Estimand framework in Oncology drug development – impact and opportunities

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on behalf of the oncology estimand working group

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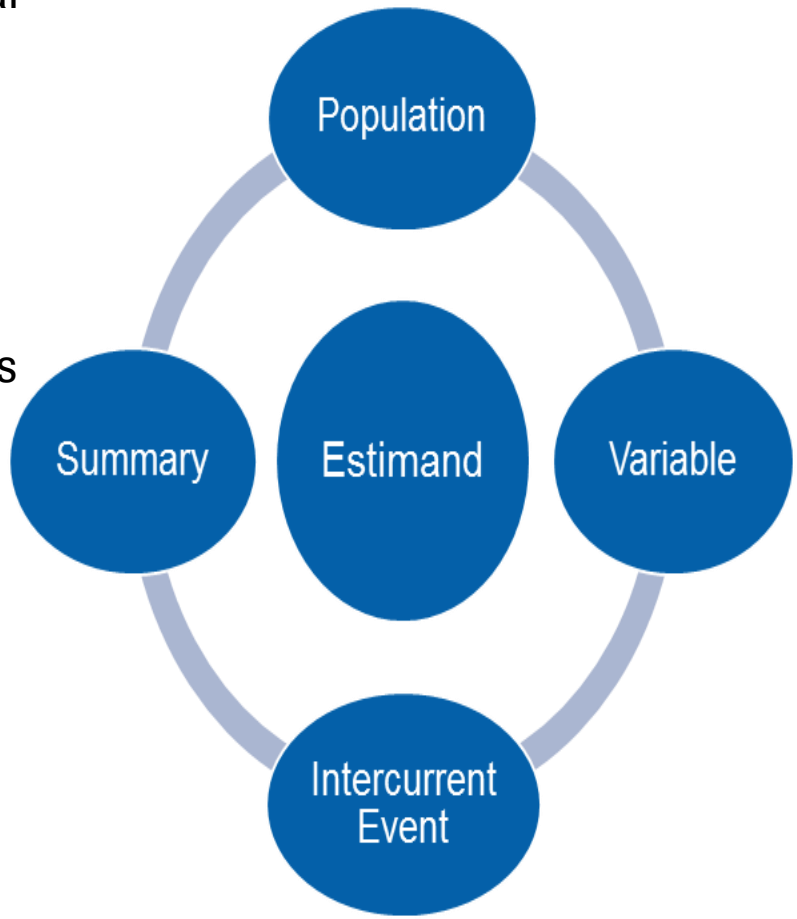
ICH E9 ESTIMAND ADDENDUM AND ONCOLOGY

ICH E9 Addendum and Estimand framework

- Draft addendum for ICH E9 Guideline Statistical Principles for Clinical Trials released in Aug 2017
- Precise definition of scientific question of interest
- Alignment between trial objectives and analysis
- **Dialogue** between sponsors, regulators, payers, physicians, and patients regarding key questions in clinical trials
- Framework reflected in several recently released EMA guidelines, but not necessarily restricted to randomized clinical trials



ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Estimand framework and possible strategies to handle intercurrent events

- Treatment Policy: occurrence of intercurrent event is irrelevant
- Composite: intercurrent event is considered component of the variable
- Hypothetical: a hypothetical scenario is envisaged in which the intercurrent event would not occur
- Principal stratification: population is defined by a patient's potential intercurrent events on either or both treatments
- While on treatment: response to treatment prior to the occurrence of the intercurrent event is of interest

ICH E9 addendum and oncology

- Why this addendum?
  - **Lack of alignment** of trial objectives and effect estimates
  - Addendum and many (early) publications focus on **longitudinally** measured endpoints, especially with missing data
- What about **time-to-event** (T2E) endpoints?
- Anticipated impact on **oncology** clinical trials? Endpoints may reflect time from randomization to
  - death (Overall Survival (OS))
  - progression or death (Progression-free Survival (PFS))
  - relapse, death, or failure to achieve protocol-specified complete remission (Event-free Survival (EFS))

