How the estimand addendum to the ICH E9 guideline helps structure clinical objectives, analyses, and conclusions

A series of oncology case studies

Stefan Englert, Jonathan Siegel, Juliane Manitz, Feng Liu and Steven Sun

On behalf of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

International Oncology Estimands Working Group

- Goal: A common understanding across industry
- As of 13 April 2021, the working group has 61 members (from Europe, US, and Asia) representing 33 companies
- EFSPI SIG (Nov 2018) and ASA Biopharm Section SWG (Apr 2019)
- In dialogue with eight Health Authorities globally
- Weblink www.oncoestimand.org

Goal of Session

The goal of this session is to bring all disciplines together and maximize awareness of the ICH E9 addendum as well as demonstrate how it helps interdisciplinary teams to formulate clinical trial objectives, design, conduct, primary, secondary, and sensitivity analyses, as well as conclusions.

There will be time allocated after each methods section to interactively deepen the knowledge and gain first-hand insights from a cross-industry international working group.

Zoom Poll 1

1. Please describe your role in drug development:
   - Investigator
   - Clinician
   - Regulatory Expert
   - Medical Writer
   - Ethics Committee Member
   - Statistician
   - Other
2. Please describe the therapeutic area you work in:
   - Late stage Oncology
   - Early stage Oncology
   - Non-oncology therapeutic area
3. Please describe your familiarity with the ICH E9 (R1) addendum
   - No exposure to ICH E9 (R1) addendum
   - Basic understanding of the concepts introduced in ICH E9 (R1) addendum
   - Applied the concepts of the ICH E9 (R1) to at least one clinical trial

Today's agenda

- Estimand framework: general introduction to the framework
- Illustrate the impact of the addendum by applying it to a series of oncology case studies:
  - Censoring mechanisms by Stefan Englert, AbbVie Inc. and Jonathan Siegel, Bayer
  - Treatment switching by Juliane Manitz, EMD Serono Inc./Merck KGaA
  - Solid tumors by Feng Liu, AstraZeneca
  - Hematology by Steven Sun, Johnson & Johnson
  - COVID-19 by Stefan Englert, AbbVie Inc.
- Closing remarks

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Zoom Poll 2

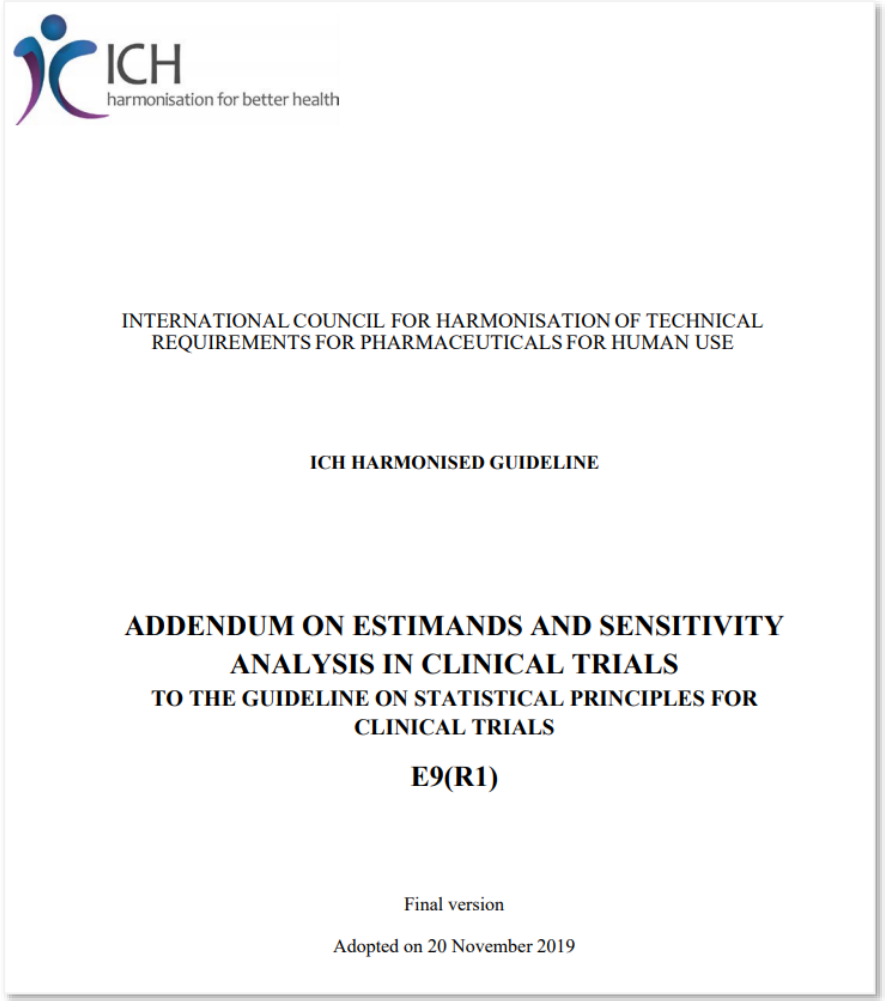
1. Have you used estimands?
    - What is an estimand?
    - I have seen examples of estimands.
    - I have been involved in the development of estimands
    - I am helping others to construct estimands”.

ICH E9 (R1) Estimand Framework

Key messages and Intentions

- Promotes **alignment** between trial objectives, design, data collection, conduct, analysis and inference
- Results in **increased transparency and more trust** in biopharmaceutical industry
- Strengthens **interdisciplinary dialogue at design stage**
  - Reduce the risk of different interpretation by relevant stakeholders (regulators, payers, patients, etc.)
- Informs **what data to collect**
- **Aligns expectations** between drug developers and regulatory bodies

Requires more precise definition of trial objective and meaningful treatment effect (i.e., an estimand)


ICH
harmonisation for better health

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

ICH HARMONISED GUIDELINE

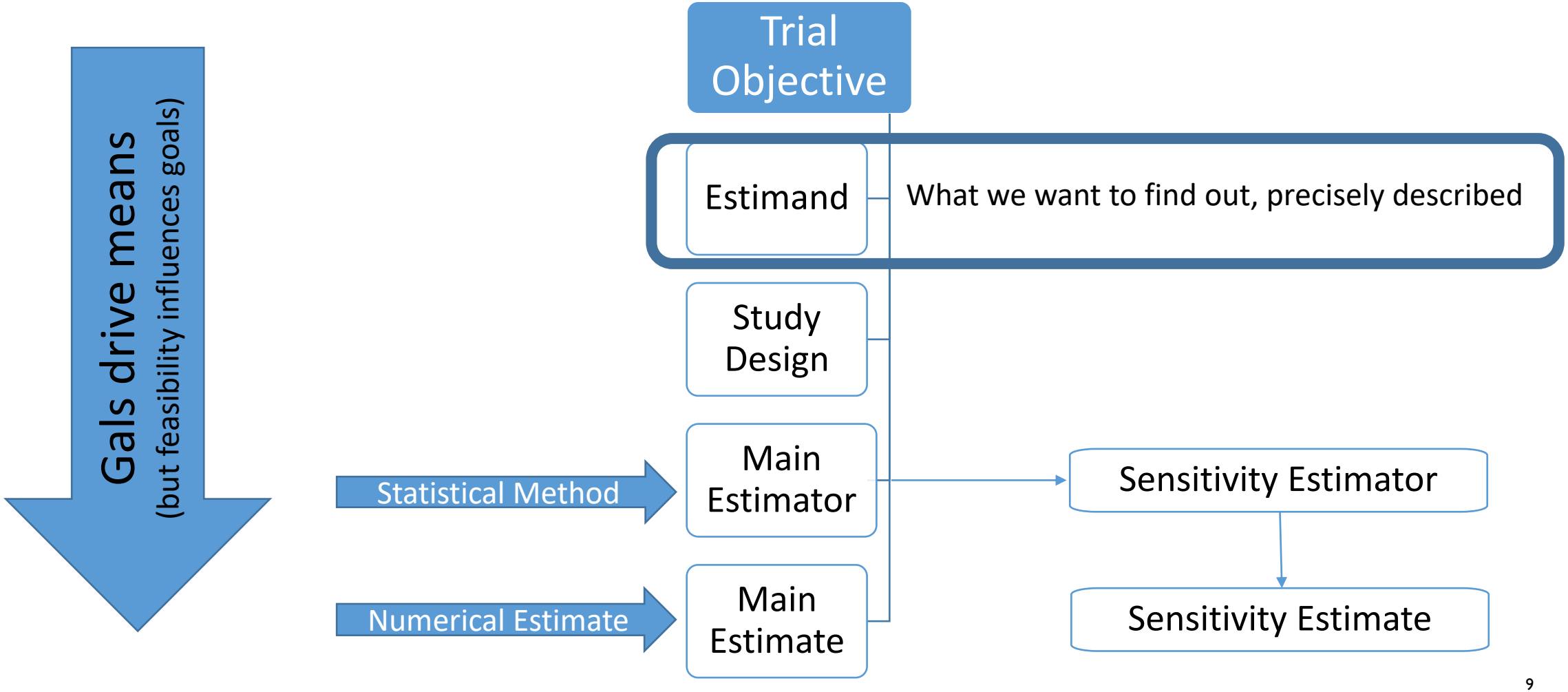
ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

