Statistical Considerations in Oncology Trials in the COVID-19 Era

Introduction to Topic

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Aim:

- To promote collaboration and engagement among different stake holders in design and analysis of cancer clinical trials to advance cancer drug development

Objectives:

- Provide a platform to participate
- Promote non-product specific scientific discussions on design and analysis of cancer clinical trials
- Foster collaboration among regulators, professional organizations, industry, academicians and patients to advance drug development with improved design of cancer clinical trials

Topic: Statistical Considerations in Oncology Clinical Trials in the COVID-19 Era – Discussion #1 Summary

Hosted by American Statistical Association Biopharmaceutical Section and LUNGevity Foundation

Focus of discussion was:

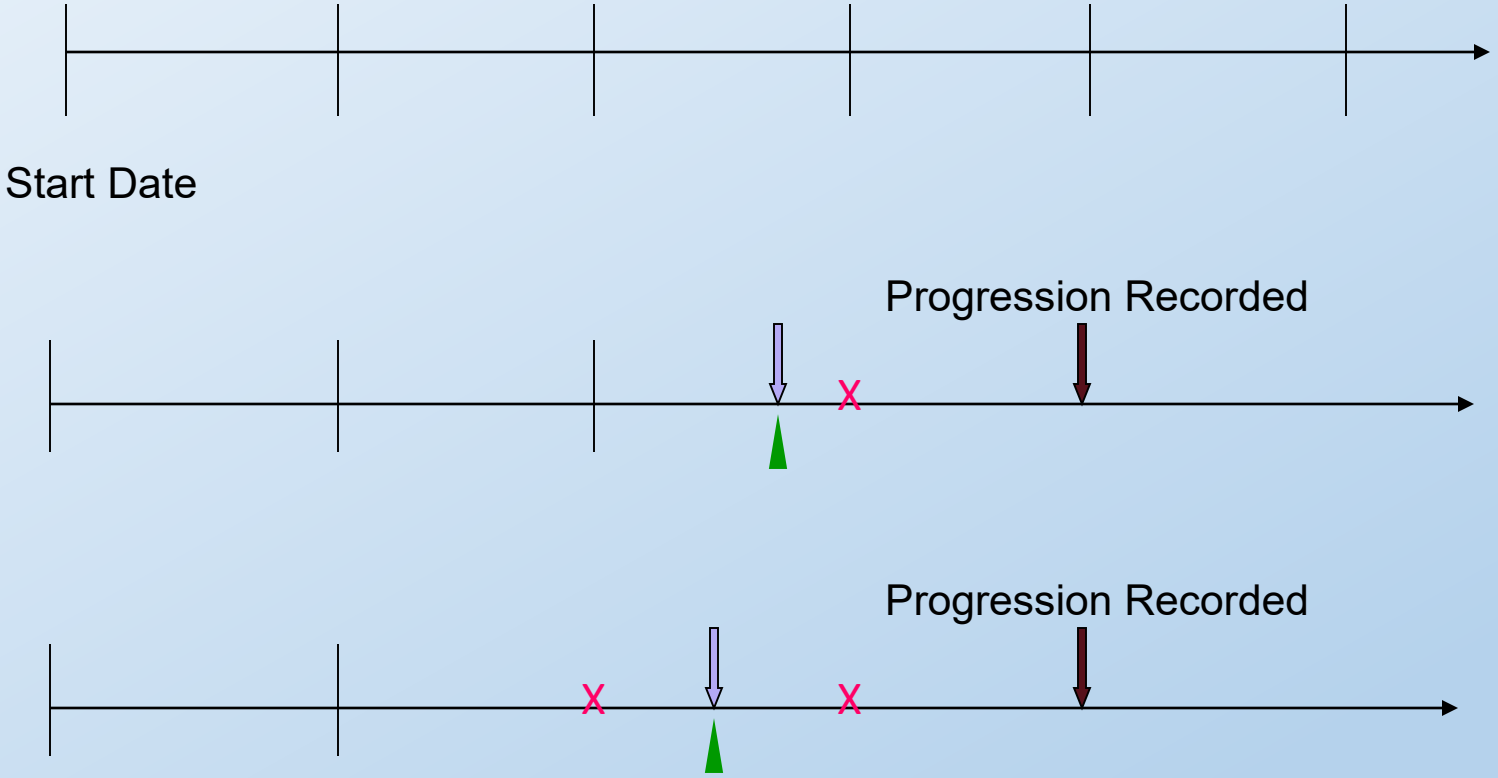
- Future randomized Oncology Trials with an objective to demonstrate benefit of an investigational drug compared to control (standard of care)
- Discussed overarching guiding principles and points to consider
  1. Defining the patient population: treatment evaluation in the overall population and pre-specified subgroup of patients – Which subgroups?
  2. Defining outcomes when mode, frequency and measurements may not be standard and changing during the study *
  3. Impact of decentralized conduct of the clinical trial: Oral drug products, later phase clinical trials; Low impact on routine lab tests; Impact on efficacy assessments?*