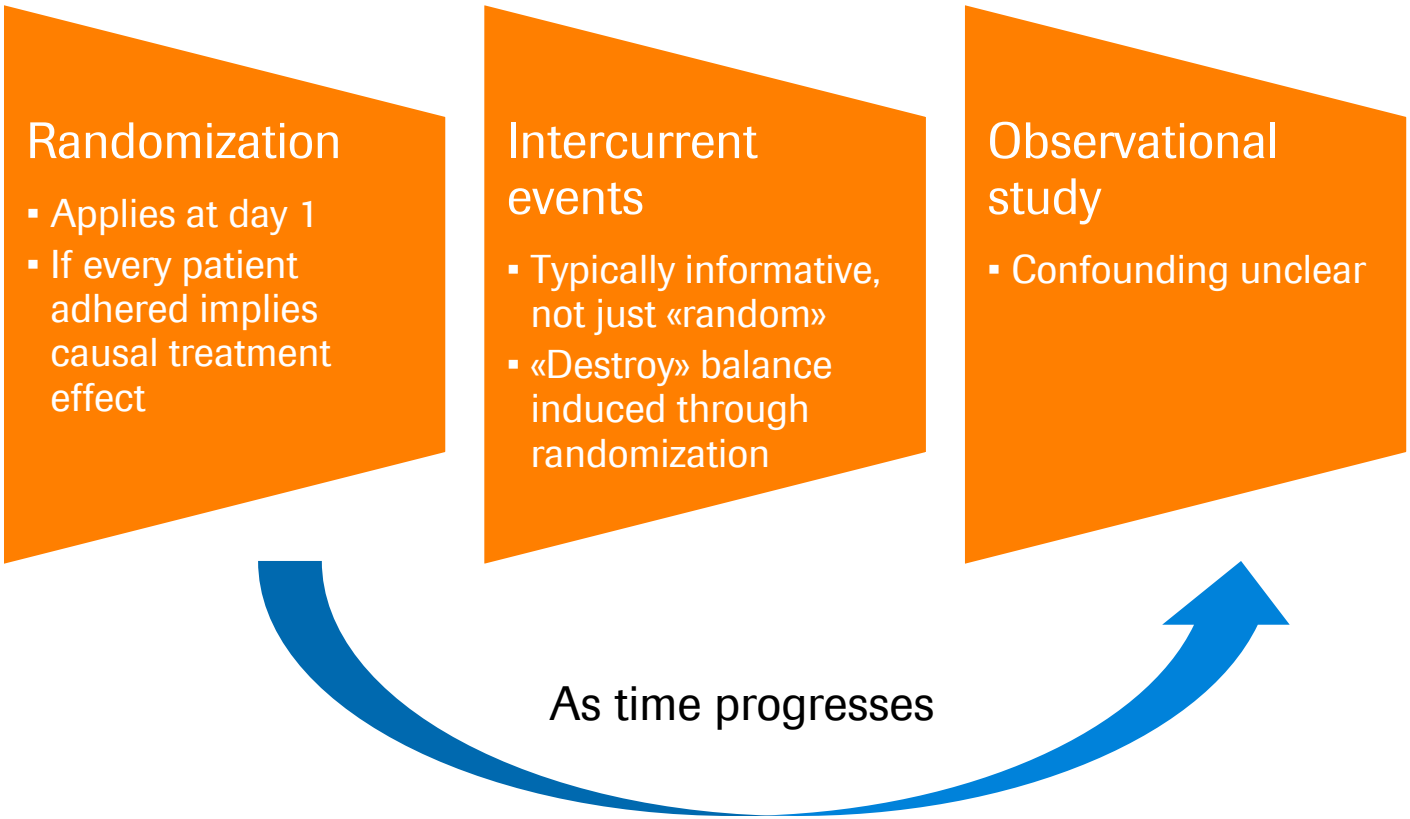
Key questions

- Key **intercurrent** events, endpoints, and estimands in oncology?
- How do five proposed strategies to handle intercurrent events apply to T2E endpoints?
- How can established methods in oncology, e.g.
  - **censoring** schemes or
  - treatment **switching**

  be embedded in addendum framework?
- What estimands are targeted by «**standard**» analyses?
- «**Missing data**» often highly informative, what implicit assumptions are we making when simply censoring?

Key questions

- Addendum will not require **causally interpretable** estimand (beyond what is induced through randomization).
- Where in drug development lifecycle may a causal interpretation make sense?