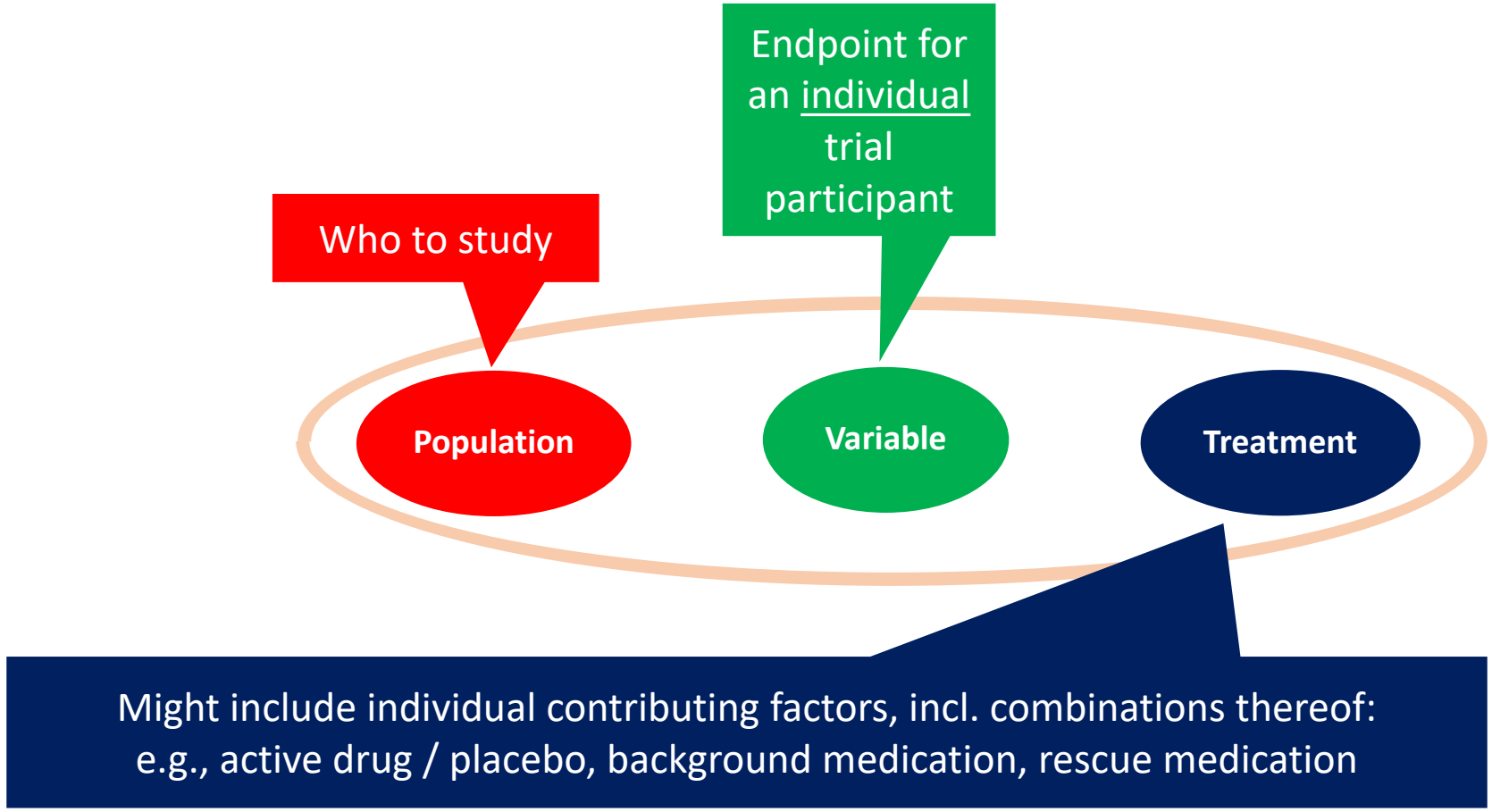
Final version

Adopted on 20 November 2019

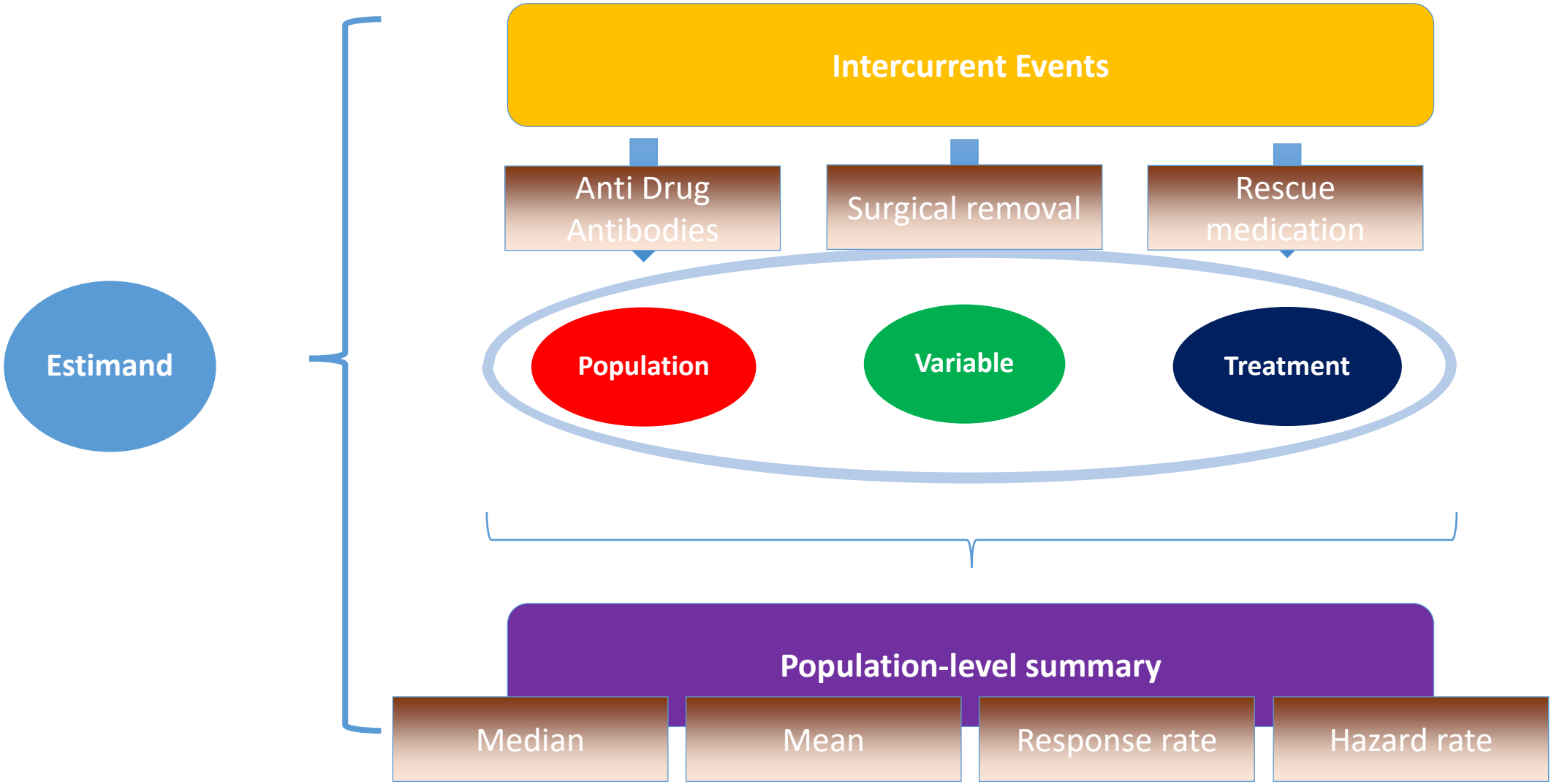
What is an estimand?



5 components of an Estimand



5 components of an Estimand



Intercurrent Events

- Addendum highlights the difficulty of assessing treatment effect in the presence of events occurring after treatment initiation that either prevent the observation of the variable or affect its interpretation (**intercurrent events**)
- Estimand framework allows **pre-specification** of (some) intercurrent events and handling of intercurrent events, resulting in pre-planned, thorough data collection and analytical methods or strategies to avoid/reduce intercurrent events, where possible
  - Predicting what intercurrent events are likely to occur and whether they are likely to be informative is critical

In an estimand framework, it is necessary to:

- Understand the actual reasons for intercurrent events
- Understand the impact these events might have on the interpretation of the actual data in light of the research question
- Pre-plan for them in close cooperation among study team members of different disciplines

Zoom Poll 3

1. What primary role is responsible for defining the estimand?
   - statistician
   - clinician
   - regulatory
   - the study team
2. Estimands should be discussed and developed
   - During protocol development
   - After the protocol has been finalized but prior to finalizing the statistical analysis plan
   - After finalizing the statistical analysis plan but prior to unblinding
3. Common intercurrent events for progression/relapse time-to-event endpoints include [multiple choice]
   - Death
   - Start of new anticancer therapy
   - Discontinuation from treatment
   - Withdrawal from study
   - Concomitant medication use

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- Closing remarks

Censoring and censoring mechanisms in oncology in light of the estimand framework

Lynda Grinsted, Feng Liu, Hans-Jochen Weber, **Stefan Englert**, Michelle Casey and **Jonathan Siegel**

On behalf of the Censoring Subteam of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

In preparation

Background

- In the past, analyses of time-to-event endpoints generally favored one or a mixture of two strategies regarding intercurrent events
  - Intention to treat approach – include all information through event or last assessment, regardless of intercurrent events
  - Simple censoring strategy – Censor prior to key intercurrent events, e.g. subsequent therapy (especially PFS)

From Guidance for Industry "Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics", U.S. Food and Drug Administration. April 2015:

APPENDIX C: EXAMPLE TABLES FOR PRIMARY PFS ANALYSIS

Examples of prespecified censoring scheme that can be used are provided in the following tables.

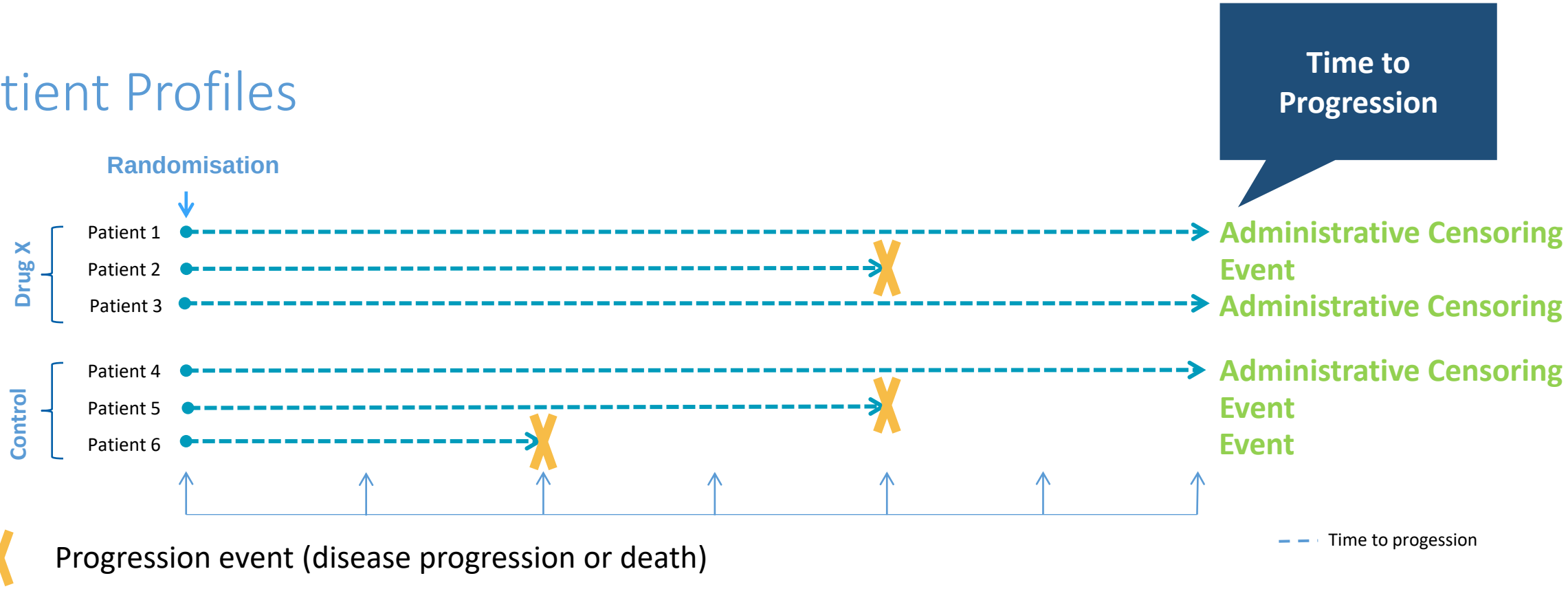
Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored

