Commentary on previous talks taking COVID-19 into account

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Basel Biometrics Section Webinar

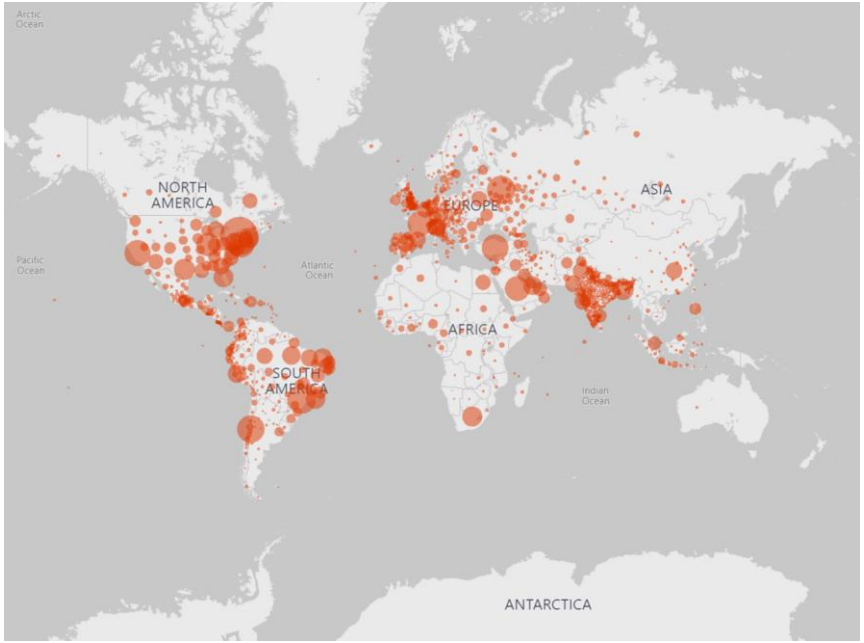
29th June 2020

COVID-19 Disease

COVID-19 is dramatically impacting communities and public health systems around the globe.

As of June 28rd:

- > 10 Million infected
- ~ 500’000 Deaths
- Significant portion of the world’s population under lockdown or under social distancing rules



Reference: COVID-19 Tracker. https://www.bing.com/covid. Last updated: June 08, 2020, 12:20 GMT

