Estimand Framework and Its Impact on Drug Development in Oncology

Steven Sun, Anja Schiel, Kunthel By,,Catherine Njue, Richard J. Cook

Chair: Jonathan Siegel

Panel Discussion, JSM 2020 Virtual Conference, August 4, 2020

Our Distinguished Panelists

Anja Schiel

Norwegian Medicines Agency and Chair, EMA Scientific Advice Working Party

- Anja Schiel has studied Biology at the Johannes Gutenberg-University, Mainz, Germany. She received her PhD from the Free University in Amsterdam in 2006 and worked several years as Post-Doc on a range of subjects focusing on oncology, immunology and molecular biology, first at the University of Leiden and later at the University of Oslo, before starting at the Norwegian Medicines Agency (NoMA) in 2013.
- At NoMA she is working as special adviser/Statistician/Methodologist both on regulatory (EMA) and HTA projects. She has been Chair of the Biostatistics Working Party for the last 3 years and currently is the Chair of the Scientific Advice Working Party at EMA. In addition, she has been heavily involved in EUnetHTA activities, with focus on parallel EMA-HTA scientific advices as Norway is member in EUnetHTAs Early dialogue working party.

Richard J. Cook

Professor of Statistics, University of Waterloo

- Richard Cook is Professor of Statistics in the Department of Statistics and Actuarial Science at the University of Waterloo.
- His research interests include the analysis of life history data, the design and analysis of clinical and epidemiological studies, and statistical methods for the analysis of incomplete data.
- He collaborates extensively with researchers in rheumatology, transfusion medicine and cancer.
- He co-authored The Statistical Analysis of Recurrent Events (Springer, 2007) and Multistate Models for the Analysis of Lifetime History Data (Taylor and Francis, 2018) with Jerry Lawless, and together they have given many short courses on these topics.
- Richard is a recipient of the CRM-SSC Prize from the Centre de recherches mathématiques (CRM) and the Statistical Society of Canada (SSC) in recognition for contributions within 15 years of a doctorate degree.
- In 2018 he was awarded the Gold Medal of the Statistical Society of Canada.
- In 2019 he was appointed Faculty of Mathematics Research Chair, and in 2020 he was named University Professor.

Catherine Njue

Biostatistics Advisor, Health Canada

- Catherine Njue is a Biostatistics Advisor for Clinical Trials in the Biologic and Radiopharmaceutical Drugs Directorate (BRDD), Health Canada. In this position, she is primarily involved in evaluating the statistical methodology of clinical trials for biologics (e.g., vaccines, blood products) and related biotechnology products and radiopharmaceuticals. She also provides statistical expertise in the drafting, review and implementation of standards and guidelines developed by Health Canada, ICH, and WHO working groups.
- Dr. Njue received her Ph.D. in Statistics from the University of Manitoba in Winnipeg, Manitoba, Canada. After two years as a Biostatistician at CancerCare Manitoba, she joined Health Canada where she remains. She has extensive experience as a statistical consultant, which began at the Statistical Advisory Service, University of Manitoba, where she worked throughout her doctoral program. At CancerCare Manitoba, she collaborated with researchers in the Department of Preventive Oncology and Epidemiology on the design and analysis of epidemiological studies. She also provided statistical consultation to researchers from various other departments within CancerCare Manitoba.

Kunthel By

Senior Statistical Reviewer, US FDA

- Kunthel By is a senior statistical reviewer in the Office of Biostatistics (OB) at the Center for Drug Evaluation and Research at FDA. He has supported both malignant and benign hematology, including myeloma, lymphoma, and leukemia. He provides statistical advice to industry regarding protocol and SAP development and reviews drug applications. Prior to oncology, Dr. By supported the Office of Surveillance and Epidemiology designing FDA-initiated observational studies focusing on drug-safety in the post-approval setting. He is also involved in regulatory discussions about non-proportionality and in the writing of FDA Guidances. His greatest life challenge is trying to figure out how to teach a 5 year old how to read.

Steven Sun

Head Statistical Sciences, CVM, Janssen Pharmaceuticals Inc.