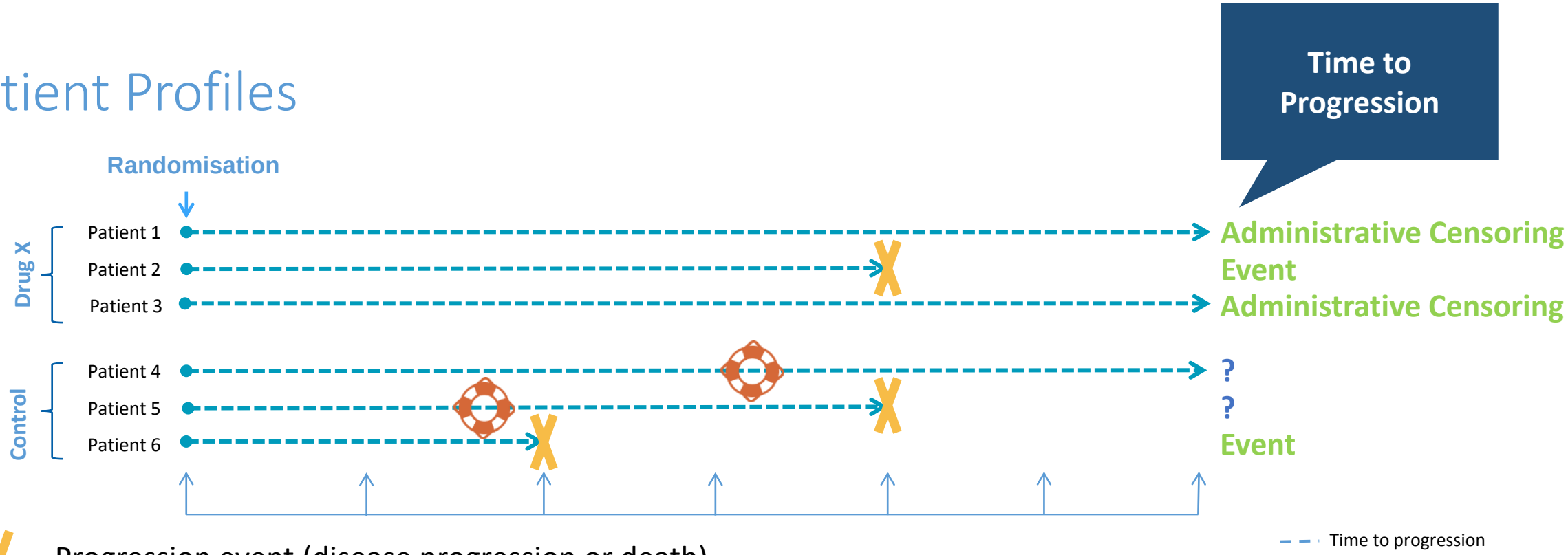
Consequences and Alternatives

- These approaches encouraged **standardized approaches** to censoring
- Alternative strategies had not previously seen much discussion.
- Intercurrent events were typically **addressed simply by censoring**, without much attention to the underlying mechanisms or whether non-informativity and other assumptions critical to censoring were scientifically appropriate.
- In an estimand framework, it is necessary to **phrase the actual reasons** for intercurrent events, understanding the impact these events might have on the interpretation of the data in light of the research question to be answered and pre-plan for them in close cooperation among study team members of different disciplines.
- The estimand framework highlights the **need for a critical discussion** on intercurrent events among key stakeholders during the design phase, resulting in both a more critical view of past strategies and potential for consideration of alternative strategies.

Patient Profiles



Patient Profiles



Progression event (disease progression or death)

Take subsequent therapy

- The treatment effect might be influenced by subsequent therapy
- In this case, subsequent therapy would be an ‘Intercurrent Event’
- Events for one endpoint can be intercurrent events for another: Radiological progression could be an intercurrent event for e.g. time to forced lung capacity deterioration.

Potential Classification of intercurrent events and strategies

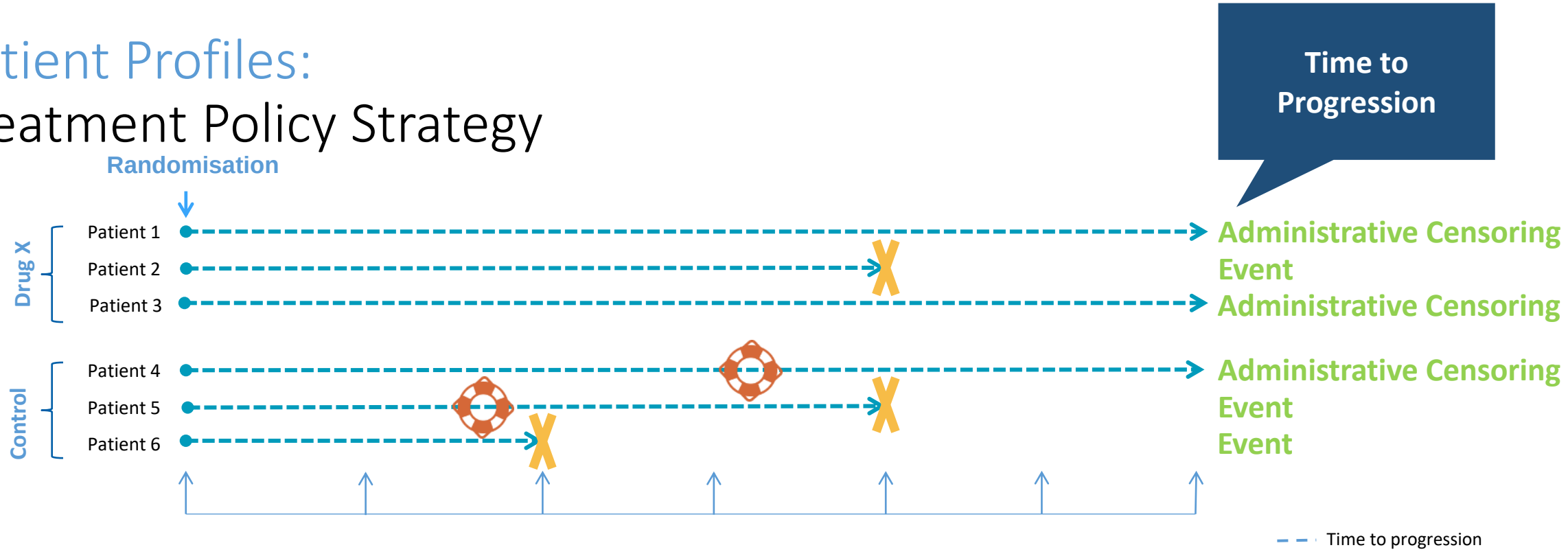
Irrespective of intercurrent event

- Decide that events do not introduce bias or alter the estimand.
- Outcome after event is still of interest
- Follow-up past event to outcome is meaningful/ feasible
- Administrative censoring assumes this.

Primary Strategy:

- Treatment Policy

Patient Profiles:
Treatment Policy Strategy



Treatment + Subsequent therapy

- The treatment effect for Drug X together with subsequent therapy (taken as required) is of interest.
- In this case, subsequent therapy would be reflected in the 'Treatment' attribute of the Estimand.
- The new approach is unbiased for the new question. But the randomized treatments are no longer compared in isolation from subsequent therapies.

Potential Classification of intercurrent events and strategies

Irrespective of intercurrent event

- Decide that events do not introduce bias or alter the estimand.
- Outcome after event is still of interest
- Follow-up past event to outcome is meaningful/ feasible
- Administrative censoring assumes this.

Primary Strategy:

- Treatment Policy

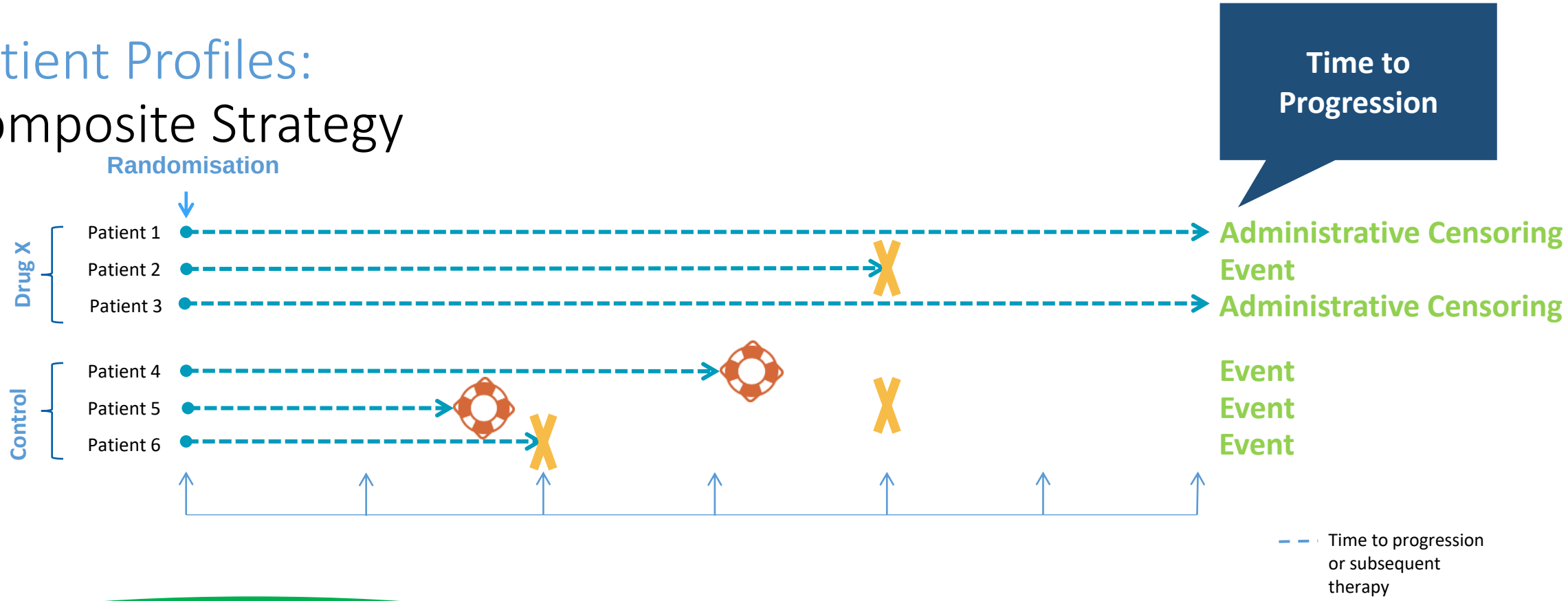
Positively informative
provide qualitative information about the event of interest

- Scientific question is what actually happened, including the intercurrent event
- Intercurrent event is informative for effect of interest
- May be appropriate when follow-up beyond intercurrent event infeasible
- Goal of methodological improvement is to better incorporate the intercurrent event into the analysis

Primary Strategy:

- Composite

Patient Profiles:
Composite Strategy



Variable + Subsequent therapy

- If subsequent therapy intake is considered an **undesirable outcome,** subsequent therapy **could become part of the endpoint** of the trial.
- In progression free survival we use a composite strategy for death

Potential Classification of intercurrent events and strategies

Irrespective of intercurrent event

- Decide that events do not introduce bias or alter the estimand.
- Outcome after event is still of interest
- Follow-up past event to outcome is meaningful/ feasible
- Administrative censoring assumes this.