Focus of Discussion #2

- Future randomized Oncology Trials with an objective to demonstrate benefit of an investigational drug compared to control (standard of care) with Progression-free Survival as primary endpoint
- Current experience in the ongoing trials
- Impact of non-standard (maybe non-protocol) mode and frequency of progression assessment on statistical properties
- How can future studies be designed accounting for non-standard, flexible tumor assessments?

Scenario: Missing Assessments

Scheduled assessments

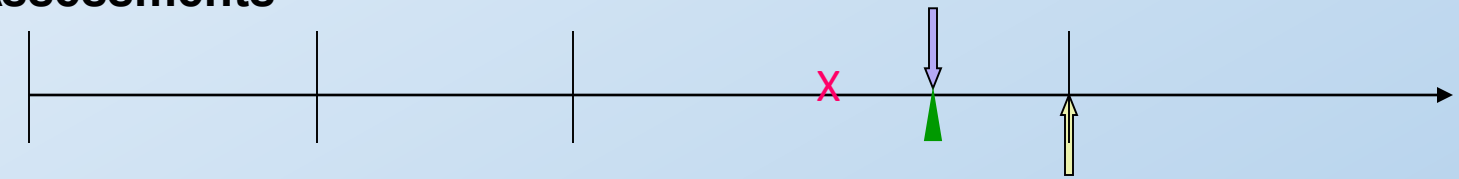


Scenario: Changing Frequency of Assessment

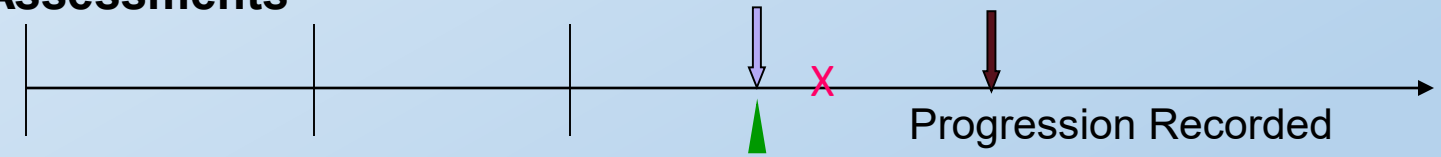
Scheduled assessments

Start Date

Assessments



Assessments



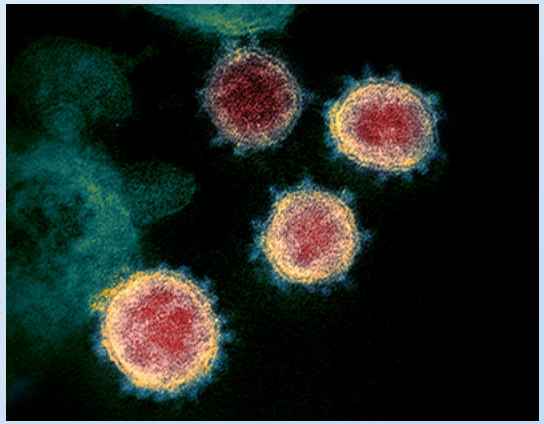
Scenarios for Consideration

- Assessments:
  - Uniformly longer frequency beyond a certain time point (example: uniformly miss alternate assessments)
  - Varying frequency
  - Any other scenarios
- What is the impact on the power, hypothesis, estimand?
- How can the study be designed to be flexible?
- What if the radiological measurement is changing between investigator site and individual patient's local imaging facility?
  - How is this different from investigator vs. independent assessment?

