). Tech. rep., Industry working group "estimands in oncology". `https://arxiv.org/abs/2006.04480`
- Meyer, R. D., Ratitch, B., Wolbers, M., Marchenko, O., Quan, H., Li, D., Fletcher, C., Li, X., Wright, D., Shentu, Y., Englert, S., Shen, W., Dey, J., Liu, T., Zhou, M., Bohidar, N., Zhao, P.-L. and Hale, M. (2020). Statistical issues and recommendations for clinical trials conducted during the covid-19 pandemic.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.0.0 (2020-04-24)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: biostatKR / survival / rpact / reporttools / xtable / probSuccess / cubature / pracma / mvtnorm / dplyr / readxl

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