Primary Strategy:

- Treatment Policy

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provide qualitative information about the event of interest

- Scientific question is what actually happened, including the intercurrent event
- Intercurrent event is informative for effect of interest
- May be appropriate when follow-up beyond intercurrent event infeasible
- Goal of methodological improvement is to better incorporate the intercurrent event into the analysis

Primary Strategy:

- Composite

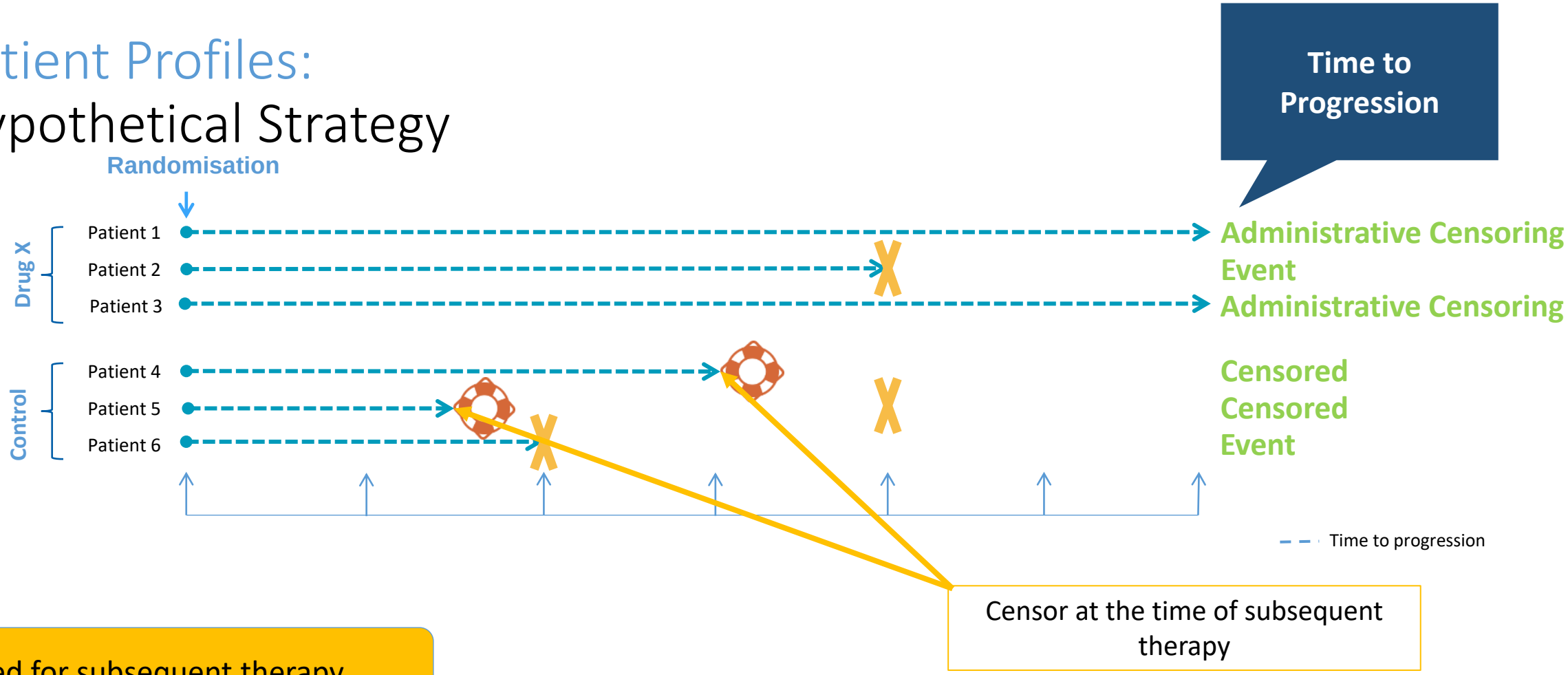
Counterfactual
confound the event of interest

- Scientific question is what would have happened if intercurrent event had not occurred.
- Intercurrent events rendered uninformative conditioned on an assumption or model
- May be appropriate when follow-up beyond intercurrent event infeasible

Primary Strategies:

- Hypothetical
- Principal Stratum

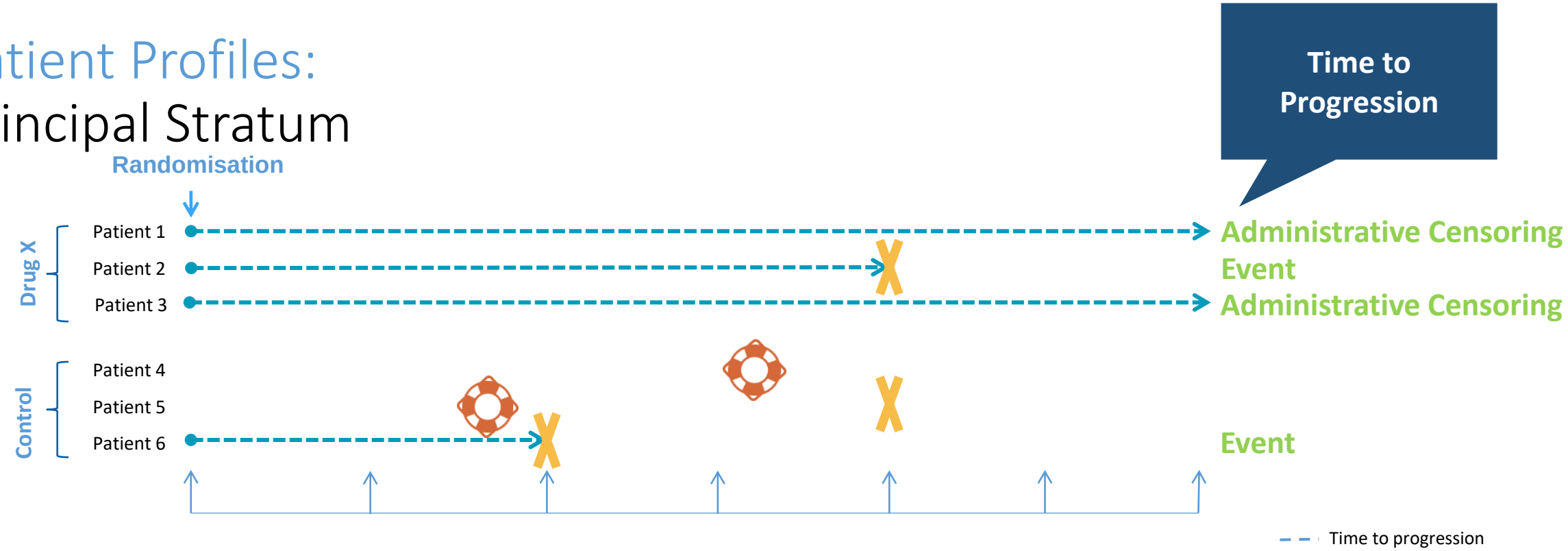
Patient Profiles:
Hypothetical Strategy



Adjusted for subsequent therapy

- The treatment effect for Drug X **adjusted for subsequent therapy**, is of interest.
- Subsequent therapy would be reflected in the '**remaining intercurrent events**' attribute of the Estimand.

Patient Profiles:
Principal Stratum



Population, without subsequent therapy

- Subsequent therapy would be altering the '**population**' attribute of the Estimand.
- Different from subgroup analysis, which is normally based off baseline characteristics

Potential Classification of intercurrent events and strategies

Irrespective of intercurrent event

- Decide that events do not introduce bias or alter the estimand.
- Outcome after event is still of interest
- Follow-up past event to outcome is meaningful/ feasible
- Administrative censoring assumes this.

Primary Strategy:

- Treatment Policy

Positively informative
provide qualitative information about the event of interest

- Scientific question is what actually happened, including the intercurrent event
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Primary Strategy:

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Counterfactual
confound the event of interest

- Scientific question is what would have happened if intercurrent event had not occurred.
- Intercurrent events rendered uninformative conditioned on an assumption or model
- May be appropriate when follow-up beyond intercurrent event infeasible

Primary Strategies:

- Hypothetical
- Principal Stratum

Irrelevant after intercurrent event

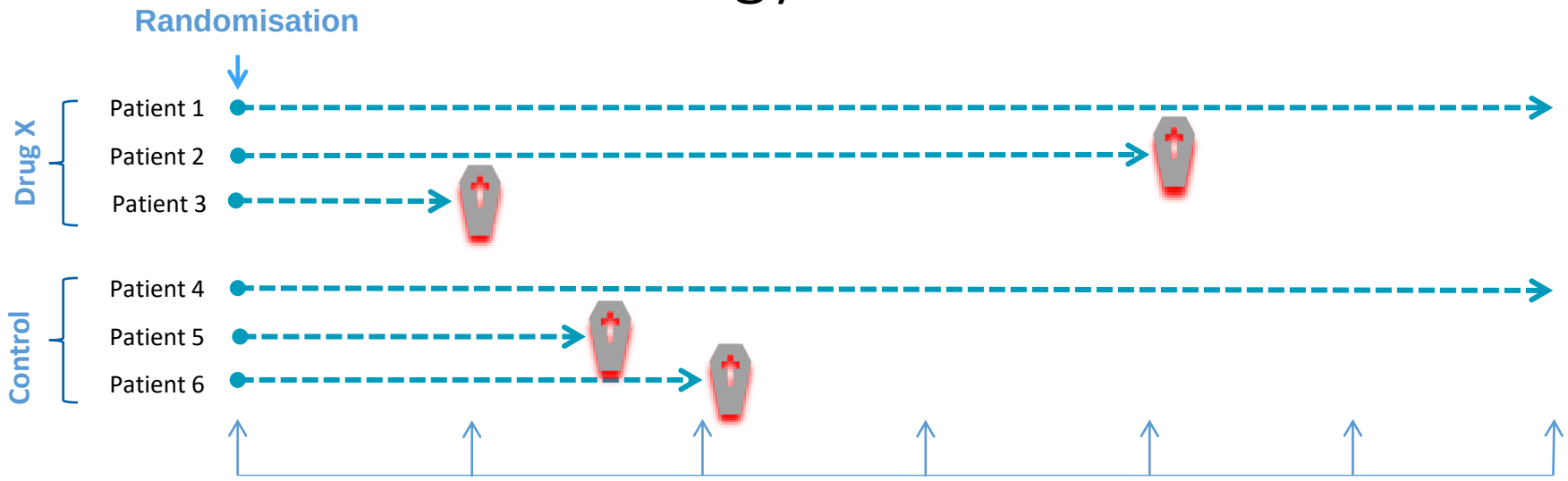
- Scientific question is about what happened prior to the intercurrent event
- Outcome after intercurrent event is considered irrelevant.

Primary Strategy

- While on Treatment

Patient Profiles:
While on Treatment Strategy

Symptom relief (Palliative Setting)



Variable prior to death

- The “while on treatment strategy” poses a research question that is only interested in the treatment effect until the intercurrent event occurs.
- A classic example is a purely palliative treatment.
- Death is not a negative outcome (not an event), but takes the patient out of the risk set. More appropriately modeled as a competing risk event than a censoring event.

5 Strategies – 5 Answers?

- There is no universal ‘correct’ strategy
- The Estimand Framework helps to make implicit assumptions transparent and helps to align at the design stage the team/sponsor/regulators on the clinical question of interest
  - Identify relevant intercurrent events
  - Align on suitable strategy for each of them
- In an estimand setting, censoring may be replaced by another implementation mechanism
  - Composite strategies will handle intercurrent events as a component of the event
  - While-on-treatment strategies may be handled with competing risk analysis
  - Hypothetical strategies may implement a causal inference model

The importance of integrating scientific question and operational feasibility

- In the estimands framework, the appropriate **strategy depends on understanding** the precise **scientific question** being addressed
- It also depends on understanding what is **operationally feasible** in the study context
- A treatment policy strategy assumes that following patients through and beyond the intercurrent event is meaningful and feasible
- When this is not feasible, it may sometimes be appropriate to consider an alternative strategy addressing a different, more feasible question.
- Addressing these issues requires **close cooperation** among statisticians, clinicians, and operational experts.