How COVID-19 impacts ongoing clinical trials

Readout/Dropout/Censor

Pre

During

Post

Enrollment period

Pre

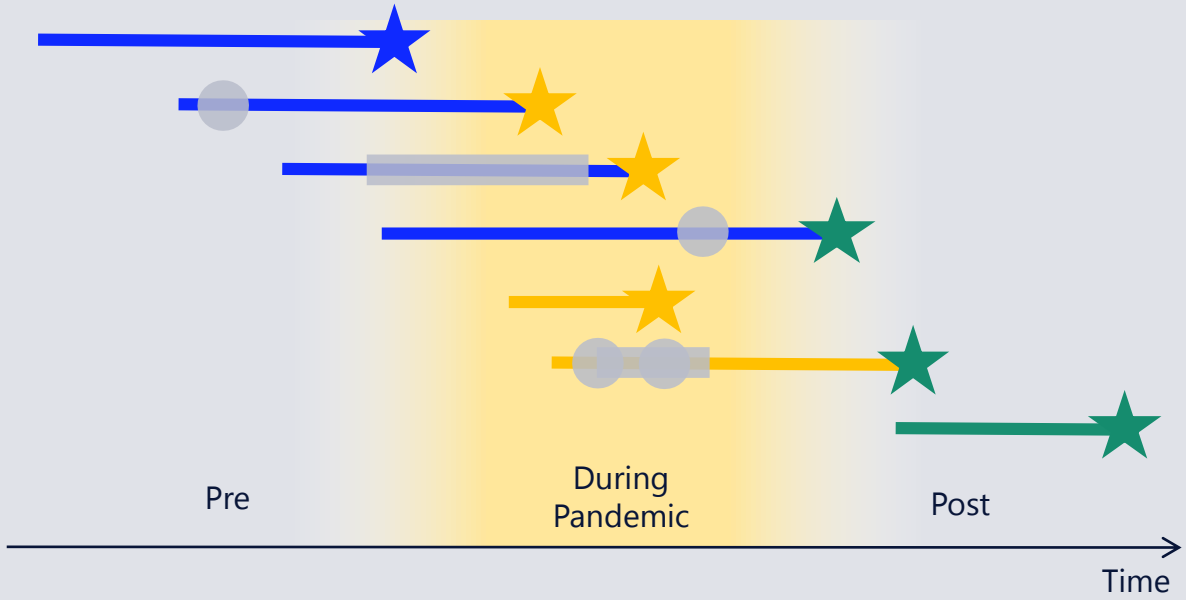
During

Post

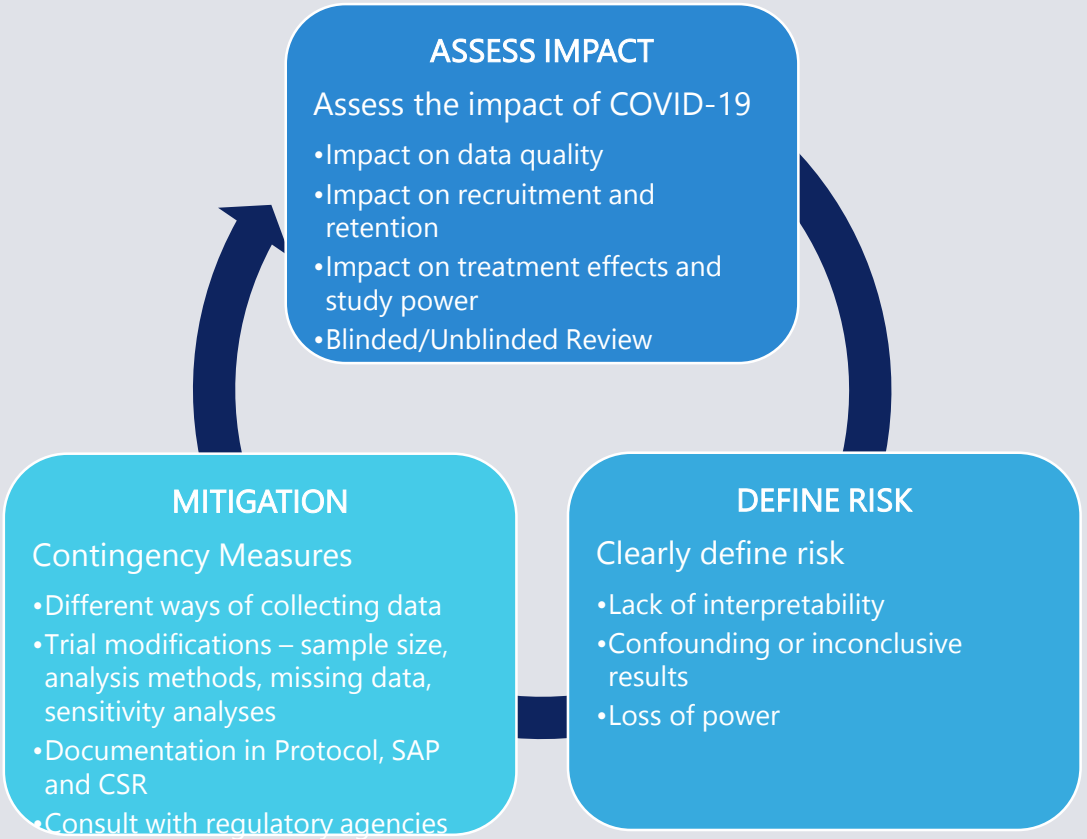
Interruption

Missed visit

Potential individual subject courses:



Key steps to assess, define and understand the impact of COVID-19 on study and data integrity



Reference: Chrissie Fletcher, GSK and R. Daniel Meyer, Pfizer on behalf of the Pharmaceutical Industry COVID-19 Biostatistics Working Group. STUDY AND DATA INTEGRITY CONSIDERATIONS FOR CLINICAL TRIALS IMPACTED BY COVID-19. DIA Webinar, May 13th 2020

