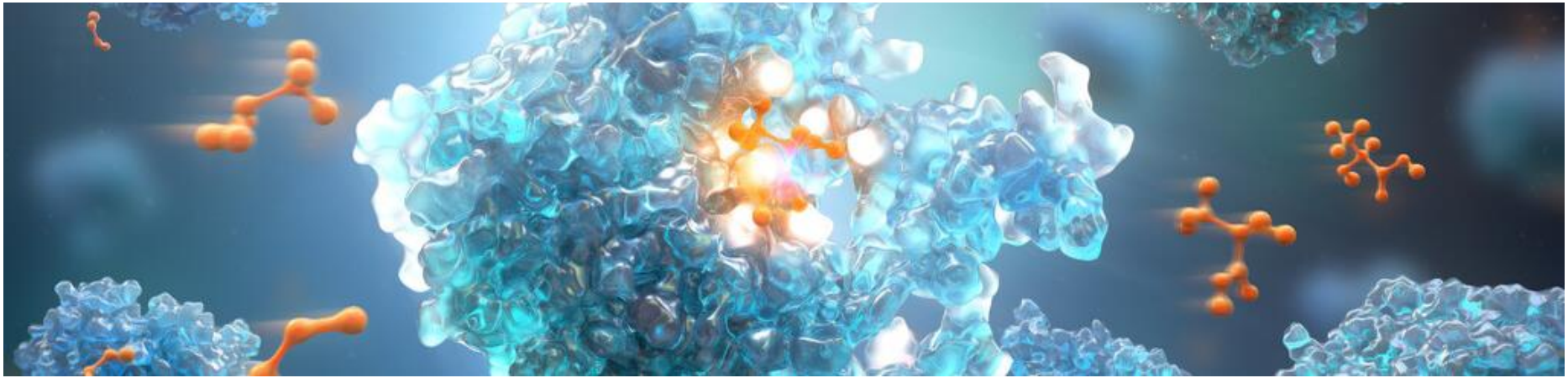
Reflections on cross pharma collaborations on the impact of COVID-19 on ongoing trials

Dr David Wright, Head of Statistical Innovation, Early Biometrics and Statistical Innovation, Data Science and Artificial Intelligence, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

FMS

13 November 2020



Acknowledgements

- Thanks to the rest of the Pharmaceutical Industry COVID-19 Biostatistics Working Group and many people at AstraZeneca for help in forming the views expressed here.
- Particular thanks to Bohdana Ratitch (Bayer) (my co-presenter at the 2nd DIA webinar) who wrote many of the slides I will present today

Contents

Pharmaceutical Industry COVID-19 Biostatistics Working Group

Institution	Member
abbvie	Jyotirmoy Dey
	Stefan Englert
AMGEN	Thomas Liu
AstraZeneca	David Wright
BAYER	Olga Marchenko
	Bohdana Ratitch
Bristol Myers Squibb	Daniel Li
	Ming Zhou
Lilly	Wei Shen
GILEAD	Gerald Crans

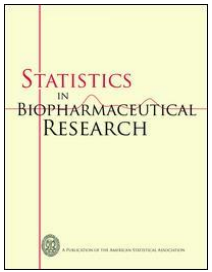
Institution	Member
gsk GlaxoSmithKline	Christine Fletcher
janssen	Norm Bohidar
Lundbeck	Ingrid Sofie Harbo
MERCK	Yue Shentu
Pfizer	R. Daniel Meyer
Roche Genentech A Member of the Roche Group	Xin Li
	Marcel Wolbers
SANOFI	Peng-Liang Zhao
	Hui Quan
Takeda	Michael Hale

This presentation reflects the views of the authors and should not be construed to represent the views or policies of their affiliated institutions and companies.

Pharmaceutical Industry COVID-19 Biostatistics Working Group

- Formed in March 2020
- Collaboration between 15 pharmaceutical companies
- So far led to 2 DIA webinars (in May and July) and 1 paper that appeared in a special edition of Statistics in Biopharmaceutical Research (written in 6 weeks!)