Rethinking Censoring and Censoring Mechanisms in Light of the Estimands Framework

- In light of the estimands framework traditional censoring tables have to be interpreted as one of several different strategies depending on endpoint definition and study design
  - If the patient can be followed past intercurrent events, the intent to treat approach can be interpreted as a treatment policy strategy – include all information through event until last assessment, regardless of intercurrent events
  - If the intercurrent event censors or stops assessment, the intent to treat approach can be interpreted as a hypothetical strategy, asking what would have happened if the intercurrent event had not occurred (for example, censoring for subsequent therapy can be interpreted as a hypothetical strategy)
  - If the intercurrent event is made an event, the approach is interpreted as a composite strategy (for example, PFS is a composite of progression and death)

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- Closing remarks

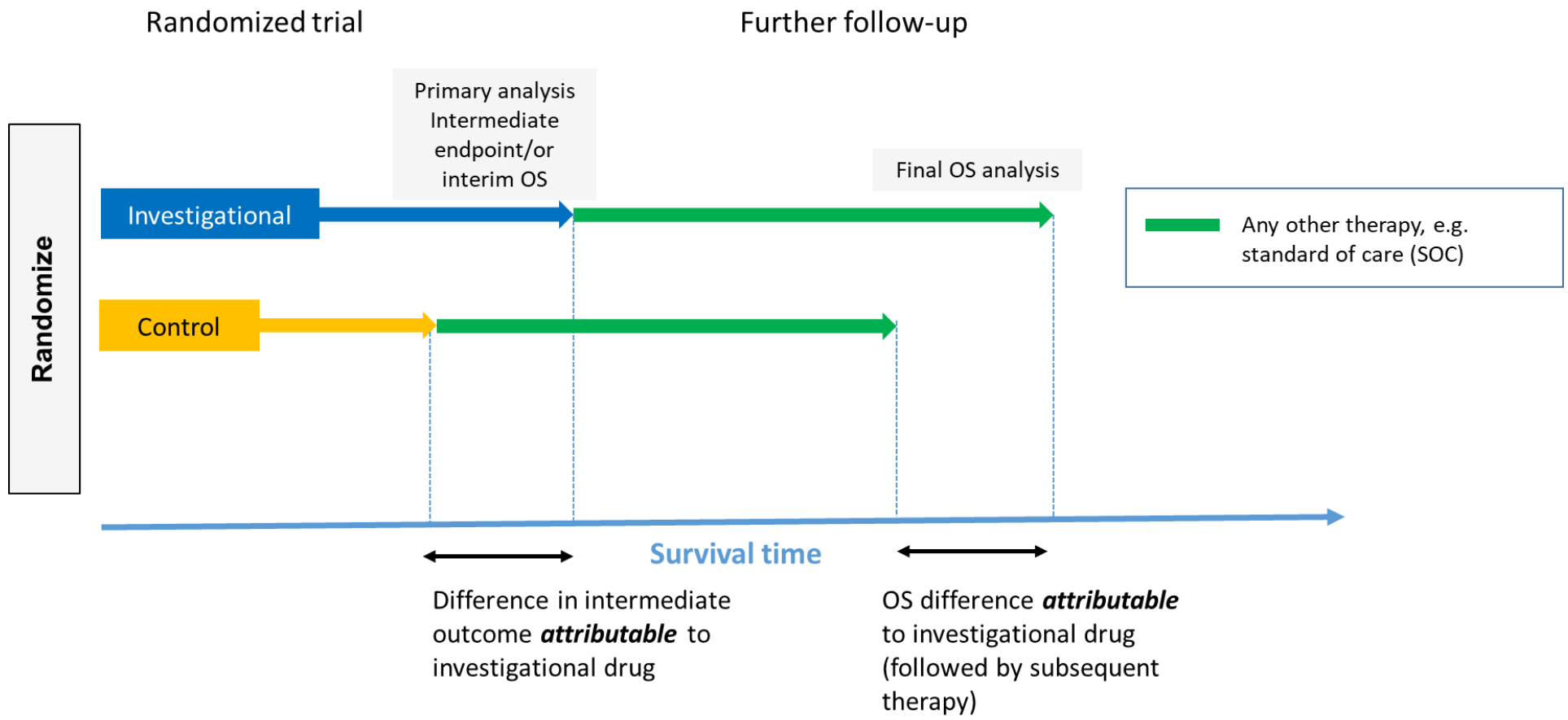
Estimands for Overall Survival in Clinical Trials with Treatment Switching in Oncology

Juliane Manitz, Natalia Kan-Dobrosky, Hannes Buchner, Marie-Laure Casadebaig, Evgeny Degtyarev, Jyotirmoy Dey, Vincent Haddad, Jie Fei, Emily Martin, Mindy Mo, Kaspar Rufibach, Yue Shentu, Viktoriya Stalbovskaya, Rui Tang, Godwin Yung, Jiangxiu Zhou

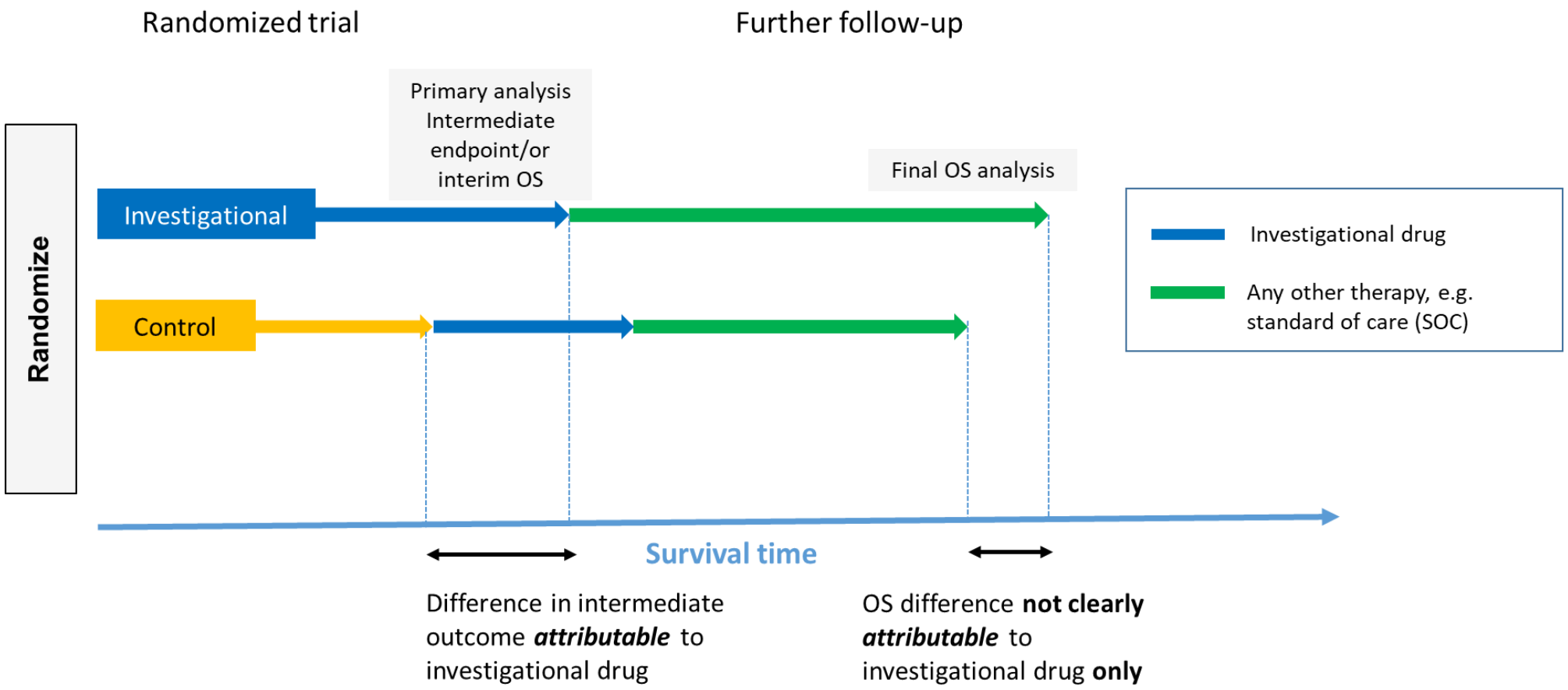
On behalf of the Treatment Switching subteam of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

Pharmaceutical Statistics, Under review

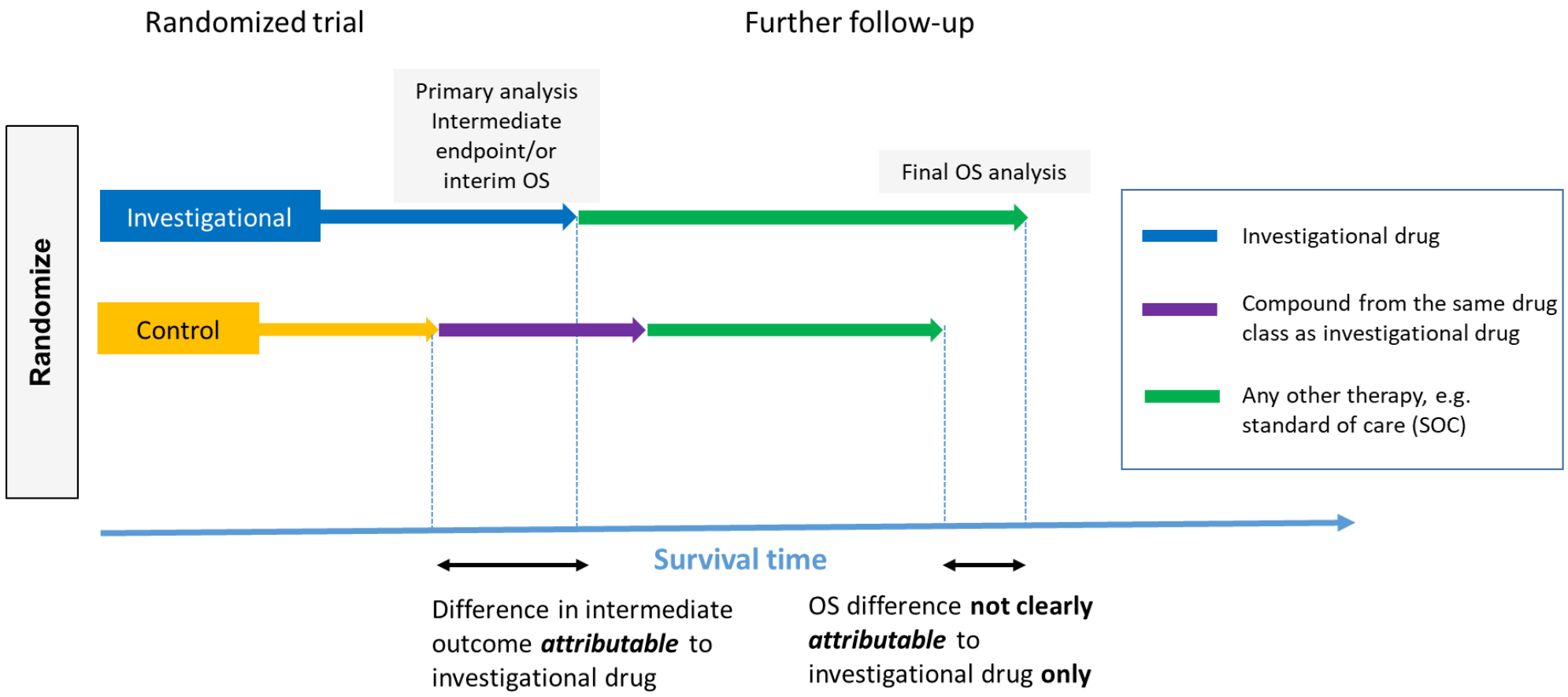
Randomized Clinical Trial in Oncology:
A Stylized Example