- Steven Sun is the Global Head of Statistical Sciences - Cardiovascular and Metabolism (CVM) TA at Janssen Research and Development. He has over 20 years of experience in the pharmaceutical industry focusing on oncology/hematology/Cardiovascular and Metabolism therapeutic areas. At Janssen, he has been the key driver for multiple major oncology products development and NDA/sNDA/MAA submissions, including the first Breakthrough Designation of oncology therapy IMBRUVICA® for B-cell malignancies and the CD38 monoclonal antibody DARZALEX® for multiple myeloma. He has extensive experience in clinical trial designs and regulatory interactions for drug labeling.
- Dr. Sun has been the invited speaker for many professional meetings including the regulatory/Industry workshop, DIA workshop, Harvard symposium, Joint Statistical Meeting and other international professional meetings. He has published more than 20 peer reviewed scientific papers in statistical and medical journals. He served as the only industry representative of advisory committee for FDA's initiative on Updating Labels for Generic Oncology Drugs.

Disclaimer - General

- The comments expressed herein are the authors' own and should not be interpreted in any way as representing their respective employers' views or policies.

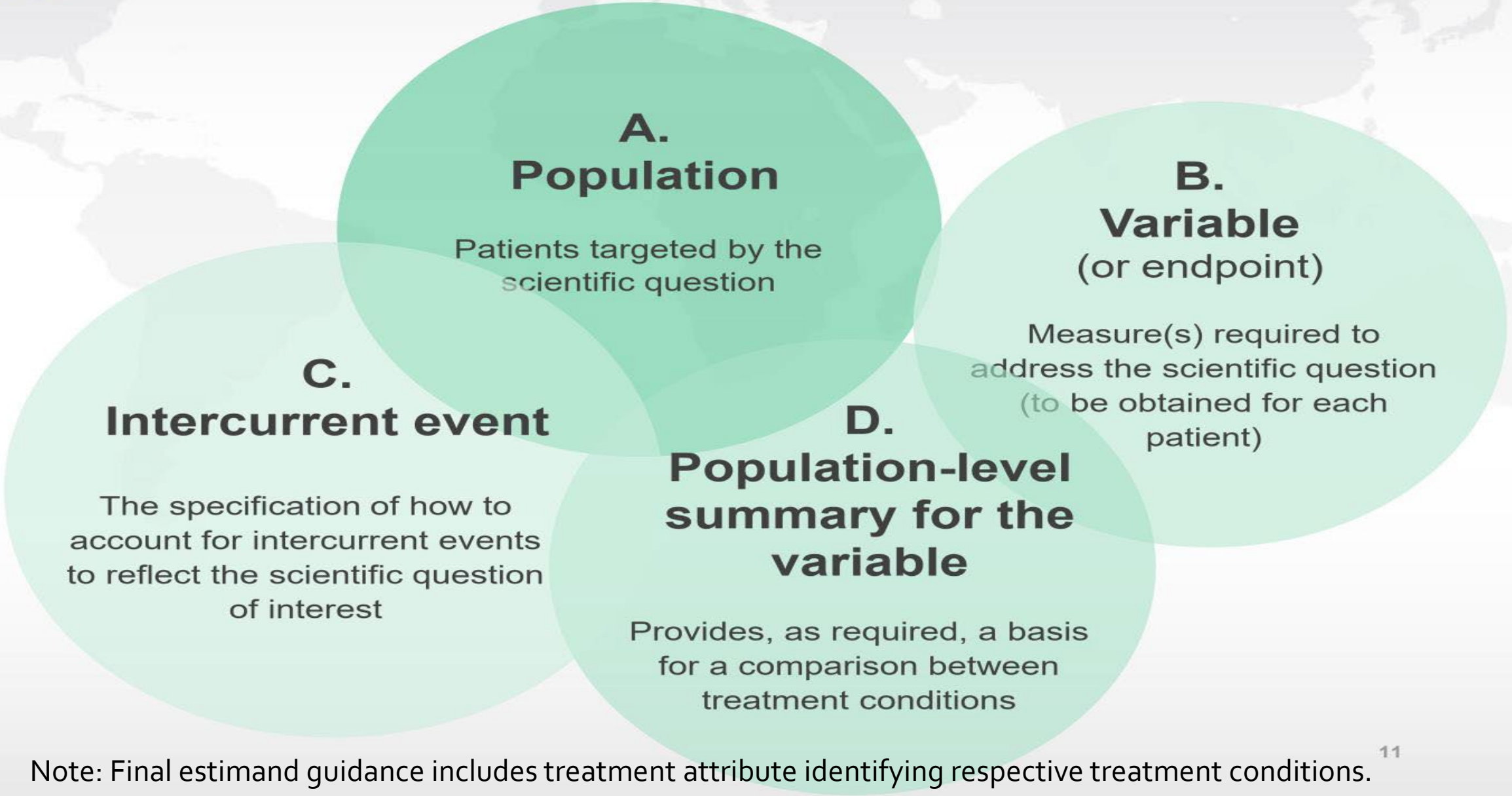
Disclaimer - FDA

The comments expressed herein are the authors' own and should not be interpreted in any way as representing FDA's views or policies.

A Bit of Background

ICH E9 (R1) Status

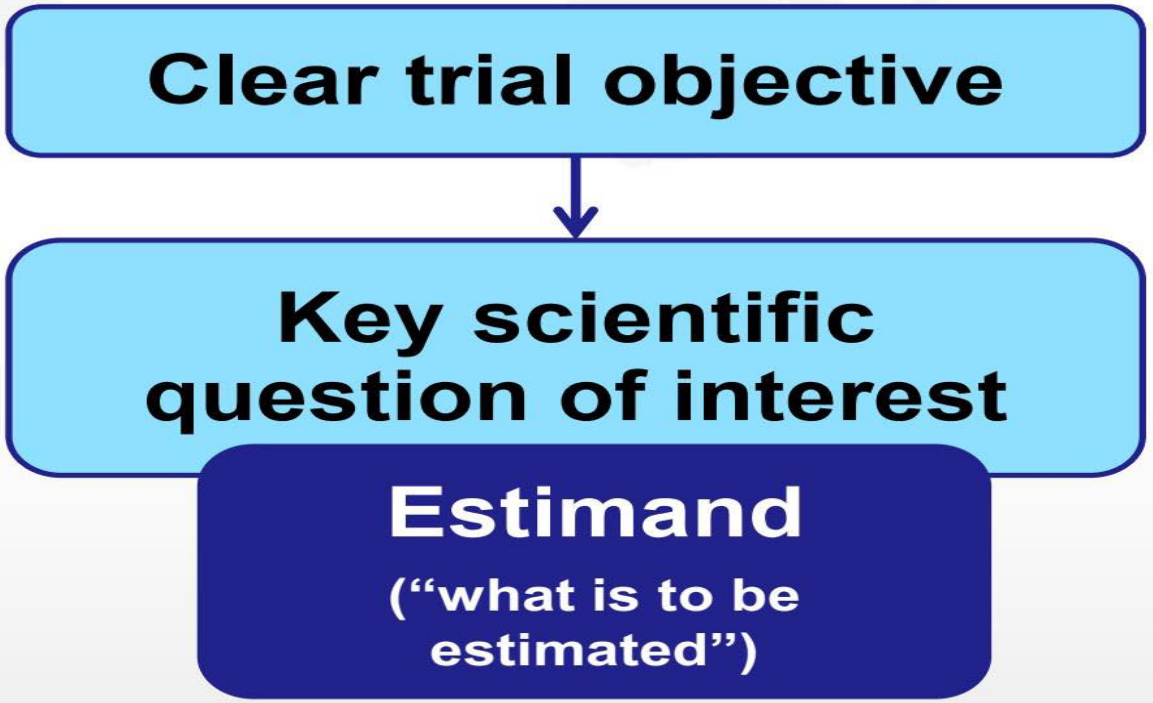
- ICH E9 (R1) "Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials" was finalized in November 2019.
- The EMA (CHMP) formally adapted the addendum on January 30, 2020. It came into effect in the EU on July 30, 2020.
- Health Canada formally implemented the addendum on July 21, 2020.
- The FDA is in the process of formally adapting the addendum.