Pharmaceutical Industry COVID-19 Biostatistics Working Group



Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

R. Daniel Meyer, Bohdana Ratitch, Marcel Wolbers, Olga Marchenko, Hui Quan, Daniel Li, ...show all

Received 29 Apr 2020, Accepted 01 Jun 2020, Accepted author version posted online: 08 Jun 2020

Comment on: Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

Sylva H. Collins & Mark S. Levenson

Received 13 May 2020, Accepted 01 Jun 2020, Accepted author version posted online: 08 Jun 2020

Under a black cloud glimpsing a silver lining: Comment on Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

Rob Hemmings

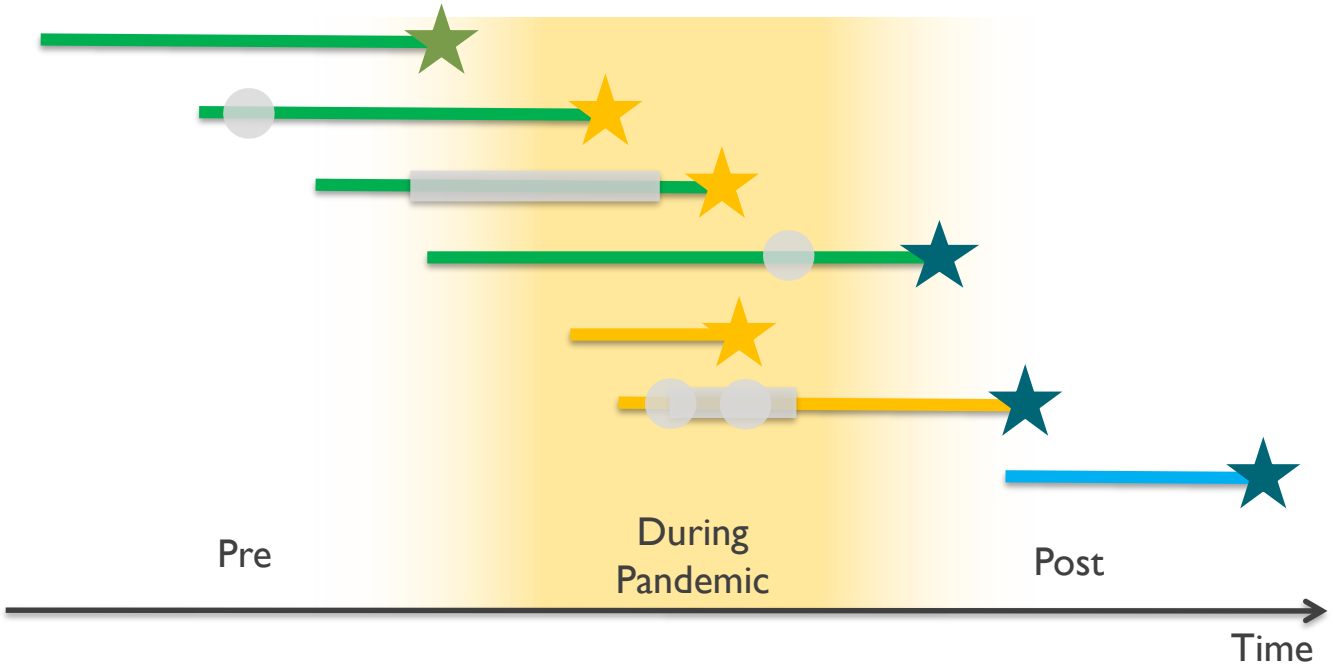
Received 25 May 2020, Accepted 08 Jun 2020, Accepted author version posted online: 25 Jun 2020

- Key dimensions of pandemic-related factors, impacts, risk assessment, mitigations, and documentation
- Implications and mitigations for estimands
- Implications and mitigations for analysis: efficacy and safety analyses, missing data, sensitivity and supplementary analyses
- Considerations for study power and probability of success
- Considerations for the DMC and interim analyses

This publication reflects the views of the authors and should not be construed to represent the views or policies of their affiliated institutions and companies.