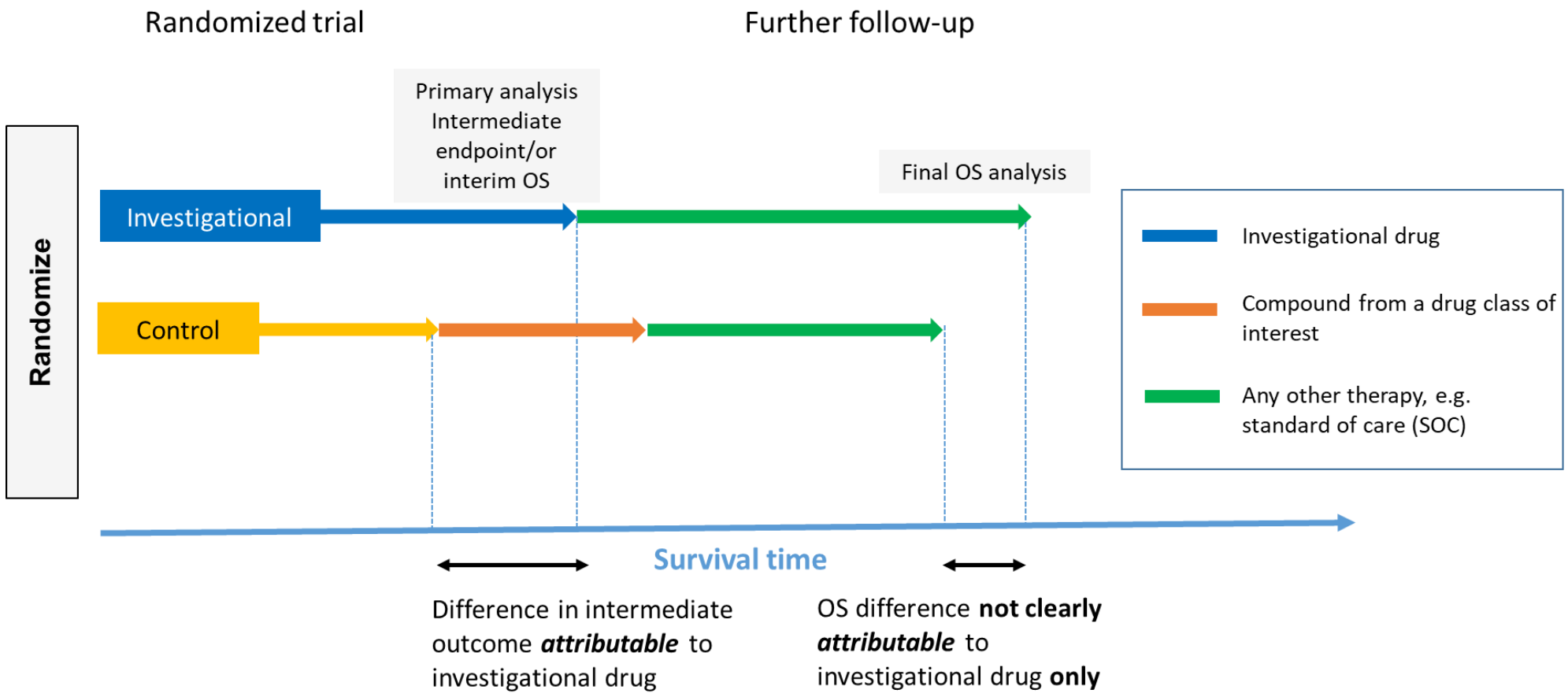
Treatment Switching Scenario 1:
Cross-over from Control to Investigational Arm



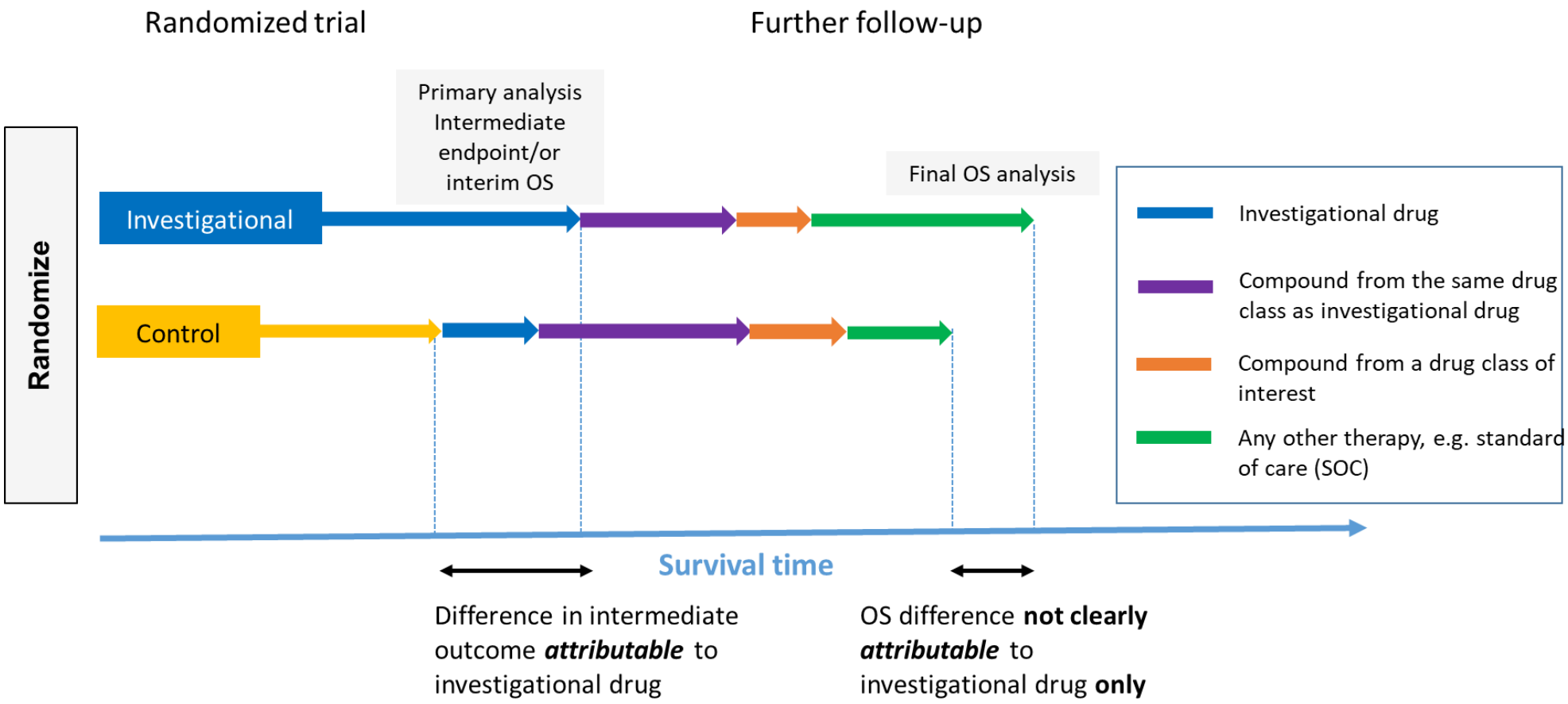
Treatment Switching Scenario 2:
From Control to Same Drug Class as of Investigational Arm



Treatment Switching Scenario 3:
From Control Arm to Drug Class of Interest



A More Realistic Example:
Mix of Treatment Switching Scenarios



What do we actually measure? What are the key questions?

- The traditional approach ignores treatment switching and rest on the following assumptions:
  - ✓Subsequent therapy reflect clinical practice (including investigational drug in later line) **in particular decision context**
  - ✓Patients receiving subsequent treatments (from same class as investigational drug and drug class of interest) and dose intensity as expected (as SOC) between investigational and control arm
- If these assumptions do not hold, we may consider to estimate the OS benefit that is attributable to the investigational drug
- The estimand framework provides a coherent framework to make the arising issues of treatment switching explicit and offers a systematic and transparent approach for assessment

Treatment Policy Strategy for Treatment Switching

- ***Objective:*** Evaluate OS benefit assuming subsequent therapies represent clinical practice
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Treatment policy
    - Crossover to investigational drug at any time: Treatment policy
    - Crossover to investigational drug at disease progression: Treatment policy
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Cox model and KM estimates using ITT approach

Hypothetical Strategy for Treatment Switching

- ***Objective:*** Evaluate OS benefit adjusted for treatment switching
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Investigational drug vs control (if there were no subsequent therapies)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Hypothetical
    - Crossover to investigational drug at any time: Hypothetical
    - Crossover to investigational drug at disease progression: Hypothetical
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Adjusted HR and CI from IPCW-weighted Cox model

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 progression	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 RPSFT model using adjusted survival times; IPCW methods could also be used	HR from two-stage method using reconstructed survival; IPCW and RPSFT methods could be used

Conclusions & Summary

- Treatment policy estimand may not be clinically relevant if subsequent therapy does not represent clinical practice
- The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
- Start to think about possible treatment switching scenarios during the planning phase of a trial
- Choose appropriate estimand according to pre-specified scientific question of interest
- Treatment switching methods which can be applied if the necessary data is collected; assumptions apply

Further reading: The corresponding manuscript is submitted: “Estimands for Overall Survival in Clinical Trials with Treatment Switching”

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  - Hematology by Steven Sun, Johnson & Johnson
  - COVID-19 by Stefan Englert, AbbVie Inc.
- Closing remarks

Estimand framework: Are we asking the right questions? A case study in the solid tumor setting

Michelle Casey, Evgeny Degtyarev, María José Lechuga, Paola Aimone, Alain Ravaud, Robert J. Motzer, **Feng Liu**, Viktoriya Stalbovskaya, Rui Tang, Emily Butler, Oliver Sailer, Susan Halabi, Daniel George

On behalf of the Solid Tumor subteam of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

Pharmaceutical Statistics, https://doi.org/10.1002/pst.2079

Background

- Prior to the framework, estimands were often the consequence of the statistical analysis
- The choice of estimand should drive the trial design, sample size, data collection, trial conduct, and analysis.
- Analyses from previously reported randomized phase 3 studies in adjuvant renal cell carcinoma are mapped to the estimand framework to illustrate how differences in endpoint definitions and censoring rules result in different scientific questions

Variety of endpoint definitions in adjuvant RCC

Clinical Trial	Imaging-Related Endpoints	Events Included in the Endpoint Definition as Published
S-TRAC (2016)[1] Sunitinib vs Placebo	DFS*	Recurrence, second primary cancer, death from any cause
ASSURE (2016)[2] Sunitinib vs Sorafenib vs Placebo	DFS*	Recurrence, second primary cancer, death from any cause
PROTECT (2017)[3] Pazopanib vs Placebo	DFS*	Local recurrence, metastasis, death from any cause
PROSPER (2017)[4] Nivolumab vs Placebo	RFS*	Disease recurrence or death from any cause
IMmotion-010 (2017)[5] Atezolizumab vs Placebo	DFS*	Local recurrence of RCC, new primary RCC, distant RCC metastasis, death from any cause
	DMFS	Distant metastasis, death from any cause
KEYNOTE-564 (2017)[6] Pembrolizumab vs Placebo	DFS*	Local recurrence, distant metastasis, secondary systemic malignancy, death from any cause
	Local disease recurrence–specific survival	Local recurrence
	Local recurrence, distant metastasis, or secondary systemic malignacy with visceral lesions	Local recurrence, distant metastasis, secondary malignancy with visceral lesion presence

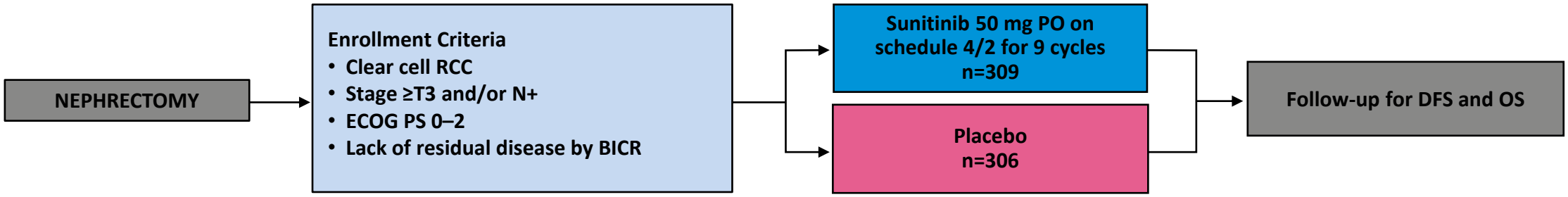
1. Ravaud, A. et al. N Engl J Med. 2016;375(23):2246-54. **2.** Haas, NB. et al. Lancet. 2016;387(10032):2008-16. **3.** Motzer, RJ. et al. J Clin Oncol. 2017;35(35):3916-23.
4. https://clinicaltrials.gov/ct2/show/NCT03055013; accessed May 3, 2019. **5.** https://clinicaltrials.gov/ct2/show/NCT03024996; accessed May 3, 2019.
6. https://clinicaltrials.gov/ct2/show/NCT03142334; accessed May 3, 2019.
*=primary endpoint
DFS=disease-free survival; DMFS=distant metastasis–free survival; RCC=renal cell carcinoma; RFS=recurrence-free survival