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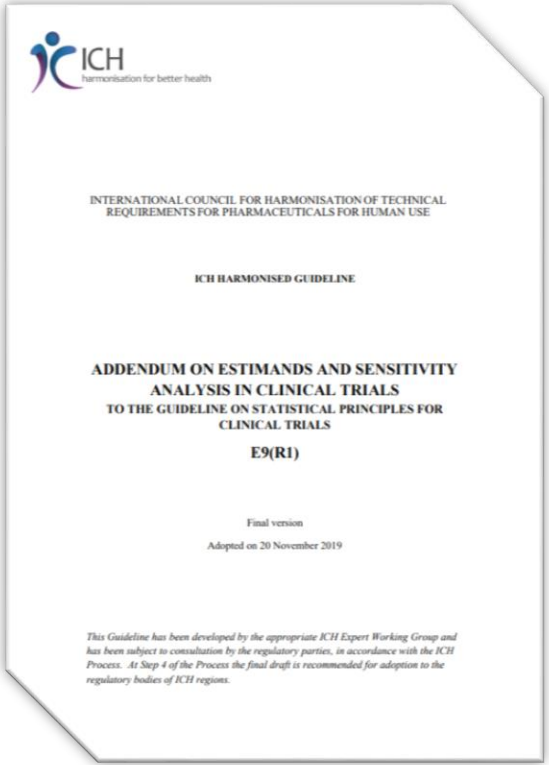
The estimand framework

A framework to align planning, design, conduct, analysis, and interpretation of a clinical trial.

Clear trial objectives should be translated into key clinical questions of interest by defining suitable estimands.

Five estimand attributes as described in ICH E9 addendum:

1. **Population** of patients targeted by the clinical question.
2. **Treatment** condition of interest.
3. **Variable** (or endpoint) to be obtained for each patient that is required to address the clinical question.
4. **Handling of other intercurrent events** (events occurring after treatment initiation that affect the interpretation/existence of measurements associated with the clinical question).
5. **Population-level summary** providing a basis for comparison between treatment conditions.


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

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

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Reference: Addendum on Estimands and Sensitivity Analyses in Clinical Trials. ICH-E9(R1)

Does COVID-19 change pre-pandemic clinical trial objective?

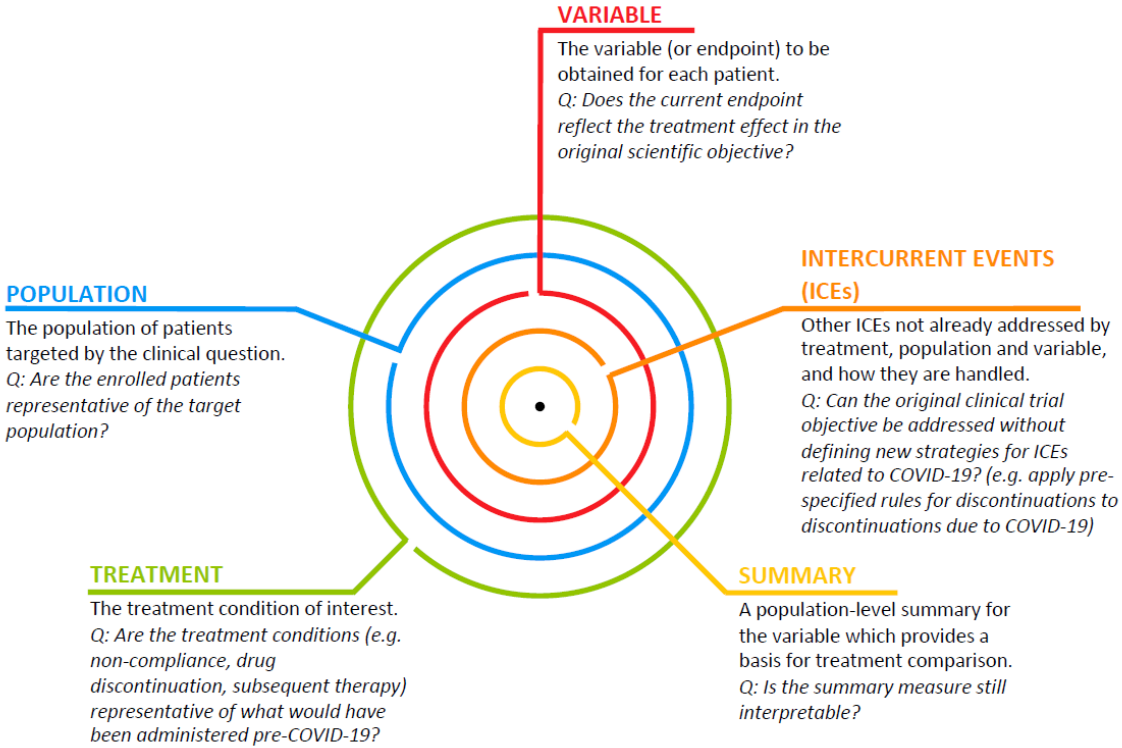
Likely not.