How COVID-19 impacts ongoing clinical trials

Potential individual subject courses:



Readout/Dropout/Censor

Pre

During

Post

Enrollment period

Pre

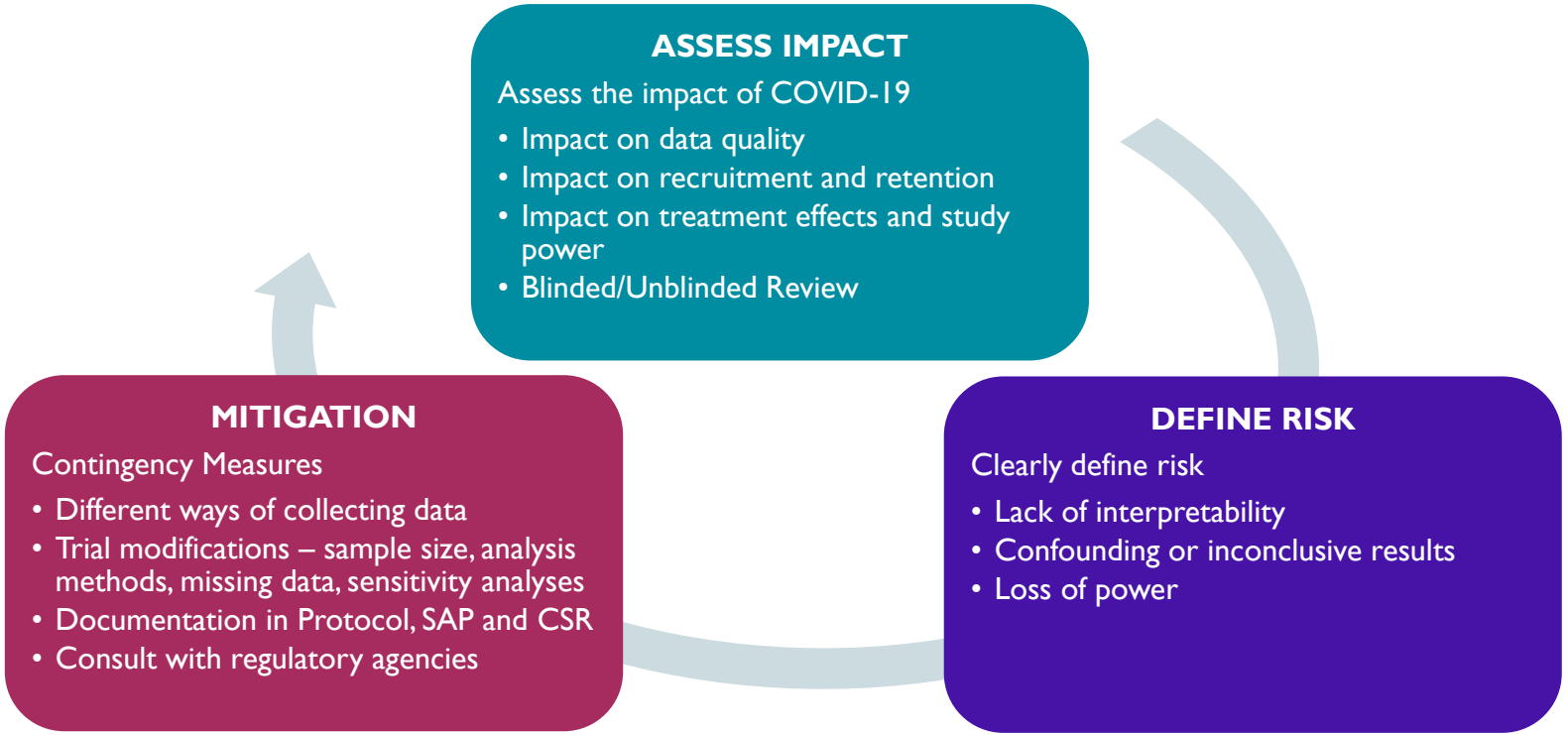
During

Post

Interruption

Missed visit

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



ASSESS IMPACT

Does COVID-19 change my research question?

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**?