Note: Final estimand guidance includes treatment attribute identifying respective treatment conditions.

A 'new' framework

Clear trial objectives should be translated into key scientific questions of interest by defining suitable estimands.



A thinking process…

1. **Therapeutic setting** and **intent of treatment** determining a **trial objective**
2. Identify **intercurrent events**
3. **Discuss strategies** to address intercurrent events
4. **Construct** the estimand(s)
5. **Align** choices on **trial design**, **data collection** and method of **estimation**
6. Identify **assumptions** for the main analysis and suitable **sensitivity analyses** to investigate these assumptions
7. **Document** the chosen estimands

Pre-addendum:

- "ITT" primary.
- Attempts to "rescue" failed OS with ad-hoc treatment switching analyses.
- Likely not all data collected that "proper modelling" requires.
- Post-hoc.

Post-addendum:

- Estimand of interest: **hypothetical**.
- EMA Q&A document that opens door to such analyses **IF**:
  - **Preplan**.
  - Ensure **quality** throughout protocol, proper data collection, and analysis.
- **Assumptions** transparent.

Estimands in Oncology WG

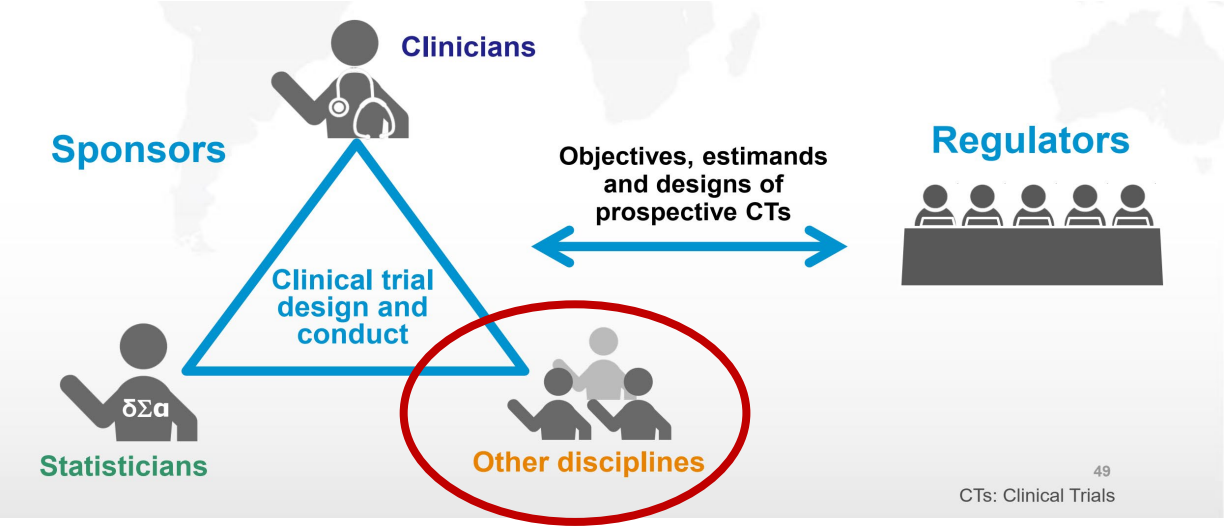
- Purpose: common understanding and consistent definitions for key estimands in Oncology across industry
- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- 34 members (15 from Europe and 19 from US) representing 22 companies
- established as EFSPI SIG (Nov 2018) and ASA Biopharmaceutical Section SWG (Apr 2019)
- collaboration with regulators from EMA, FDA, Japan, China, Taiwan, and Canada