Logistics for Discussion

- Please mute your microphones
- To draw attention of the moderator please raise your hand
- When recognized by the moderator please unmute your microphone to make comments
- Please use chat box to ask questions
- These discussions will not be recorded
- No consensus statement

A152022: Alliance COVID-19 Pandemic Study



Sumithra J. Mandrekar
Mayo Clinic
Group Statistician, Alliance for Clinical trials in Oncology

Virtual Discussion on: Statistical considerations in oncology clinical trials in the COVID-19 era
American Statistical Association Biopharmaceutical Section
And the Oncology Center of Excellence

February 11, 2021

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

Daniel Li, Bristol Myers Squibb

on behalf of the Pharmaceutical Industry COVID-19 Biostatistics Working Group

February 11th , 2021

Pharmaceutical Industry COVID-19 Biostatistics Working Group

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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

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- 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

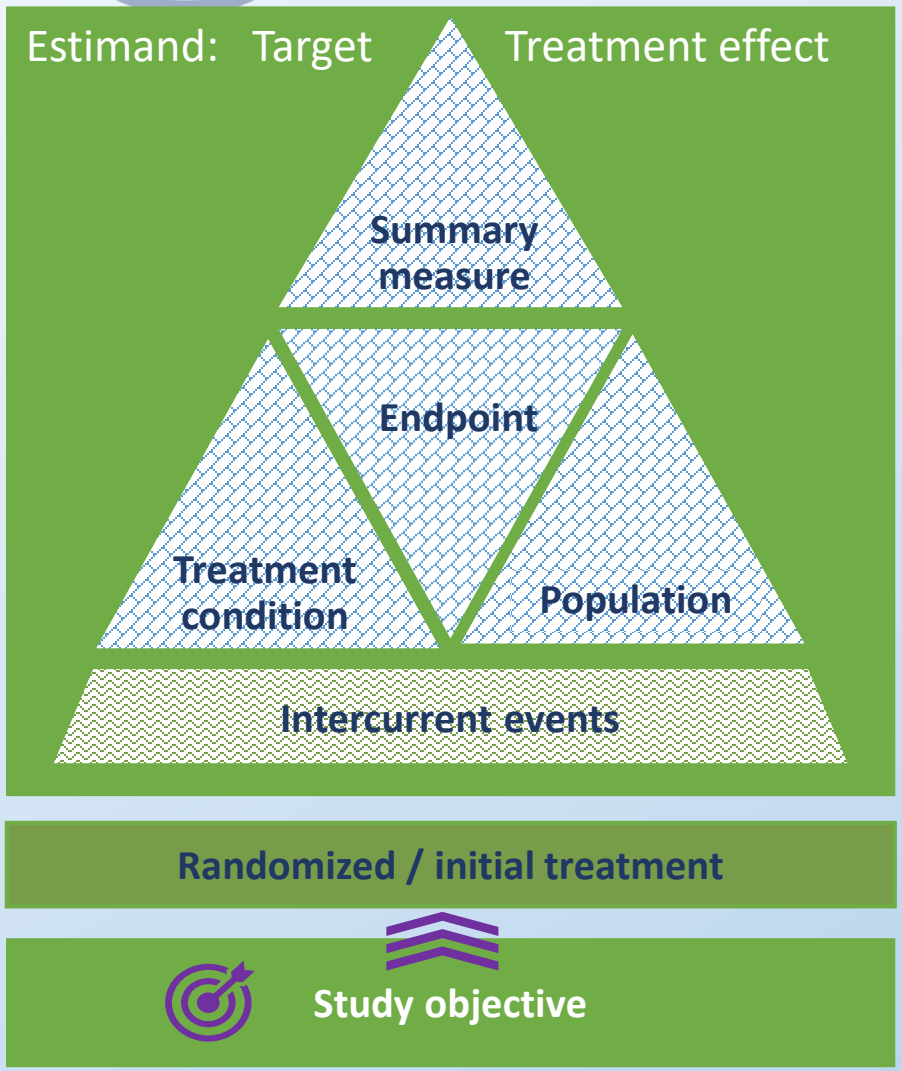
COVID-19 Disruptions to Clinical Trials

Factor	Example of Impact/ Risk
Quarantines, travel limitations, site closures or reduced availability of site staff **Interruptions to supply chain of experimental drug and/or other medications** **COVID-19 infection / treatment**	• Missed or delayed visits and assessments • Study treatment interruption • Different investigators / different measurement modalities • COVID-19 disease effect on study endpoints

Target of Estimation in Context of COVID-19

- Studies designed prior to the global COVID-19 pandemic, and most new studies not testing treatment for COVID-19, are meant to investigate the effect of treatments in the absence of the pandemic.
- "Ignoring" pandemic-related impacts in data collection and analysis may result in estimating a treatment effect confounded by pandemic-related factors.
  - Inference may not align with the original scientific question
  - Study conclusions may not generalize to post-pandemic clinical care
- **Primary study objectives should continue targeting treatment effects free of confounding by COVID-19 pandemic factors.**
  - How do we account for the pandemic-related disruptions yet remain consistent with the study objectives?