Addressing intercurrent events - example

- Imagine a Phase III study of an experimental treatment as an add-on to a standard background therapy in patients with moderate/severe Chronic Obstructive Pulmonary Disease (COPD)
- Long-term symptom control (over one year) needs to be demonstrated

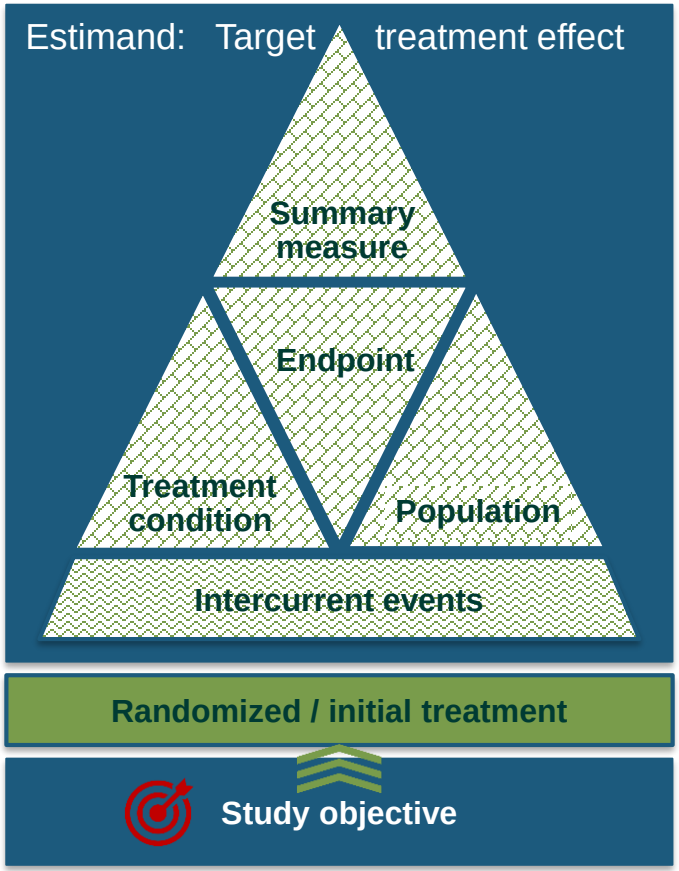
Plan before the pandemic

- It was anticipated that most study treatment discontinuations would be due to treatment-related reasons (lack of efficacy or toxicity).
- There are no effective treatment alternatives for participants who discontinue randomized treatment prematurely - expected to remain on the background therapy only.
- Effect of incomplete treatment on the endpoint measured over one year is of interest.
- Therefore, all treatment discontinuations were planned to be addressed using the treatment policy strategy.

Reality during the pandemic

- In the context of COVID-19 pandemic, participants may also discontinue study treatment due to:
  - Site operation disruptions
  - Participant's perception of increased risk versus benefit from the study participation
  - Complications of COVID-19 infection and start of COVID-19 therapy in a hospital setting
  - COVID-19 death
- Doesn't make sense to use the treatment policy strategy for COVID-19 related intercurrent events.

Estimand framework – unnecessary complication or a helpful tool ?

