

Industry Working Group on Estimands in Oncology

ASA SWG and EFSP/PSI SIG

September 2020

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Today's agenda

- Summaries of current papers
 - Estimand framework: Are we asking the right questions? A case study in the solid tumor setting (by solid tumor subteam)
 - Hematology subteam: Estimands in Hematology trials (by hematology subteam)
 - What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? (collaboration with Adelphi Values)
 - Principal Stratum Strategy: Potential Role in Drug Development (by causal subteam)
 - Estimands for Overall Survival in Trials with Treatment Switching (by treatment switching subteam)
 - The importance of censoring mechanisms in selecting appropriate estimands (by censoring subteam)
 - Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework (by COVID-19 taskforce)
- Future taskforces

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

submitted

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

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

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

Adjuvant RCC

- **Overarching scientific question:** “Does the new treatment prolong patients’ DFS time?”
- **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

Key Differences Across Trials

	S-TRAC	PROTECT	ATLAS
Population	≥T3 and/or N+	T2, G3 or G4, N0; ≥T3 and/or N+	T2, any grade, N0; ≥T3 and/or N+
DFS	Recurrence, second primary cancer , death from any cause	Local recurrence, metastasis , death from any cause	Recurrence, second primary cancer , death from any cause
Handling of intercurrent events	<i>Composite</i> : deaths and second primary malignancy <i>Hypothetical</i> : subsequent therapy had not been administered	<i>Composite</i> : deaths <i>Treatment policy</i> : second primary malignancy <i>Hypothetical</i> : subsequent therapy had not been administered	<i>Composite</i> : deaths and second primary malignancy <i>Hypothetical</i> : subsequent therapy had not been administered
Equivocal findings	Latest date used	Earliest 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	Tumor imaging at baseline, every 16 weeks during first 3 years, every 6 months 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.

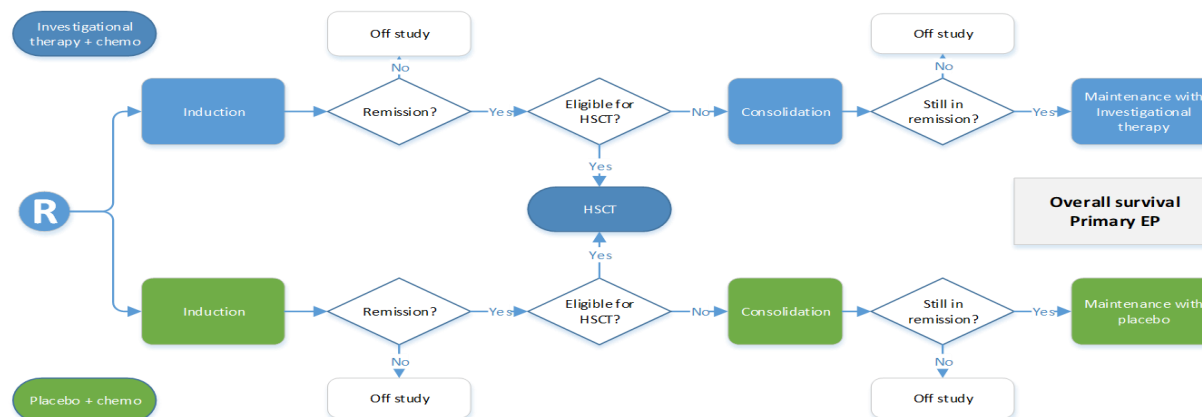
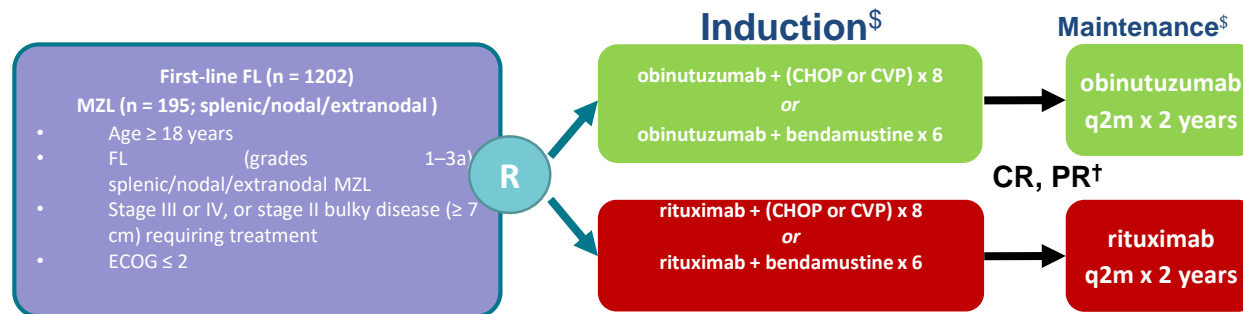
Estimands in Hematology trials

submitted

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

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

Conclusion

- 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

What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials?