ONCOLOGY ESTIMANDS WORKING GROUP

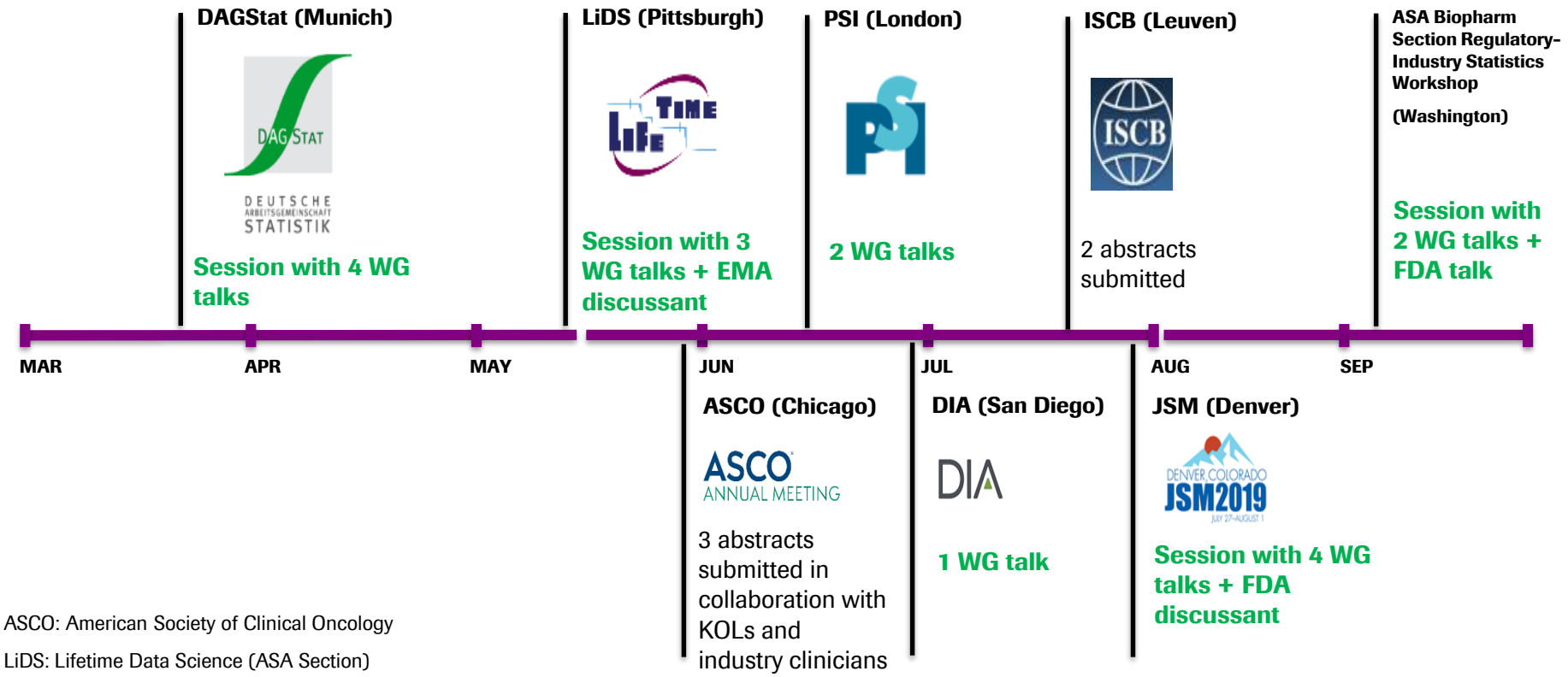
Estimands in Oncology WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 31 members (14 from Europe and 17 from US) representing 19 companies
- established as EFSPI SIG for Estimands in Oncology in Nov 2018, seeking WG status in the ASA Biopharm Section
- close collaboration with regulators from EMA, FDA, Japan, China, Taiwan, Canada

EFSPI SIG: Special Interest Group of European Federation of Statisticians in Pharmaceutical Industry

Estimands in Oncology WG
Communication plan for 2019

- whitepaper(s) and presentations at statistical and clinical conferences
- plans to further engage with Clinical community beyond ASCO



ASCO: American Society of Clinical Oncology

LiDS: Lifetime Data Science (ASA Section)

Oncology estimand working group – subteams

1. Causal estimands in T2E setting (Kaspar Rufibach)
   - Bjoern Bornkamp's talk in this session
2. Treatment switching (Viktoriya Stalbovskaya)
   - Viktoriya Stalbovskaya's talk in this session
3. Censoring mechanisms and their impact on interpretation of estimands (Jonathan Siegel)
4. Case studies in solid tumors (Evgeny Degtyarev)
5. Case studies in hematology (Steven Sun)
   - Hans-Jochen Weber's talk in this session

EXAMPLES

To censor or not to censor?