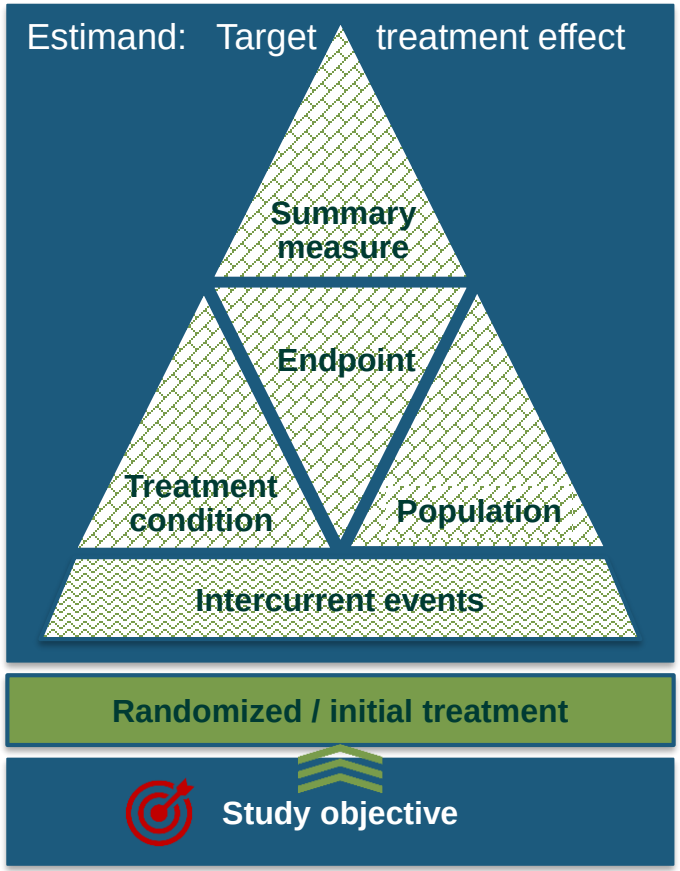


- Estimand framework as the means to detail the study objective and define targeted treatment effect using five attributes.
- COVID-19 pandemic disruptions may impact the estimated treatment effect, with impact potentially exerted via any of the five estimand attributes

- Study treatment interruptions
- Alternative methods of assessment
- COVID-19 hospitalizations, therapies, deaths

If estimands were not formally defined, still useful to assess the impacts systematically and as basis for regulatory discussions

Estimand framework – unnecessary complication or a helpful tool ?



- Intercurrent events (ICEs): Events occurring after treatment initiation that affect either interpretation or existence of (efficacy) measurements
  - » Post-randomization treatment changes, e.g., discontinuation of randomized treatment; rescue medication
  - » Events that render subsequent outcomes non-ascertainable, e.g., death
  - » Events that stratify participants into subsets with different patterns of outcomes, e.g., infection status
- ICE Strategy: Define how the ICE and/or outcomes after the ICE are factored into the treatment effect estimate

Addressing intercurrent events – general framework

Consider possible ICEs - changes in randomized/initial treatment or terminal events

- Study treatment permanently discontinued (with or without switch to an alternative therapy for study disease);
- Study treatment temporarily interrupted or compliance significantly reduced (with or without changes in concomitant therapy for study disease);
- Death

Consider reasons for ICEs

Not pandemic-related:

- ICEs due to treatment-related reasons (LOE, tolerability)
- ICEs due to other reasons, not related to the pandemic

Address the ICEs as originally planned, even if such ICEs occur during the pandemic

Pandemic-related:

- ICEs with the primary reason related to the pandemic

Address the ICEs considering pandemic-related factors contributing to the occurrence of ICEs

Study Treatment Accessibility

- Drug supply interruption;
- Site unavailable to administer/dispense study treatment;
- Study treatment available but participant is unable/unwilling to get study treatment due to personal pandemic-related reasons.

Participant's COVID-19 Infection Condition

- Positive for COVID-19 and alive;
- Deceased due to COVID-19;
- Suspected COVID-19 infection;
- Exacerbation of underlying health issues due to reduced healthcare access.

Participant's COVID-19 Concomitant Treatment(s)

- Treated for COVID-19 (pharmacologically, oxygen);
- Hospitalized, not in ICU;
- Admitted to ICU.

Treatment policy strategy

- Generally
  - Applicable for ICEs that mark a change in randomized/initial treatment, but not for terminal events; and
  - The entire treatment sequence (both the reason for change and the changed therapy) is relevant and there is interest to include its effect in the estimate of the overall treatment effect.
  - Most useful and generalizable when treatment change rules are well-defined and are relevant to future clinical practice.

- For pandemic related ICEs
  - In most cases, pandemic-related reasons of ICEs (e.g., disruptions with study treatment availability) and the effect of COVID-19 infection/therapies on the study outcomes would not be of interest with respect to the original study objective(s), and conclusions would not generalize to clinical care in "post-pandemic world" .
  - Use of this strategy may be justifiable if the percentage of participants with such events is low and this strategy was planned for similar non-pandemic related treatment changes.
  - Note if patient receives treatment for COVID-19 infection after an earlier non-pandemic related ICE then using treatment policy for the infection and post infection period may not be appropriate.

Composite strategy

- Generally
  - Applicable for the ICEs which are important clinical events that lead to an immediate conclusion about success or failure of treatment.
  - The estimated treatment effect represents an effect on both the clinical measurement and occurrence of ICE, therefore, it is important that the ICE can be interpreted together with the clinical measurement as a meaningful combined outcome.