The current COVID-19 outbreak may lead to a need to **reaffirm** the **original** research question or consider new exploratory research question:

1. How would Drug A compare to Drug B **in the absence of COVID-19 pandemic**?
2. In specific situations: how does Drug A compare to Drug B **in the presence of possible individual COVID-19 infections**?

Estimand – COVID-19 Impact Assessment

Degtyarev *et al*. pose a key question for each attribute to facilitate COVID-19 impact assessment on whether the planned analysis of an ongoing clinical trial can still address the original clinical trial objective.



Reference: Degtyarev et al. Assessing the Impact of COVID-19 on the Objective and Analysis of Oncology Clinical Trials – Application of the Estimand Framework. https://oncoestimand.github.io/

Implications and Mitigations for Analyses

The scale of impact is unprecedented, but when **viewed individually**, many of the issues are **well defined and feasible to address**.

Meyer *et al*. have developed strategies and recommendations to address issues related to estimands, missing data, validity and modifications of statistical analysis methods:

- Considerations for Efficacy Analyses
- Implications and Mitigations for Missing Data
  - Assessing and Documenting Pandemic-related Missingness
  - Handling of Missing Data in Main Analyses
- Considerations for Sensitivity and Supplementary Analysis
  - Sensitivity to Delayed Assessments and Missing Data
  - Sensitivity to Alternatives to Protocol-specified Study Data Collection
  - Challenges in Understanding the General Pandemic Effect on Trial Outcomes
- Considerations for Safety Analyses

Reference: Meyer et al. Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic. https://arxiv.org/abs/2005.10248

Implications and Mitigations for Analyses

The estimand framework allows for **different strategies** to be used **for different types of ICEs.**

Strategies for handling **non-pandemic** related ICEs should remain **unchanged**.

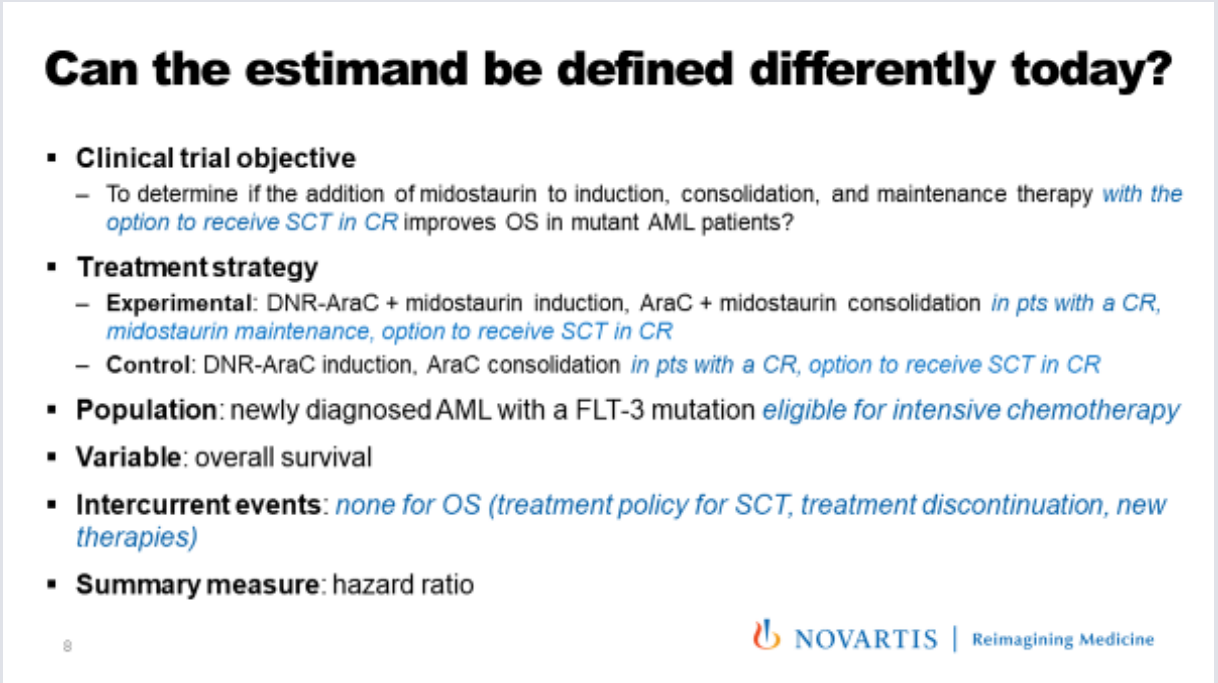
Meyer *et al*. have developed a list of key pandemic related intercurrent events that can be considerd.