- Handling of **alternative anticancer treatment (intercurrent event) in PFS analysis prior to observed progression or death** ?

- Cheson et al (2007, 2572 citations on 5th March) and FDA guideline:
  - «... such patients **should be censored**...»
  - «imputes» PFS for these patients using those who benefitted from treatment and had longer follow-up
  - potential risk of non-random censoring
  - **Hypothetical** estimand
    - in T2E setting censoring can also be applied for while on treatment estimand

To censor or not to censor?

- Fleming et al (2009, 105 citations), and also EMA guideline:
  - «...patients **should not be censored** at the time other treatments are initiated when analyzing the PFS end point…»
  - **Treatment policy** estimand
- «This induces strongly dependent censoring because the true time to progression for that patient is replaced by the true time to progression of other patients who also were free of progression at month *x*, but did not need other treatments at that time.»
- Treatment policy estimand favoured to avoid non-random censoring
- Change the question of interest because of challenge in analysis?
- Thinking should be reversed:
  Trial objective → estimand → estimator.

Sensitivity or supplementary – why bother?

- **Sensitivity** analyses: target same primary estimand under different assumptions, explore robustness of estimation and data limitations
- **Supplementary** analyses: target different estimand than primary, provide additional insights into the understanding of the treatment effect
- Why bother?
  - **currently high number of additional analyses performed** inconsistently described as «sensitivity» or «supportive»
  - no clear estimand targeted, interpretation difficult considering high number of analyses with unclear purposes

→ **Less additional analyses** expected **post-addendum** with **clarity** about purpose and **interpretation**

Sensitivity or supplementary?

- **Investigator-** vs. **independently** assessed radiological assessments
  - estimators of the same estimand with expected concordance
    → one sensitivity of the other

- **Stratified** vs. **unstratified** estimate?
  - Stratified Cox model: Distinct baseline hazard functions for each stratum, common hazard ratio across strata.
  - Unstratified: Identical baseline hazard for each stratum.
  - Same baseline hazard = modeling assumption
    → unstratified sensitivity of primary stratified estimator.

Sensitivity or supplementary?

- Conditional effect:
  - Average effect of treatment on individual, i.e. of **moving a subject from untreated to treated**.
  - Estimated from regression coefficient for treatment assignment indicator variable in multiple regression model.
- Marginal effect:
  - Average effect of **moving entire population from untreated to treated**.
  - Unadjusted estimate in RCT.

Estimand	Linear regression	Logistic regression	Cox regression	Aalen additive model
Unadjusted	Marginal	Marginal	Marginal	Marginal
Covariate-adjusted	Effect collapsible, i.e. marginal = conditional	Conditional	Conditional	Effect collapsible, i.e. marginal = conditional

- Do not routinely run adjusted and unadjusted analysis → they may target **different estimand**! One supplementary of the other.
- First define estimand, then estimator.

Opportunities for statisticians

- Embrace and develop **new methods** for T2E endpoints:
  - Competing risk and multi-state models.
  - Causal methods to deal with confounding variables or post-randomization events.
  - Replace naive (often misleading!) analyses through e.g. analyses based on principal stratification.
- Evaluate **bias – variance tradeoffs**, offer alternative solutions:
  - censoring,
  - non-proportional hazards,
  - …
- If well justified, more **flexible approaches** might become accepted by Health Authorities
  - Hypothetical OS estimand with treatment switching.
- Involve broader teams **early** in trial planning in estimand discussion.

Conclusions

- Addendum will bring more **transparency** around
  - connection of trial objective to estimand and estimator,
  - bias-variance trade-off of a given estimator,
  - handling of «missing» data,
  - interpretation of trial results and added value of drugs.
- Opportunity for **structured dialogue** between all **stakeholders** ensuring key questions understood and addressed in study design and study conduct (e.g. data collection).
- Reduce overall number of (unfocused) analyses.
- Addendum has potential to change way we design and analyze trials.
- **Leadership opportunity** for statisticians that are able to connect clinical to statistical questions.
- Ideal outcome of addendum: **RCTs + epidemiology + causal inference**.

Thank you for your attention.

References

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BACKUP

Doing now what patients need next