- For pandemic related ICEs
  - In most cases, ICEs due to pandemic-related reasons (e.g., disruptions with study treatment availability) cannot be interpreted as evidence of study treatment effectiveness or tolerability.
  - Use of this strategy may be justifiable for some ICEs in studies of respiratory conditions where COVID-19 complications may be considered as a form of unfavorable outcome.

Hypothetical strategy

- Generally
  - Appropriate when the ICE is a confounding factor for inference about the treatment condition of interest; and
  - The objective is to estimate a treatment effect under a scenario where confounding is removed, but such scenario is impossible to realize in the study due to ethical or operational reasons; therefore a hypothetical scenario is assumed.
  - The endpoint value at the planned time point after the ICE cannot be observed under the hypothetical scenario and will need to be modeled / estimated.

- For pandemic related ICEs
  - This strategy would be a natural choice for pandemic-related study treatment discontinuations in many settings, with the hypothetical scenario "if participant did not discontinue study treatment".
  - It may be considered for ICE of COVID-19 death, with the hypothetical scenario "if participant did not die", in disease areas with minimal mortality where death is not a component of the endpoint.
  - How the outcome is modeled under the hypothetical scenario in analysis may depend on the pandemic-related factors contributing to the ICE, the study disease, participant characteristics, and the nature of the endpoint.

Addressing deaths due to COVID-19

- In disease areas with minimal mortality where death (due to any causes) is not a component of the endpoint, a hypothetical strategy for deaths related to COVID-19 infections may be recommended.
- For studies in severe diseases and/or elderly populations where death is part of the endpoint, more than one estimand may be of interest to fully characterize the treatment effect:
  - Estimand using a hypothetical strategy for deaths related to COVID-19 infections would evaluate the benefit of treatment in the absence of COVID-19 (e.g., when the disease is eradicated or effective treatment options emerge in the future).
  - Estimand that includes COVID-19-related deaths in the endpoint, i.e., which uses a composite strategy, would evaluate the benefit of treatment in the presence of COVID-19 in the patient population; or constitute a conservative approach reflecting severity of the underlying risk factors associated with study disease.
    - It is acknowledged that in trials that include elderly, frail, or immunocompromised participants, it may be difficult to adjudicate a death as caused by COVID-19 or whether the participant died with COVID-19.

Missing and unobserved data

- Despite best efforts, sponsors should prepare for the possibility of increased amounts and/or distinct patterns of missing data.
- Some collected data may be deemed unusable (e.g., out-of-window).
- Missingness is not an ICE in itself.
- Missingness may or may not occur with an ICE.
- Target outcomes are unobservable under hypothetical scenarios.

Missing and unobservable data

ICE occurred

- **Composite**
- **While-on-treatment**

→ **No missing data**
Data after ICE are not useful for the estimand

- **Hypothetical**

→ **Unobservable data**
Data cannot be observed under the hypothetical scenario

→ **What would the outcome have been under the hypothetical scenario?**

Consider pandemic-related factors similar to those listed on slide 13

- **Treatment policy**
- **Principal stratification**

No ICE

→ **Missing data**
Data would have been appropriate for the estimand but not available

- Missed assessment
- Incomplete assessments
- Delayed, out-of-window assessment
- Withdrawal from study

→ **What would the outcome have been given the nature of the ICE and estimand strategy?**

→ **What would the outcome have been given that the participant still adheres to treatment?**

Pandemic-related factors and missingness mechanism

Reasons for missing / unobservable values could be pandemic-related or not (see factors discussed for ICEs)

Pandemic-related factors

- Structural, e.g., government enforced closures or sites stopping study-related activities
  - Can be considered MCAR
- Participant-specific, e.g.,
  - Individual concerns for COVID-19 or individual COVID-19 infection and complications
  - Participants with milder disease or lower treatment response may be more inclined to discontinue the study
  - If reasons for missingness, ICEs, relevant covariates and early outcomes are captured, may often be considered MAR
  - Sometimes, may need to be modeled under MNAR

Missingness mechanism

- Missing Completely at Random (MCAR): probability of missingness is independent of all participant-related factors or, conditional on pre-randomization covariates, the probability of missingness does not depend on either the observed or unobserved outcomes.
- Missing at Random (MAR): conditional on pre-randomization covariates and observed outcomes, probability of missingness does not depend on unobserved outcomes.
- Missing Not at Random (MNAR): probability of missingness depends on unobserved study outcomes.
- Implication of MCAR / MAR is that missing values can be modelled based on available data from "similar" participants.