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

Examples of Estimand and Analysis Strategies for Study Treatment Discontinuations

… 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.*
… severe complications of COVID-19 infection and/or start of COVID-19 therapy	**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.*
… death due to COVID-19	**Estimand strategy:**	- Hypothetical 'if the disease is eradicated or effective treatment options emerge in the future'. - Composite strategy 'constitute a conservative approach reflecting severity of the underlying risk factors associated with study disease'
	Analysis strategy:	- Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.* - Considered as an event in the time-to-event endpoint definition.

*This includes possibility of discontinuing later due to non-pandemic related reasons.

Additional Analyses in Context of COVID-19

- Additional Sub-group Analyses
  - Clinical Trial periods with respect to COVID-19 outbreak onset and duration
  - Geographical regions
  - Data sources
- Additional Analyses to Assess the Impact of Missing Data
  - Sensitivity analyses to assess departure from MAR assumption
  - Borrowing historical data/RWD/epidemiological
- Additional Safety Analyses
  - Summary of COVID-19 infections or other AE of interest due to COVID-19
  - Summary excluding a) data after COVID-19 infection, b) events related to COVID-19 infection

Alternatives to Protocol-Specified Data Collection Modalities

- Exchangeability of alternative needs to be assessed.
  - External validation
  - Blinded data comparisons between modalities
- Sensitivity analysis regarding alternative modalities of data collections
  - Include only data collected according to the original protocol and treat other modalities as missing
  - Modeling the interaction of between treatment and assessment methods
  - Bayesian analysis “borrowing” information from alternative data modalities using power or hierarchical priors

Summary

- Continual cycle of assess / define / mitigate
- Estimand framework valuable for characterizing impacts on data
  - Even if study not originally defined in those terms
  - Pandemic-related intercurrent events
- Accommodating missing and perturbed data in analyses
  - Pandemic missing data often are MCAR or MAR
  - Rich array of methodology available including multiple imputation
- Characterize overall pandemic impact on trial

Selected References

***Statistics in Biopharmaceutical Research*, special issue on COVID-19**

- "Statistical Issues and Mitigations for Pharmaceutical Clinical Trials Conducted During the COVID-19 Pandemic. (with discussion)" Pharmaceutical Industry COVID-19 Biostatistics Working Group https://doi.org/10.1080/19466315.2020.1779122.
- "Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework." Oncology Estimands Working Group
- "Challenges in Assessing the Impact of the COVID-19 Pandemic on the Integrity and Interpretability of Clinical Trials." Akacha et al

FDA Guidances

- Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry
- Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

EMA Guidances

- Guidance on the management of clinical trials during the COIVD-19 (coronavirus) pandemic
- Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

How can the estimand framework support decentralized trials?

Evgeny Degtyarev (Novartis) & Kaspar Rufibach (Roche)

on behalf of the oncology estimand working group

Acknowledgments

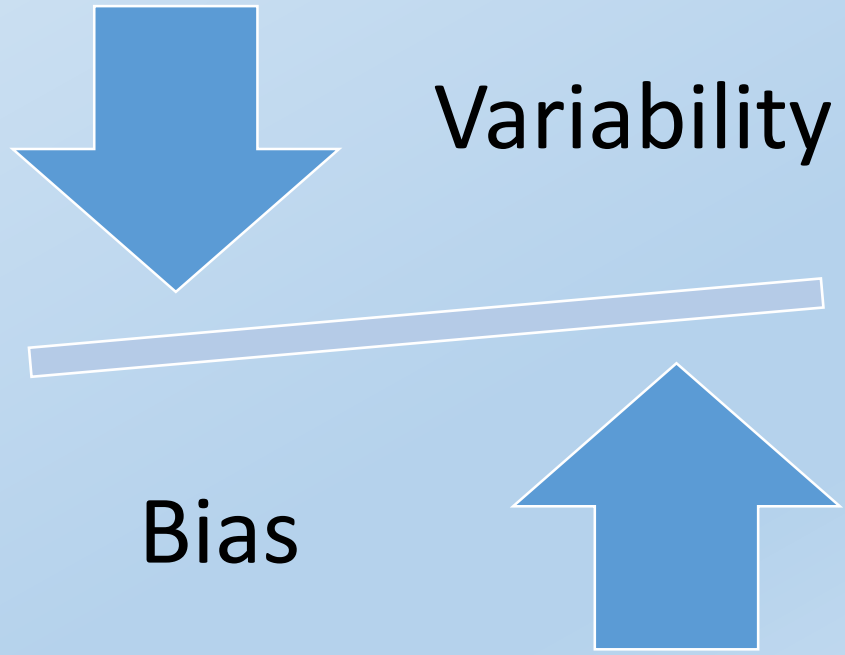
- We represent the oncology estimand working group and acknowledge input from group members.
- Input from Frank Bretz, Hans-Jochen Weber, Michael Wenger, Emmanuel Zuber (all @Novartis) gratefully acknowledged.
- *European special interest group "Estimands in oncology", sponsored by PSI and EFSPI*.
- ASA scientific working group of the *ASA biopharmaceutical section*.
- www.oncoestimand.org