Subject's Study Treatment Condition	Study Treatment Accessibility	Subject's COVID-19 Infection Condition	Subject's COVID-19 Concomitant Treatment(s)
• Discontinued and no new treatment started • Discontinued and switched to alternative/SoC • Interrupted or compliance significantly reduced • Interrupted or compliance significantly reduced with changes in the concomitant study disease therapy	• Drug supply interruption • Site unavailable for administration/dispensing • Study treatment available but subject is unable/unwilling to get study treatment due to personal pandemic-related reasons	• Known COVID-19 infection • Positive for COVID-19 • Deceased due to COVID-19	• Subjects treated for COVID-19 (pharmacologically, oxygen, etc.) • Hospitalized, not in ICU • ICU

COVID-19 Pandemic. https://arxiv.org/abs/2005.10248

Commentary on: Renaud Capdeville (Novartis)

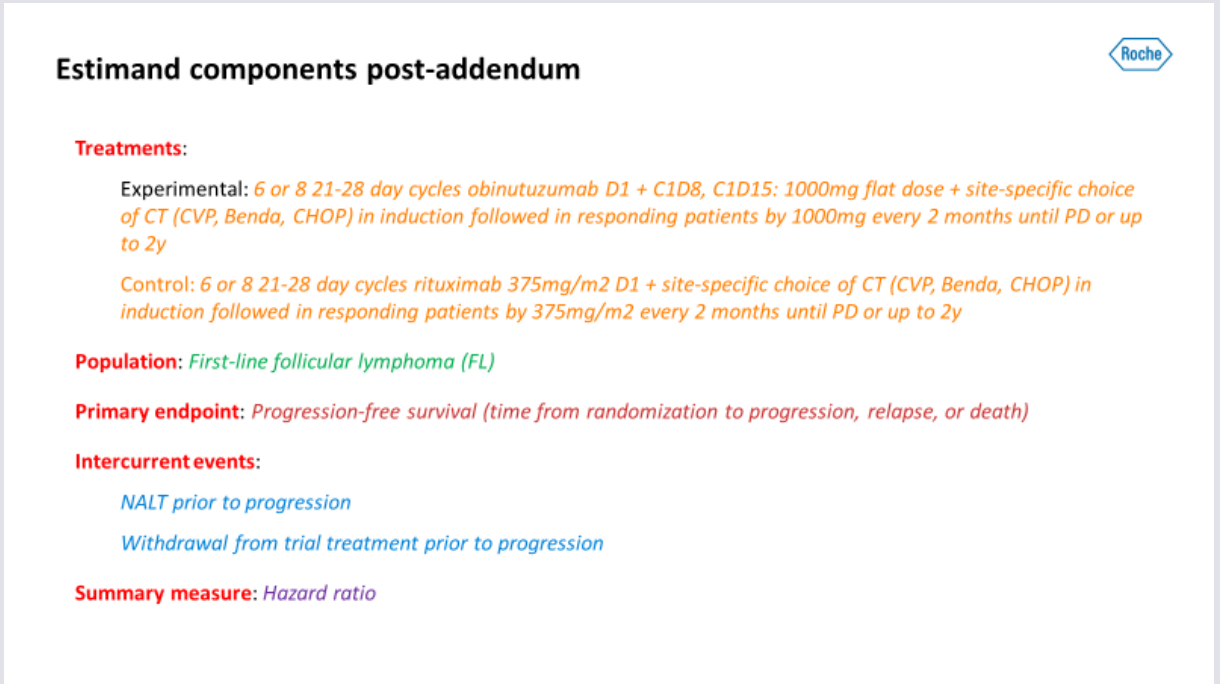
Challenges and open questions in hematology:
RATIFY



Reference: Renaud Capdeville. Basel Biometrics Section Webinar

Commentary on:
Tina Nielsen (Roche)