Strategies for pandemic-related missing and unobservable data

Model / impute

Include participants in the analysis set with partial data

Many methods are readily available, e.g.:

MCAR or MAR

- Direct likelihood, e.g., mixed models for repeated measures (MMRM)
- Generalized linear (mixed) models
- Negative binomial model
- Cox proportional hazards regression

MNAR

- Pattern-mixture model framework
- Selection model framework
- Shared parameter model framework

Multiple imputation can be useful to impute missing values when

- A direct likelihood method cannot be used;
- Imputation model needs to adjust for auxiliary covariates;
- Imputation model needs to be estimated from a specific reference group (subset) and/or with deviations from MAR

Exclude

Exclude participants from the analysis set

MCAR

- May be considered for data missing/unobservable due to structural reasons if available data for affected participants at a site would contribute little or no information about the treatment effect
- To avoid bias, exclude all participants at a given site who would have had endpoint assessment during disruptions period, regardless of post-randomization outcomes (see FDA, 2020 guidance)

When MAR may not be appropriate: Example of missing data under treatment policy strategy

Context

- Participant in a COPD study discontinued treatment due to an AE.
- The ICE is planned to be addressed with the treatment policy strategy.
- After the start of the pandemic, participant withdraws from the study, which results in missing data.
- Reason for study withdrawal: participant's condition deteriorated and they are worried that clinic visits would increase their risks associated with COVID-19.

Consideration and strategy for handling missing values

- Pre-discontinuation efficacy outcomes may have been favorable, but would be expected to worsen after treatment discontinuation.
- Worsened outcomes are not fully captured and may be more severe than in participants who remained in the study.
- An MNAR approach could assume worse outcomes than what would be predicted by a model estimated from participants who discontinued study treatment but remained in the study (see e.g., the "attributable estimand approach" in Darken et al., 2020).
- The extent of "worse" should be clinically plausible and investigated in sensitivity analyses, e.g., tipping point.

Feasibility considerations for estimation with missing / unobservable data

- Missing / unobservable outcomes are often modelled based on data from other "similar" participants with observed data, possibly with some additional assumptions.
- It is, therefore, important to ensure that the observed data and chosen models are adequate for predicting (implicitly or explicitly) the missing and unobserved outcomes / treatment effect.

Feasibility considerations for estimation with missing / unobservable data

- Questions to be considered:
  - Are reasons and contributing factors for the ICEs and missed assessments well documented for proper attribution?
  - Are there adequate observed data in participants whose characteristics overlap with characteristics of participants with missing / unobserved data to minimize extrapolation?
  - Does the predictive model have a good fit, predictive accuracy, and/or leads to robust inference?
  - Is there sufficient understanding of expected disease trajectories or external data to check plausibility of imputations and/or to make additional assumptions?
  - What is the effect of the amount of missing / unobserved data on statistical power?
- If such questions are part of risk assessment and mitigation, favorable answers to these questions should be feasible in most trials.

Summary

- The estimand framework provides a systematic pathway for assessing the impact of the pandemic.
- Pandemic-related intercurrent events will likely need to be defined to properly and rigorously account for unexpected pandemic effect.
- A hypothetical estimand strategy is a natural way to investigate the effect of a treatment in the absence of the pandemic.
- Most pandemic-related missing/unobserved data are likely MCAR or MAR, especially if missingness is due to structural reasons, but additional considerations may apply, especially for certain diseases and participant-specific missingness.

