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

How COVID-19 impacts ongoing clinical trials

Potential individual subject courses:

- **Readout/Dropout/Censor**
  - Pre
  - During
  - Post

- **Enrollment period**
  - Pre
  - During
  - Post

- **Interruption**
- **Missed visit**

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

ASSESS IMPACT
Assess the impact of COVID-19
• Impact on data quality
• Impact on recruitment and retention
• Impact on treatment effects and study power
• Blinded/Unblinded Review

DEFINE RISK
Clearly define risk
• Lack of interpretability
• Confounding or inconclusive results
• Loss of power

MITIGATION
Contingency Measures
• Different ways of collecting data
• Trial modifications – sample size, analysis methods, missing data, sensitivity analyses
• Documentation in Protocol, SAP and CSR
• Consult with regulatory agencies

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.

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?
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.

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

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 considered.

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

Challenges and open questions in hematology:
RATIFY

Can the estimand be defined differently today?

- **Clinical trial objective**
  - To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy with the option to receive SCT in CR improves OS in mutant AML patients?

- **Treatment strategy**
  - **Experimental**: DNR-AraC + midostaurin induction, AraC + midostaurin consolidation in pts with a CR, midostaurin maintenance, option to receive SCT in CR
  - **Control**: DNR-AraC induction, AraC consolidation in pts with a CR, option to receive SCT in CR

- **Population**: newly diagnosed AML with a FLT-3 mutation eligible for intensive chemotherapy

- **Variable**: overall survival

- **Intercurrent events**: none for OS (treatment policy for SCT, treatment discontinuation, new therapies)

- **Summary measure**: hazard ratio

Reference: Renaud Capdeville. Basel Biometrics Section Webinar
Challenges and open questions in hematology: GALLIUM

Commentary on:
Tina Nielsen (Roche)

Estimand components post-addendum

Treatments:

Experimental: 6 or 8 21-28 day cycles obinutuzumab D1 + C1D8, C1D15: 1000mg flat dose + site-specific choice of CT (CVP, Bend, CHOP) in induction followed in responding patients by 1000mg every 2 months until PD or up to 2y

Control: 6 or 8 21-28 day cycles rituximab 375mg/m2 D1 + site-specific choice of CT (CVP, Bend, CHOP) in induction followed in responding patients by 375mg/m2 every 2 months until PD or up to 2y

Population: First-line follicular lymphoma (FL)

Primary endpoint: Progression-free survival (time from randomization to progression, relapse, or death)

Intercurrent events:

NALT prior to progression
Withdrawal from trial treatment prior to progression

Summary measure: Hazard ratio

Reference: Tina Nielsen. Basel Biometrics Section Webinar
Commentary on: Tina Nielsen (Roche)

Challenges and open questions in hematology:
GALLIUM

Detailed trial objective post-addendum

The trial will compare 6 or 8 21-28 day cycles of obinutuzumab D1 + C1D8, C1D15: 1000mg + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 1000mg every 2 months until PD or up to 2y with 6 or 8 21-28 day cycles of rituximab 375mg/m2 D1 + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 375mg/m2 every 2 months until PD or up to 2y in patients with previously untreated follicular lymphoma.

The primary comparison of interest is the hazard ratio of progression-free survival.

The primary comparison of progression-free survival will be made regardless of whether patients withdraw from treatment or receive new-anti lymphoma therapy prior to disease progression.

Reference: Tina Nielsen. Basel Biometrics Section Webinar
Commentary on: Hannes Buchner (Staburo) & Ingolf Griebsch (Boehringer Ingelheim)

Treatment switching: challenges, estimands, and estimators

<table>
<thead>
<tr>
<th>Description of Treatment Switching</th>
<th>Type of Treatment Switching</th>
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<tbody>
<tr>
<td>From control arm to investigational arm</td>
<td>Cross-over</td>
</tr>
<tr>
<td>From control arm to same drug class as investigational arm</td>
<td>Treatment Switching, can be analyzed using cross-over methods</td>
</tr>
<tr>
<td>From control or investigational arm to drug (class) of interest</td>
<td>Treatment Switching</td>
</tr>
</tbody>
</table>

Reference: Hannes Buchner & Ingolf Griebsch. Basel Biometrics Section Webinar
Commentary on: Hannes Buchner (Staburo) & Ingolf Griebsch (Boehringer Ingelheim)

Treatment switching: challenges, estimands, and estimators

<table>
<thead>
<tr>
<th>Estimands in clinical trials with treatment switching</th>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td>Evaluate OS benefit assuming subsequent therapies represent clinical practice</td>
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<tr>
<td>Evaluate OS benefit adjusted for treatment switching</td>
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<tr>
<td>Evaluate OS benefit adjusted for treatment crossover</td>
</tr>
<tr>
<td>Evaluate OS benefit adjusted for treatment crossover at disease-related time-point</td>
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<table>
<thead>
<tr>
<th><strong>Estimand</strong></th>
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<tr>
<td><strong>Population</strong></td>
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<tr>
<td>Defined through appropriate I/E criteria to reflect the target patient population for approval</td>
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<table>
<thead>
<tr>
<th><strong>Variable / Endpoint</strong></th>
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<tbody>
<tr>
<td>Overall survival: Time from randomization to death</td>
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</table>

<table>
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<tr>
<th><strong>Treatment condition of interest</strong></th>
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<tbody>
<tr>
<td>Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including investigational drug)</td>
</tr>
<tr>
<td>Investigational drug vs control (if there were no subsequent therapies)</td>
</tr>
<tr>
<td>Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Handling of intercurrent events (IEs)</strong></th>
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<tbody>
<tr>
<td>IE: Start of subsequent therapy at any time</td>
</tr>
<tr>
<td>Treatment policy</td>
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</tbody>
</table>

| 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 |

<table>
<thead>
<tr>
<th><strong>Population level summary</strong></th>
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<tr>
<td>Kaplan–Meier estimates; hazard ratio (HR) with confidence interval (CI)</td>
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<table>
<thead>
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<th><strong>Estimation</strong></th>
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<tbody>
<tr>
<td>Cox model and KM estimates using ITT approach</td>
</tr>
<tr>
<td>Adjusted HR and CI from PCW - weighted Cox model, weighted KM estimates using adjusted survival times; PCW methods could also be used</td>
</tr>
<tr>
<td>HR from RSPTT model using reconstructed survival; modified KM estimates using reconstructed survival times; PCW and RSPTT methods could be used</td>
</tr>
</tbody>
</table>


25.06.2020
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)
abbvie