Adjuvant RCC

- **Overarching scientific question**:
  "Does the new treatment prolong patients' DFS time?"
  - Or "Does the drug improve DFS if no patient had received new therapy" vs "Does the drug improve DFS and delay the start of new therapy"
- **Fundamental issue**: lack of harmonization on the definition for time-to-event endpoints, as has been discussed in the DATECAN initiative.
  - "disease recurrence" could be local recurrence, metastatic recurrence, contralateral kidney cancer, second primary cancer, deaths due to RCC, and/or deaths due to causes other than RCC.
- **Estimand framework**: facilitate the discussions about various patients' journeys and help to refine the question of interest

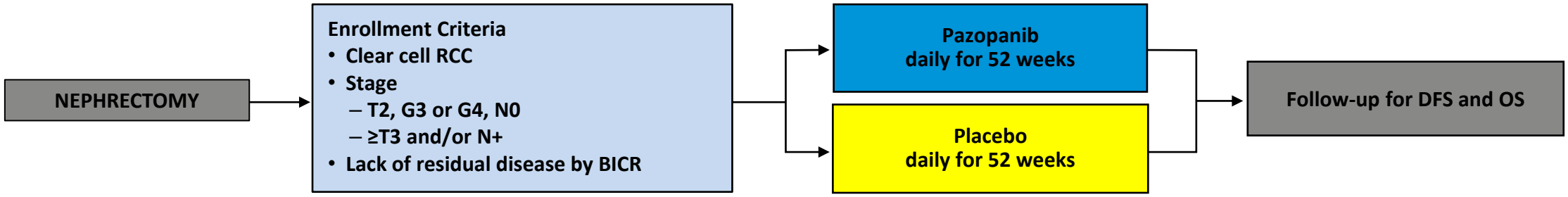
Study designs: S-TRAC and PROTECT

S-TRAC (NCT00375674)



- **Primary endpoint: disease-free survival**

PROTECT (NCT01235962)



BICR=blinded independent central review; DFS=disease-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PO=by mouth; RCC=renal cell carcinoma

Key Differences Across Trials

	S-TRAC	PROTECT
Population	≥T3 and/or N+	**T2, G3 or G4, N0**; ≥T3 and/or N+
DFS	**Recurrence, second primary cancer**, death from any cause	**Local recurrence, metastasis**, death from any cause
Handling of intercurrent events	*Composite*: deaths and **second primary malignancy** *Hypothetical*: subsequent therapy had not been administered	*Composite*: deaths *Treatment policy*: **second primary malignancy** *Hypothetical:* subsequent therapy had not been administered
Equivocal findings	**Latest date used**	Earliest date used
Schedule	Tumor imaging at baseline, every 12 weeks during the first 3 years, then every 6 months thereafter until the time of the final analysis	Tumor imaging at baseline, weeks 20, 36, and 52 during year 1, every 6 months during years 2–5, and yearly thereafter

Conclusions

- In the past little attention was given to the fact that different definitions and censoring rules (e.g. censoring vs. not for subsequent anticancer therapy) address different clinical questions.
- If the handling of intercurrent events is not explicitly stated, it can lead to the need for additional work, differences in the interpretation of results, and/or the lack of ability to perform requested analyses if data are not appropriately captured.
- The estimand framework seeks to increase transparency on the treatment effect of interest
- Despite the new estimand framework, differences across trials will remain (e.g some additional differences among the trials, eg, investigator vs BICR assessments, time of assessments, and time of events for equivocal new lesions), highlighting the need to provide sensitivity analyses to assess the robustness of the primary estimand.

Today's agenda

- Estimand framework: general introduction to the framework
- **Illustrate the impact of the addendum by applying it to a series of oncology case studies:**
  - Censoring mechanisms by Stefan Englert, AbbVie Inc. and Jonathan Siegel, Bayer
  - Treatment switching by Juliane Manitz, EMD Serono Inc./Merck KGaA
  - Solid tumors by Feng Liu, AstraZeneca
  - **Hematology** by Steven Sun, Johnson & Johnson
  - COVID-19 by Stefan Englert, AbbVie Inc.
- Closing remarks

Estimands in hematologic oncology trials

Steven Sun, Jochen Weber, Emily Butler, Kaspar Rufibach, Satrajit Roychoudhury

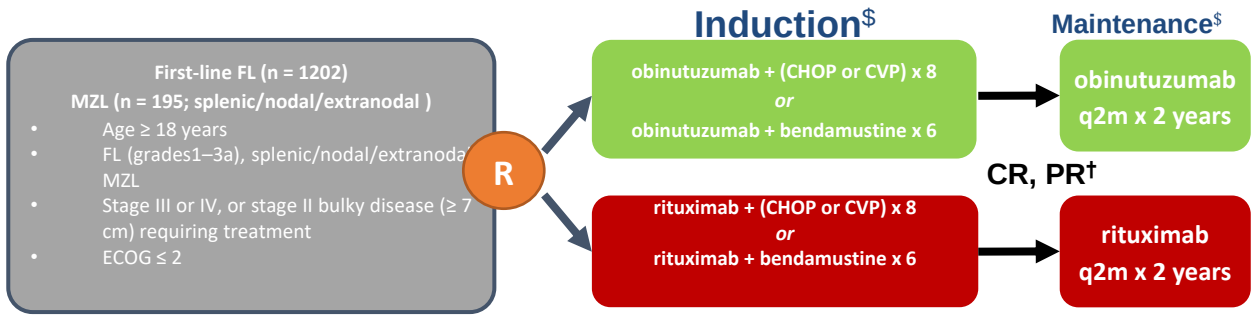
On behalf of the Hematologic subteam of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

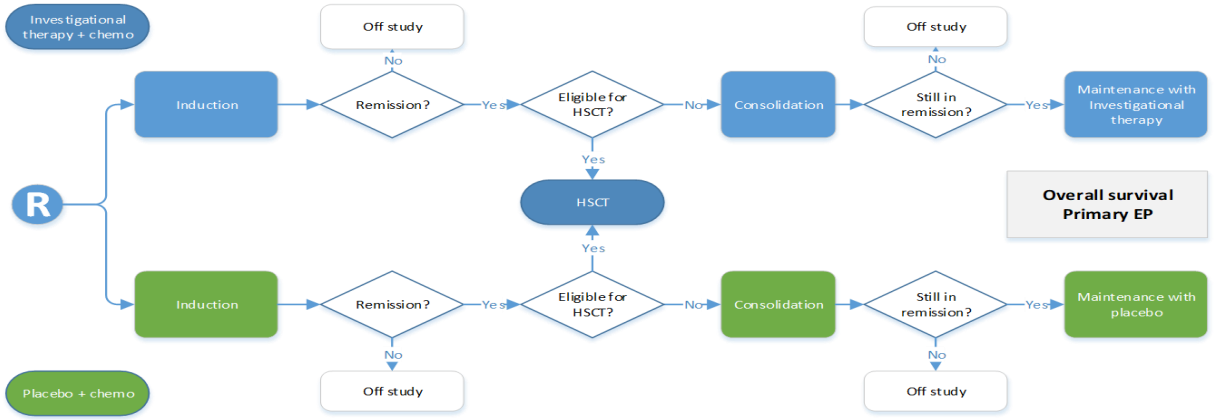
Pharmaceutical Statistics, http://doi.org/10.1002/pst.2108

Scope of the paper

Clinical trials in patients with hematological malignancies often present unique challenges for trial design due to complexity of treatment options and existence of potential curative but highly risky procedures, e.g. stem cell transplant or treatment sequence across different phases (induction, consolidation, maintenance).

Based on 3 case studies, we illustrate how to apply the estimand framework in hematological clinical trials and how the estimand framework can address potential difficulties in trial result interpretation.





- Application of estimand framework to three case studies
  - Scientific question
  - Study primary objective
  - Attributes of primary estimand
  - Analyses for PFS and OS
    - Main analysis
    - Sensitivity analyses
    - Supplementary analyses
- Impact on trial design, data collection, and data analysis

Protocol defined objective pre-addendum
GALLIUM study

The primary objective for this study is as follows:

To evaluate the efficacy of Obinutuzumab (GA101, RO5072759) plus chemotherapy followed by Obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma, as measured by investigator-assessed progression-free survival (PFS)

- Objective: How do we measure the effect?
- Definition of PFS:
  - Starting new anti-lymphoma therapy (NALT) prior to progression?
  - Withdrawal from trial treatment prior to progression?

Estimand components post-addendum
GALLIUM study

Treatments:

Experimental: *6 or 8 21-28 day cycles obinutuzumab D1 + C1D8, C1D15: 1000mg flat dose + 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*

Control: *6 or 8 21-28 day cycles 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*

Population: *Patients with previously untreated 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*

Common analyses performed for endpoint PFS (GALLIUM study)

Analysis method	Objective and key assumptions	Sensitivity or supplementary	Rationale	Recommendation
Stratified cox regression using PFS by independent review committee (IRC-PFS)	Impact of potential reader-evaluation bias in the treatment effect estimate. IRC-PFS is perceived as less biased compared with INV-PFS since this is an open-label study. As in the main analysis, patients are assumed to be consistently followed with disease assessment beyond subsequent therapy	Sensitivity analysis	Analysis corresponds to the same primary estimand as stated in the Table 2. It is considered as data limitation for disease assessment	Same disease assessment criteria should be used for both investigators' assessment and IRC assessment. IRC assessment may introduce bias due to informative censoring. The bias due to informative censoring may be worse than the potential bias by investigators' assessment
Unstratified Cox regression	Impact of heterogeneity in placebo effect for meaningful strata on treatment effect estimate. The assumption refers to common baseline risk among different strata	Sensitivity analysis	Same estimand as in Table 2. The main analysis assumes different baseline risk across different strata. This analysis checks the heterogeneity assumed in the main analysis and explores how robust the overall findings are	Useful analysis for checking robustness of the main analysis
Censoring at subsequent therapy	Subsequent therapy impacts the interpretation of treatment effect	Supplementary analysis	Different strategy for intercurrent event and hence it corresponds to different estimand. It is a hypothetical strategy and estimation via simple censoring assumes non-informative censoring at subsequent therapy use	Useful analyses to understand the treatment effect from different perspectives. In the past, the FDA could accept this as the main analysis while the EMA often preferred treatment policy strategy for the intercurrent event of subsequent therapy
Covariate-adjusted analysis (multi-variate Cox regression analysis)[22]	Impact of important baseline covariates on treatment effect. Covariates adjustment reduce variability of the effect estimate	Supplementary analysis	The analysis addresses a different scientific question. i.e., what is the treatment benefit of Obinutuzumab in terms of PFS for patients who have covariates valued at population means. Covariate adjusted multivariate Cox regression provides a conditional treatment effect rather than marginal treatment effect.	Interpretation should be careful, and results may not be consistent since it does not address the same estimand

Conclusions

- The estimand framework facilitate communications between stakeholder (e.g., HAs) and sponsor. It emphasizes articulation of scientific questions
- Proportional hazard assumption for PFS analysis may not hold for hematology studies with multiple treatment phases which are potentially curative. Different population level summary other than commonly used HR is needed
- In typical hematology studies a complicated treatment sequence is applied. The underlying estimand addresses the treatment effect of the whole sequence. There are limitations to quantify the contribution of an individual treatment phase in such studies.