«Traditional» clinical trial

- Scientific experiment designed to **assess effect of new treatment**:
  - Precisely and
  - Unbiased.

- Pandemic experience in Decentralizing:

  option for future trials?



What changes if we decentralize trials? Bias might be reduced

- Decentralized trials offer potential to be **more inclusive**:
  - geographically,
  - minorities,
  - etc.

→ Reduce **bias** generated through narrow in- and exclusion criteria in «traditional» clinical trials.

What changes if we decentralize trials? Variability might increase

- Potential **increase in variability**:
  - endpoint measurements (e.g. local vs. central assessments),
  - treatment scheduling,
  - adherence,
  - etc.

- If variability increases:
  - Might miss potentially effective treatment.
  - Missed opportunity & **potential risk for patients**.

Implications

- Need data to understand **bias – variance tradeoff**!
- «Decentralized» vs. «traditional» false dichotomy: first decentralize «simple» assessments → low hanging fruits.
- **How do decentralized trials need to look like to generate scientific evidence we need for new drugs?**

The estimand framework – tool to get clarity on the research question

- Dec 2019: final version of ICH E9 estimand addendum published.
- **Broadly implemented** in industry. More and more requested and appreciated by stakeholders: trial sponsors, regulators, payers, ...
- Various **X-industry working groups** supporting implementation.
- Facilitates precise definition of the research question accounting for different **patient journeys**.

How can estimand framework support decentralized trials?

- Goal of estimand framework: **Systematic alignment** of
  - trial objectives,
  - design,
  - data collection,
  - conduct,
  - analysis and inference.

- Beneficial for **every type of trial**.

- «Traditional» vs. «decentralized» trials:
  - No change in question of interest expected.
  - But different patient journeys may be observed.

Early treatment discontinuation → initiation of new anticancer treatment

- Risk of **more** new anticancer treatments?
  - IMP delivered at home instead of the clinic.
  - «Less skin in the trial game» of local HCP providers.
  - Unexpected safety events: have to be managed at local HCP level.

- Potential of **fewer** new anticancer treatments?
  - «Burden of trial» may be lower → patients may stay longer on treatment.

- Impact on EFS, PFS, OS: depends on type, timing, and frequency of new anticancer treatment.

Conclusions

- Decentralized trials:
  - We appreciate their potential for being more **inclusive**.
  - **Precisely answering scientific question** remains paramount. We want to do it well!
  - Appreciate regulatory guidance.

- Estimand framework:
  - Very **useful to structure thinking for every type of trial**.
  - Useful to **assess impact of Covid-19 on ongoing trials**.
  - Useful to think about differences between «traditional» and decentralized trials.

- Key: Generate sufficiently precise evidence that we can bring drugs to even more patients.

- **Opportunity for collaboration** between patients + regulators + payers + industry.

Backup

The estimand framework and Covid-19: case for hypothetical estimand strategies?

- Patient Journey's → E. Zuber's talk LUNGevity - FDA Webinar about COVID-19 impact (4th August):
  - Assessment of benefit in clinical trial: needs to account for anticipated patient journeys.
  - Impact of pandemic on patient journeys neither foreseen nor addressed at trial design stage.

- Ongoing trials: Designed assuming
  - **No major disruption of healthcare systems**.
  - **No highly infectious disease** with severe complications
  - for which **no effective therapy** available.