Challenges and open questions in hematology:
GALLIUM



Reference: Tina Nielsen. Basel Biometrics Section Webinar

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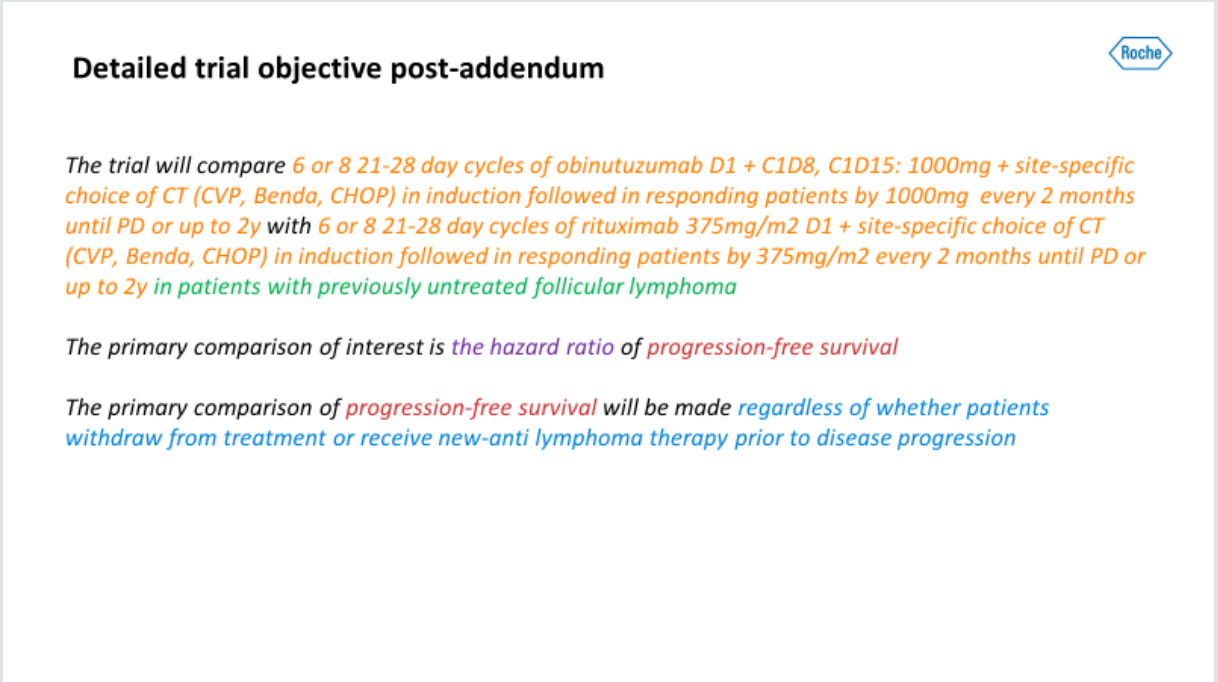
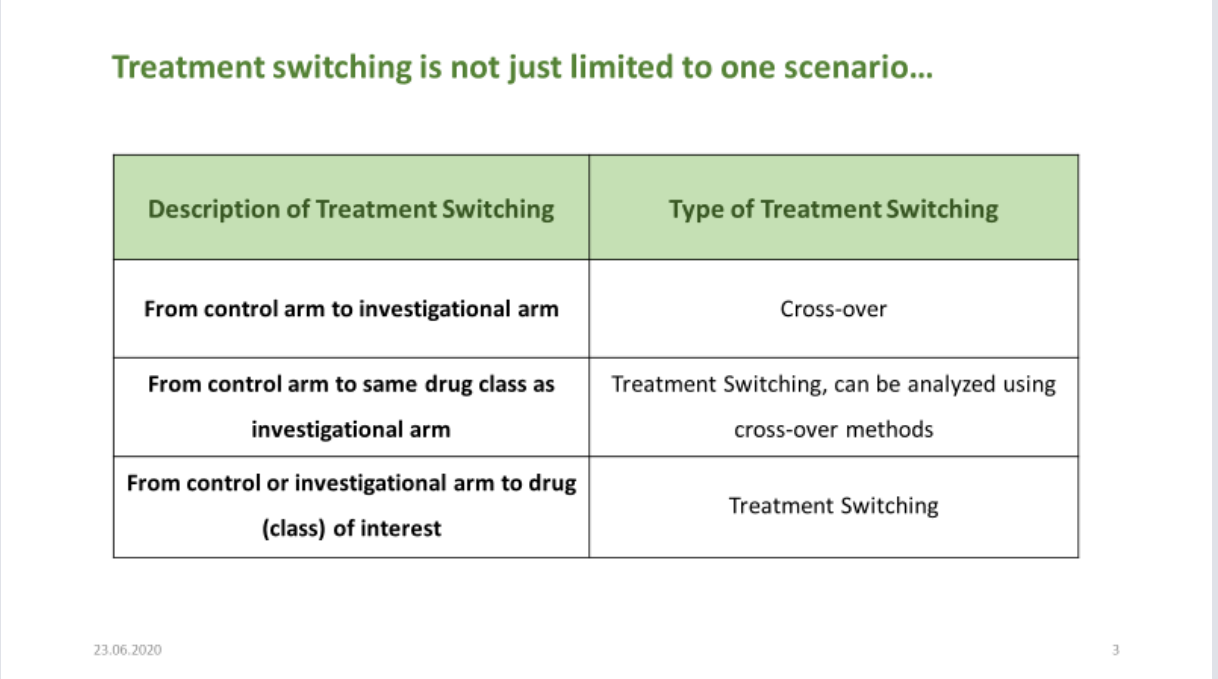