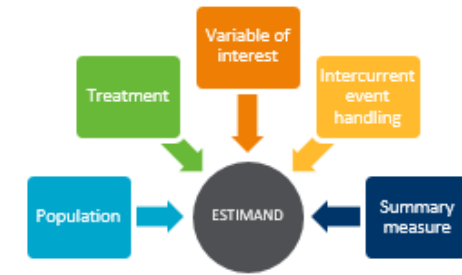
Journal of Patient-Reported Outcomes
<https://doi.org/10.1186/s41687-020-00218-5>

Rachael Lawrance, Evgeny Degtyarev, Philip Griffiths, Peter Trask, Helen Lau, Denise D'Alessio, Ingolf Griebisch, Gudrun Wallenstein, Kim Cocks, Kaspar Rufibach

PROs: Problem statement

- Patient Reported Outcomes (PROs) are frequently included as secondary objectives in oncology clinical trials
- Historically these objectives have often not been very specific e.g. “assess health related quality of life during the study”
- The estimand framework provides an ideal opportunity to engage with PRO researches in the development of much clearer objectives and appropriate estimands in clinical trials
- Patient focused outcomes must be considered early in development of study protocols to ensure that relevant data is collected to meet the future needs of regulators, health technology authorities & to communicate to patients

PROs – building an example estimand



- Taking a simple objective:

“What is the effect of treatment X on patient’s quality of life?”

- Considering timeframes of treatment, subsequent treatment options, intercurrent events (such as treatment discontinuation, death) then
- Refining to be an example detailed estimand statement:

“In advanced breast cancer patients, what is the difference in mean severity of pain score (as measured with the EORTC QLQ-C30) between treatment X followed by subsequent antineoplastic therapy and concomitant pain medication (as needed) compared with treatment Y followed by subsequent antineoplastic therapy and concomitant pain medication (as needed), after 6-months from randomisation or death (whichever occurs first), regardless of study treatment discontinuation?”

- Not one single approach – sensitivity approaches may also be needed.
- Early discussions on all aspects important - not just PRO instrument to be included

PROs: Conclusions

- More work to be done on this topic
- SISAQoL Recommendations published Jan 2020 in Lancet Oncology:
 - International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol 2020; 21: e83–96.
- Building on the SISAQoL recommendations and combining with estimand framework will benefit all
- Examples and application key, as well as more detailed consideration of appropriate analysis strategies for handling intercurrent events, particularly death

Principal Stratum Strategy: Potential Role in Drug Development

submitted

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Satrajit Roychoudhury, Heinz Schmidli, Yue Shentu, Marcel Wolbers

<https://arxiv.org/abs/2008.05406>

Principal Stratum Strategy: Potential Role in Drug Development

- One of the five intercurrent event (IE) strategies in ICH E9(R1)
- Target population: Trial *subpopulation (principal stratum)* in which IE would not (or would) occur
 - Subsetting on *potential outcomes* of IE on one or both treatment arms
- Want to make causal statement but cannot rely on randomization
 - Typically requires strong assumptions for estimation (similar as in observational studies)
- Subpopulation (principal stratum) membership not known at baseline and often also not known at end of study

Principal Stratum Strategy: Potential Role in Drug Development: Examples

- Many examples of practical relevance in drug development
 - Treatment effect in patients experiencing specific post-baseline event
 - Early response, relapse, anti drug antibody development, high or low drug exposure
 - Vaccine trials (effect on disease severity for patients that get infected)
 - see causal subteam paper for more details*
- Question often not related to primary objective of the trial
 - But important follow-up questions to characterize how the treatment effects vary across subgroups defined by post-baseline events
 - Might have implications on how the drug is used in practice and labelling

*<https://arxiv.org/abs/2008.05406>

Principal Stratum Strategy: Potential Role in Drug Development: Recommendations

- Principal stratum strategy has potential to lead to more clarity for these complex questions
 - more appropriate analyses (transparent & more plausible assumptions)
 - avoid seemingly „simple analyses“ with unclear interpretation & assumptions
- Assumptions
 - typically should be context specific & using scientific background information
 - scientific rationale for utilized assumptions can be strong
 - causal inference literature developed a number of different approaches
- Recommendation to perform sensitivity analyses
 - Directly modifying quantities affected by assumptions

Estimands for Overall Survival in Trials with Treatment Switching

submitted

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

Summary

- ITT estimand for OS is meaningful if subsequent therapy reflect clinical practice (including investigational drug in later line) **in particular decision context**
 - The reality of varying access to innovative treatment across study centers and countries presents additional challenges
- Questionable if ITT yields clinically meaningful comparison if subsequent therapies do not reflect clinical practice (e.g. patients from SOC arm crossover to investigational drug not approved as next-line therapy after SOC)
 - Hypothetical estimand appears to be more relevant in such situations
- The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
- There are treatment switching methods which can be applied if the necessary data is collected in the eCRF. As all other methods, they rely on certain assumptions
- **Different treatment switching methods can answer different scientific questions!!**