References

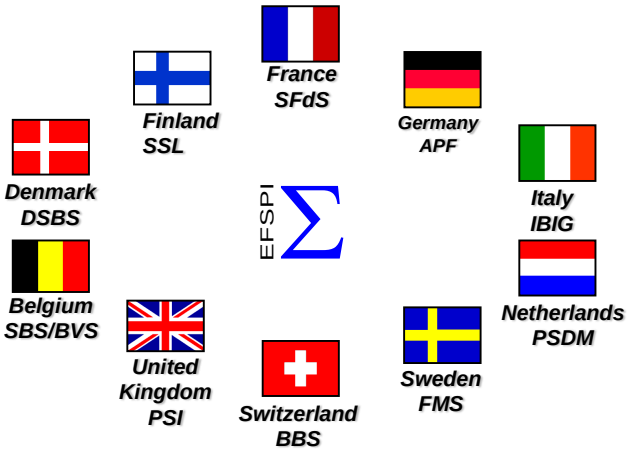
- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, Guidance for Industry, Investigators, and Institutional Review Boards (March 2020, Updated on June 03, 2020)
- FDA Guidance on Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry (June 2020)
- EMA Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic. Version 3 (28/04/2020)
- EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials (draft)
- ICH Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1)
- Statistical Issues and Mitigations for Pharmaceutical Clinical Trials Conducted During the COVID-19 Pandemic. COVID-19 Pharmaceutical Industry Working Group, accepted for publication in *Statistics in Biopharmaceutical Research*.
- Rob Hemmings (2020) Under a black cloud glimpsing a silver lining: Comment on Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic, Statistics in Biopharmaceutical Research, DOI: 10.1080/19466315.2020.1785931
- Sylva H. Collins & Mark S. Levenson (2020) Comment on: Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic, Statistics in Biopharmaceutical Research, DOI: 10.1080/19466315.2020.1779123
- Darken, P, Nyberg, J, Ballal, S, Wright, D. The attributable estimand: A new approach to account for intercurrent events. Pharmaceutical Statistics. 2020; 1– 10. https://doi.org/10.1002/pst.2019
- Nguyen, C.D., Carlin, J.B. & Lee, K.J. Model checking in multiple imputation: an overview and case study. Emerg Themes Epidemiol 14, 8 (2017).
- Elena Polverejan & Vladimir Dragalin (2020) Aligning Treatment Policy Estimands and Estimators—A Simulation Study in Alzheimer's Disease, Statistics in Biopharmaceutical Research, 12:2, 142-154, DOI: 10.1080/19466315.2019.1689845
- Considerations on impact of COVID-19 on estimands in oncology clinical trials compiled by industry working group "Estimands in Oncology", most recent version available on http://tinyurl.com/oncoestimand

Feedback from meeting between industry stakeholders and Biostatistics Working Party at European Medicines Agency – October 2nd 2020

BSWP virtual stakeholder meeting

2nd October 2020

European Federation of Statisticians in the Pharmaceutical Industry



European Federation of Pharmaceutical Industries and Associations

Impact of COVID-19 on Methodological Aspects of Ongoing Clinical Trials - 1

- Fundamental question of interest: Evaluation of the efficacy of a medicine in the presence or absence of the pandemic? A post COVID-19 world must consider pandemic related intercurrent events (ICEs) differently to non-pandemic ICEs. Does BSWP agree?
  - Does BSWP feel strongly that an estimand strategy that addresses the question of the efficacy of the drug in a post COVID-19 world be added to all analysis plans?
  - Should this be the primary analysis in any dossier submitted after a vaccine becomes widely available in the EU?
- FDA's guidance https://www.fda.gov/media/139145/download recommends excluding all patients from a site which was closed for a period of time because of COVID-19. Alternative approaches are available that allow information of data collected before the pandemic started to be included in the primary analysis. What are BSWPs views on this?

Impact of COVID-19 on Methodological Aspects of Ongoing Clinical Trials - 2

- IDMCs' – can BSWP confirm that the use of an IDMC to evaluate the impact of COVID-19 on a study would be an unusual situation and that this evaluation will normally be done by the sponsor in a blinded fashion.
  - IDMCs may have access to unblinded information and thus unable to conduct a fair assessment
- Telemedicine – the pandemic may have resulted in alternative methods of data collection for a period of time. What is BSWP's view on the use of these data in a dossier and the focus sponsors should put on providing evidence of the reliability of these data?
  - Are there any concerns regarding data integrity and how this should be addressed?

Any questions?