Reference: Tina Nielsen. Basel Biometrics Section Webinar

Commentary on: Hannes Buchner (Staburo) & Ingolf Griebsch (Boehringer Ingelheim)

Treatment switching: challenges, estimands, and estimators



Reference: Hannes Buchner & Ingolf Griebsch. Basel Biometrics Section Webinar

Commentary on: Hannes Buchner (Staburo) & Ingolf Griebsch (Boehringer Ingelheim)

Treatment switching: challenges, estimands, and estimators

Estimands in clinical trials with treatment switching

OBJECTIVE	*Evaluate OS benefit assuming subsequent therapies represent clinical practice*	*Evaluate OS benefit adjusted for treatment switching*	*Evaluate OS benefit adjusted for treatment crossover*	*Evaluate OS benefit adjusted for treatment crossover at disease-related time-point*
ESTIMAND				
Population	Defined through appropriate I/E criteria to reflect the target patient population for approval			
Variable / Endpoint	Overall survival: Time from randomization to death			
Treatment condition of interest	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)	Investigational drug vs control (if there were no subsequent therapies)	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)	Sequence of Investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)
Handling of intercurrent events (IEs)				
IE: Start of subsequent therapy at any time	Treatment policy	Hypothetical	Treatment policy	Treatment policy
IE: Crossover to investigational drug at any time	Treatment policy	Hypothetical	Hypothetical	Treatment policy
IE: Crossover to investigational drug at disease – related time point	Treatment policy	Hypothetical	Hypothetical	Hypothetical
Population - level Summary	Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)			
ESTIMATION	Cox model and KM estimates using ITT approach	Adjusted HR and CI from IPCW – weighted Cox model; weighted KM estimates	HR from RSPFT model using adjusted survival times; bootstrapped CI; KM estimates using adjusted survival times; IPCW methods could also be used	HR from two – stage method using reconstructed survival; modified KM estimates using reconstructed survival times; IPCW and RPSFT methods could be used

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Reference: Hannes Buchner & Ingolf Griebsch. Basel Biometrics Section Webinar

Commentary on: Anja Schiel (Norwegian Medicines Agency)

Regulator's view: Experience with the estimand framework in oncology

Does everyone see the opportunities?

- No, the uptake of the framework has not been comparable in all disease areas
- The main driver for the use of the framework are in fact the intercurrent events!
- In solid tumours, depending on the line we investigate, the advantage of the Estimand framework is not always clear
  - 'We have always done it that way….. '
- Mature discussions on all aspects of the framework are actually only seen in certain areas with a 'blank canvas'
  - Alzheimer's disease and Huntington's disease

Reference: Anja Schiel. Basel Biometrics Section Webinar

Summary

With respect to COVID-19, the original objectives of the trials should be maintained; but some impact to planned estimands may be unavoidable. Pandemic-related intercurrent events will likely need to be defined to properly and rigorously account for some, previously unexpected, pandemic effects.

In this regard the estimand framework

1. helps to align planning, design, conduct, analysis, and interpretation of a clinical trial
   (as originally planned)
2. provides various stakeholders a common language to discuss the impact of COVID-19 in a structured and transparent manner
   (based on feedback received from various representatives of pharmaceutical companies during impact assessment of COVID-19)


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