Estimands in clinical trials with treatment switching

OBJECTIVE	<i>Evaluate OS benefit assuming subsequent therapies represent clinical practice</i>	<i>Evaluate OS benefit adjusted for treatment switching</i>	<i>Evaluate OS benefit adjusted for treatment crossover</i>	<i>Evaluate OS benefit adjusted for treatment crossover at disease-related time-point</i>
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

The importance of censoring mechanisms in selecting appropriate estimands

in preparation

Jonathan Siegel, Michelle Casey, Stefan Englert, Lynda Grinsted, Nathalia Kan-Dobrosky, Shoubhik Mondal, Steven Sun, Jochen Weber, Jiangxiu Zhou

BACKGROUND

- In the past, analyses of time-to-event endpoints generally favored one or a mixture of two strategies regarding intercurrent events
 - Treatment policy strategy – include all information through event or last assessment, regardless of intercurrent events
 - Simple hypothetical strategy - Censor prior to key intercurrent events, e.g. subsequent therapy (especially PFS)
- 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 estimands framework, it is necessary to **understand 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 estimands 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.

GOALS OF THE CENSORING MECHANISMS SUBTEAM

- Goals
 - Identify areas where past assumptions about censoring require greater scrutiny, and understanding of censoring mechanisms can provide insight into strategy selection
 - Identify challenge where alternative strategies would add value.
 - Map existing time-to-event cancer endpoint guidances into estimand framework
 - Identify general survival analysis and censoring concepts and map these into the estimands conceptual framework
 - Goals and definitions
 - Intercurrent events and strategies (hypothetical, while-on-treatment, composite)
 - Assumptions and sensitivity analyses

POTENTIAL CLASSIFICATION OF INTERCURRENT EVENTS AND STRATEGIES

Uninformative

- Uninformative events do not introduce bias or alter the estimand.
- Outcome after event is still of interest
- 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
- 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 a model

Primary Strategies:

- **Hypothetical**
- **Principal Stratum**

Irrelevant

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

Primary Strategy

- **While on Treatment**

Goal is to develop examples and map censoring rules in existing guidance to these strategies

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

Statistics in Biopharmaceutical Research

<https://doi.org/10.1080/19466315.2020.1785543>

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

Assessing the impact of COVID-19 on the clinical trial objective and analysis of oncology clinical trials

Application of the estimand framework

I. 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

II. PROBLEM STATEMENT

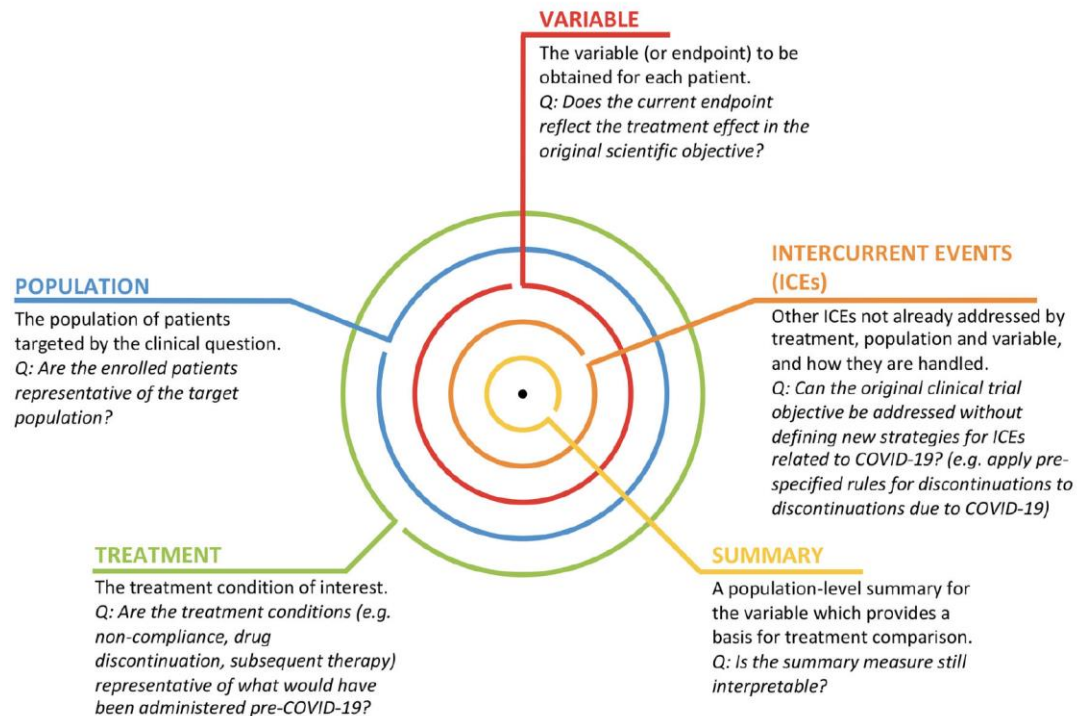
Following EMA and FDA's call to minimize risks to trial integrity, we have been asking and seeking answers to TWO questions:

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.