- Intercurrent events (indirect impact): independently of disease or treatment
  - primarily caused by disruption of healthcare system or
  - patients' desire to minimize traveling.
  - **Hypothetical strategy potentially reasonable**.
  - Caveat: estimand needs to be estimable under plausible assumptions.

- Estimand framework: very useful to assess impact of pandemic on trial objectives, estimand, and estimation.

Potential impact of decentralization on PFS

- Effect in **world where no new anticancer treatments** would be given?
  - Estimated through censoring at new anticancer treatment.
  - Hypothetical strategy.

- Effect understanding **new anticancer treatment as part of treatment strategy**?
  - Estimated based on observed PFS time irrespective of new anticancer treatment.
  - Treatment policy strategy.

- Estimand framework can bring clarity on the question we are asking.

Potential impact of decentralization on PFS

- Hematology:
  - Bone marrow: key in response assessments.
  - Local HCP able to perform an aspirate / biopsy?

- Radiological assessments for determination of (absence of) PD:
  - Adds another layer: local imaging center - local investigator (country-specific PI) – central assessment.
  - Clarity needed who decides on treatment based on radiological assessment.

Potential impact of decentralization on EFS and OS

- EFS:
  - New anticancer treatment typically counted as event.
  - Subjectivity in initiation of new anticancer treatment might have even bigger impact than for «traditional» endpoints.

- OS:
  - Intercurrent event of new anticancer treatment typically absorbed in **treatment attribute** (treatment policy strategy).
  - Change in frequency and timing of new anticancer treatment → impact on duration of experimental treatment.

Further comments

- Implications of DCTs may vary dependent on the setting.
- Useful to identify settings with little impact of decentralization and settings requiring a bit more time to understand potential impact on the generated evidence.
- Estimand framework could facilitate structured comparison of different indications:
  - Rare *populations* may be less suitable as large sites have more experience in diagnosis, treatment and disease assessment.
  - Knowledge about *treatment*: if it's first indication, likely more early discontinuations than if it's the fifth indication and safety profile is well established; complexity of treatment also relevant – double-blind trials likely less impacted.
  - *Endpoint*: different response criteria – settings with more complex response criteria may require more pre-work.

Statistical Aspects of Clinical Trial Conduct During Covid-19

Erik Bloomquist, PhD **Office of Biostatistics**

Math Statistician - Team Leader **OTS/CDER/FDA**

Division of Biometrics V

Disclaimer: This talk reflects the views of the speaker and should not be construed to represent FDA's views or policies.

Clinical Trial Guidance (2020)

- The safety of trial participants is paramount.
- The agency acknowledges there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures.
- Trial conduct may be affected by the outbreak, but trial validity should be maintained during and after the outbreak.
- Sponsors should avoid trial modifications based on data that may introduce bias into the interpretation of trial findings.

COVID-19 Statistical Survey Results (Aug 2020)

1. Most companies have re-opened enrollment for at least some trials.
2. Most have implemented some form of virtual/remote monitoring/local imaging steps to ease participant burden.
3. About half have made minor adjustments to their SAPs (sensitivity analyses).
4. Most have not adjusted follow-up schedules or number of tests required.
5. Most have not made major adjustments to their SAPs
6. Most have not had major statistical issues.

De-centralized Trials

- De-centralized aspects of clinical trials may become more common in future oncology trials.
- Statisticians will play a major role in this effort. Aspects to consider include:
  - Will the reliance on non-centralized site reads lead to biased results?
  - Will some patients still need confirmatory scans?
  - Does a highly variable follow-up schedule bias results or lead to a lower power?

Follow-Up Example

Consider the following simple trial. Two-arm randomized trial (cntl/trt medians = (9 months, 14 months), with 200 patients per arm. Enrollment completed in 1-year, follow-up 2 years, 1000 simulations.

1. Assuming a fixed follow-up schedule (10 weeks +/- 1 week)
    - Power = 92%
    - Median average = 5.11 months

2. Assuming a random follow-up over 2 years with a random number of scans per patient (average = 10).
    - Power = 87.2%
    - Median average = 5.02 months

Concluding Thoughts

- Flexible follow-up may help improve patient representation, especially for senior and rural populations.
- Detailed work should be done on aspects of the follow-up schedule on trial endpoints.
- Audits and hybrid follow-up approaches should be considered to provide data that these changes are not-biasing or affecting trial conclusions.