- Emphasis of this paper is placed on the recommendation of description of estimands and careful selection of sensitivity analyses and supplementary analyses for hematological trials. Data collection and analysis should also be aligned in coherent manner to avoid disconnect between trial objectives and estimands
- The paper also proposed estimand template language for both SAPs and study protocols

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  - Hematology by Steven Sun, Johnson & Johnson
  - **COVID-19** by Stefan Englert, AbbVie Inc.
- Closing remarks

Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework

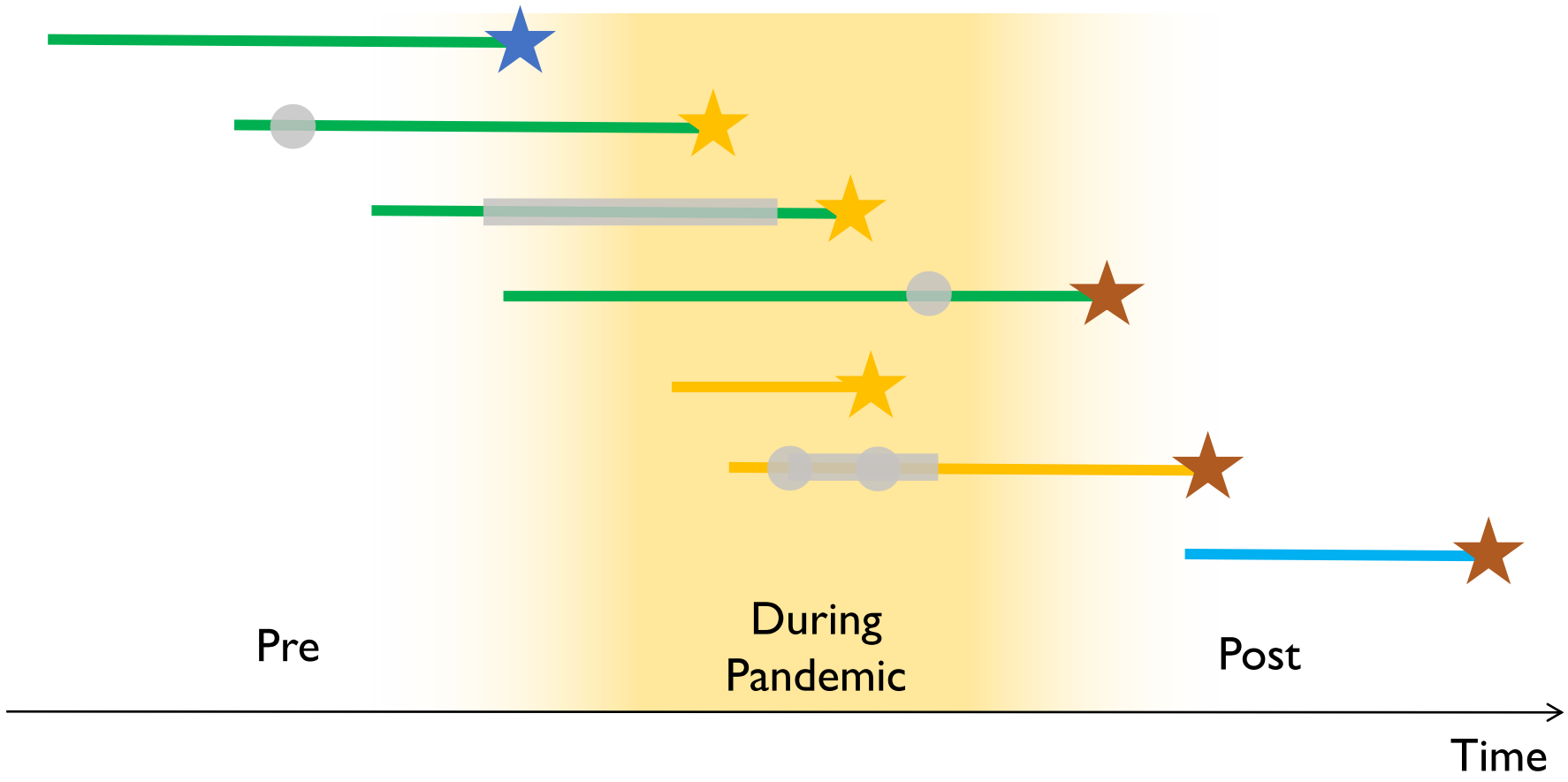
Evgeny Degtyarev, Kaspar Rufibach, Yue Shentu, Godwin Yung, Michelle Casey, **Stefan Englert**, Feng Liu, Yi Liu, Oliver Sailer, Jonathan Siegel, Steven Sun, Rui Tang, Jiangxiu Zhou

On behalf of the COVID-19 task force of the **European special interest group "Estimands in oncology"** (www.oncoestimand.org)

Statistics in Biopharmaceutical Research, https://doi.org/10.1080/19466315.2020.1785543

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

Background

COVID-19 is having a detrimental impact on patients with underlying disease and ongoing clinical trials.

- Direct impacts
  - Infections
  - Deaths
- Indirect impacts
  - Increased demands on the health service
  - Travel restrictions
  - Measures of social distancing

… leading to clinical site closures, treatment interruptions/discontinuations, delayed/missed trial visits

Problem Statement

Following EMA and FDA's call to minimize risks to trial integrity, we have been asking and seeking answers to TWO questions:

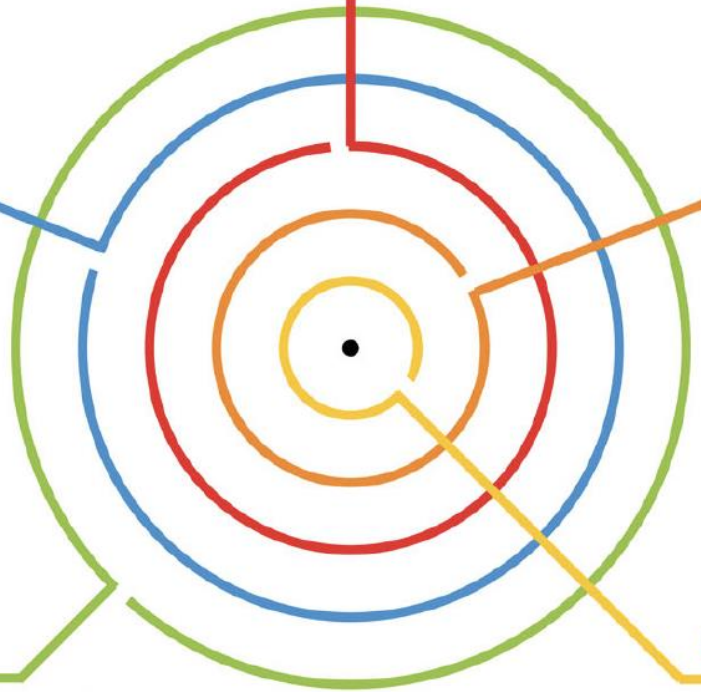
1. What risks does COVID-19 pose to interpretability of trial results?
2. What measures can stakeholders take to curb those risks?

We argue that the objective of ongoing oncology trials should relate to a world without ongoing COVID-19 pandemic. This is guided by two assumptions:
(A) this objective is consistent with pre-pandemic trial objectives,
(B) this pandemic will eventually end.

Methods

The estimand framework facilitates a precise definition of the target of estimation, which is useful for structuring discussions about the impact of COVID-19 and mitigative measures one can take (clarifying the estimand, modifying the estimator, introducing a new estimand, etc.).

Methods



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?

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

Addressing intercurrent events – general framework

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- 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

Pandemic-related:

- ICEs with the primary reason related to the pandemic

Addressing intercurrent events – general framework

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Pandemic-related:

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

Addressing intercurrent events – general framework

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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.

Examples of estimand and analysis strategies for study treatment discontinuations

ICE: Discontinuation of study treatment due to ….		COPD study	
… site operation disruptions	Estimand strategy:	Hypothetical "if participant did not discontinue study drug at that time"	
	Analysis strategy:	Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.	
… participant's perception of increased risk versus benefit from the study	Estimand strategy:	Hypothetical "if participant did not discontinue study drug at that time"	
	Analysis strategy:	Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.	Predict outcome under the assumption of lower-than-average treatment effect in similar participants who did not discontinue.
… severe complications of COVID-19 infection and start of COVID-19 therapy	Estimand strategy:	Composite strategy as an unfavorable outcome	
	Analysis strategy:	Count as endpoint event or designate an unfavorable endpoint value	

Results

- We used the estimand framework to identify several sources of potential bias.
  1. Change in enrolled patients during/after pandemic (Population): important to assess but periods difficult to define.
  2. Treatment discontinuation or interruptions (ICEs): may require non-conventional strategies depending on the nature of the ICE, e.g. hypothetical strategy or principal stratification to address ICEs resulting from COVID-19 infection or disruption of public healthcare system
  3. And more …
- Dependent on the stage of the trial and impact of COVID-19, the initially planned analysis may still provide a sufficiently precise answer.
  - Supplementary/secondary analyses could be described in an amendment
- Trial-specific discussions between sponsors and regulators are important before implementing any change to the study estimand.

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Estimands have been used in all COVID-19 Vaccine Trials

Moderna

A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19

AstraZeneca

Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults

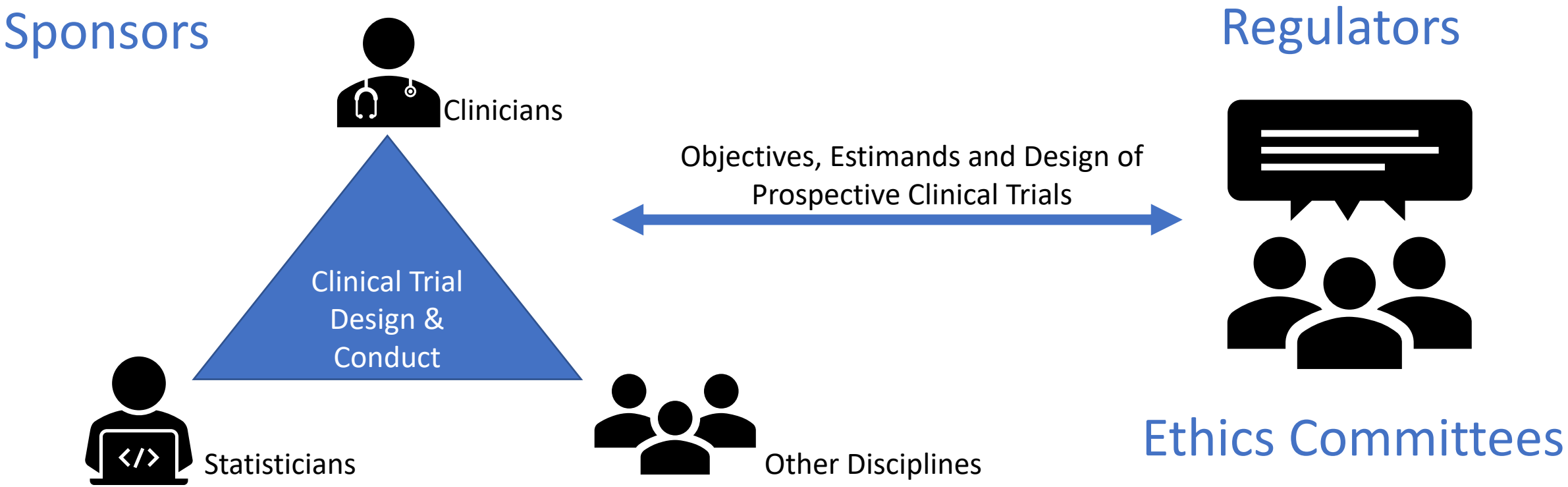
Pfizer/BioNTech

Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Each have defined in the study protocol:
Estimands and relevant intercurrent events

Your Role: Construction of Estimand

It is a multi-disciplinary undertaking and should be the subject of discussion between sponsors and regulators



Questions?

Slides will soon be available on: www.oncoestimand.org