III. 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.).



IV. RESULTS

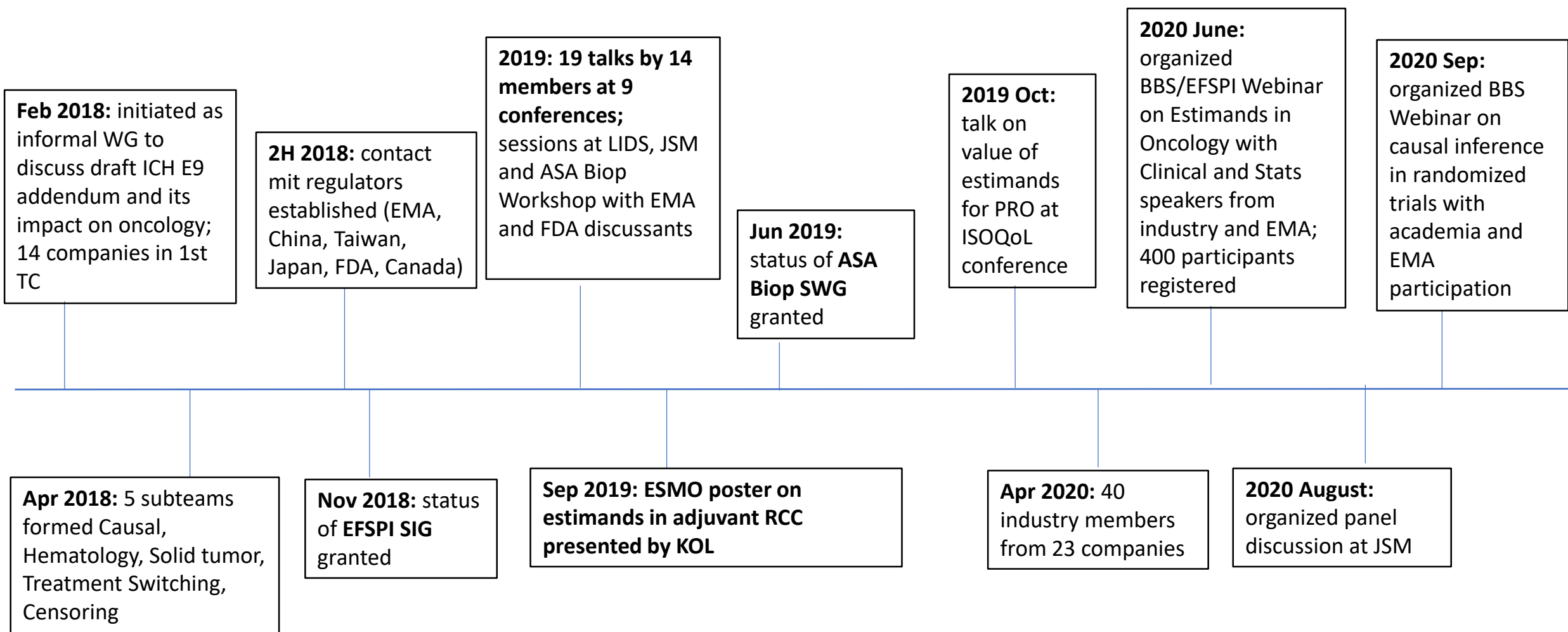
- We used the estimand framework to identify several sources of potential bias.
 1. Change in enrolled patients during/after pandemic (Population): important to assess but periods difficult to define.
 2. Treatment discontinuation or interruptions (ICEs): may require non-conventional strategies depending 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.

Future taskforces

- New taskforces to start in Q4 (more details in the spreadsheet)
 - Clinical engagement
 - Principal stratification and treatment switching
 - Time to response and DOR
 - Estimands and PRO
 - Follow-up quantification
 - RWD
 - Conditional vs. marginal
 - Time to event endpoints with prognostic or predictive biomarker subgroups
- HAs welcome to join any of the taskforces
- Any other topics of interest for HAs?

Back-up

Milestones and achievements



www.oncoestimand.org includes links to recordings and slides from recent BBS webinars as well as presentations from other conferences

TCs with Health Authorities from China, Canada, USA, Japan, UK and Taiwan planned in Sep 2020 to present current status and invite to future collaborations