Questions for the Panel

- 1) Does the addendum's "framework to align planning, design, conduct, analysis, and interpretation" live up to its promise of facilitating interactions between stakeholders?
- 2) How is the estimands framework impacting academic methodological and applied research?
- 3) To what extent is the estimands framework affecting study objectives, design, sample size, development time of trials, and conduct as distinct from purely statistical topics (variable definitions, sensitivity analyses)?
- 4) On a spectrum between pure burden (addendum adds more protocol/SAP text and more sensitivity analyses to accomplish the same thing) and strategic opportunities (door to new strategies leading to approvability in previously unapprovable situations, or use of previously unacceptable estimators), where do you think the addendum is currently perceived?
- 5) What are experiences from industry with health authorities and HTA bodies, and vice versa?

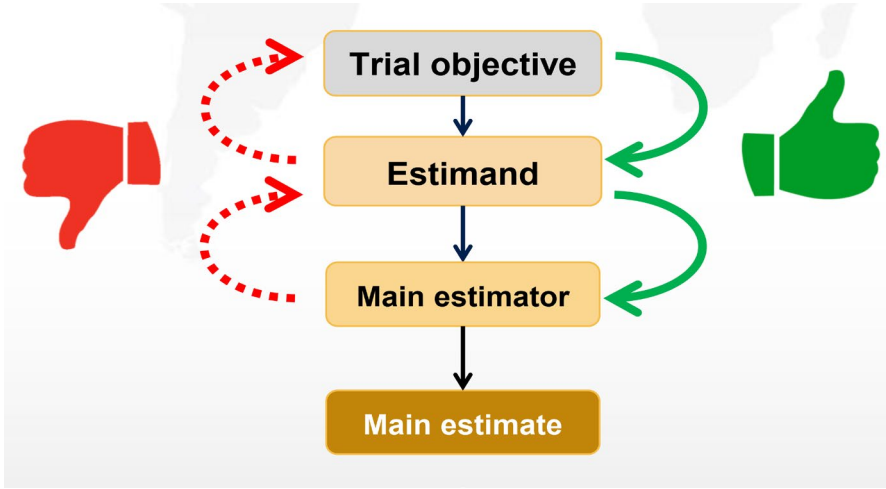
Question #1

Does the addendum's "framework to align planning, design, conduct, analysis, and interpretation" live up to its promise of facilitating interactions between stakeholders?



- We have found a common language that has improved the communication between stakeholders
- Understanding the need for multi-disciplinary thinking has increased

- There is still a tendency to do some retro-fitting or rather ‘do what we have always done’
- In some indication areas the advantage of using the framework is not obvious



Norwegian Medicines Agency

#2) How is the estimands framework impacting academic methodological and applied research?

Increased awareness of *post-randomization confounding*, impact of *model misspecification*, and *deeper conceptual challenges* in clinical trials

Increased tension between *desire for simple single number summaries* of treatment effects for decision making and *need for more elaborate models* to describe complex processes

Increased thinking about settings where weighting can "fix" problems and awareness of when it can't

Model specification issues

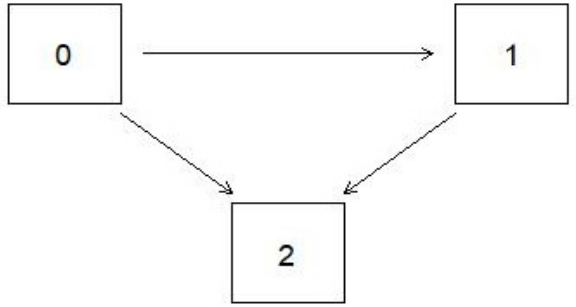
- causal inference with non-proportional hazards

Post-randomization complications introducing time-dependent confounding

- dependent study withdrawal
- non-compliance
- co-interventions (post-progression rescue treatments)

Inherently deeply challenging problems

- causal inference about intervention effects on *non-fatal responses* when *mortality is non-negligible*



Multistate models: A framework for considering post-randomization complications

Richard Cook
UNIVERSITY OF WATERLOO

Question #3

- To what extent is the estimands framework affecting study objectives, design, sample size, development time of trials, and conduct as distinct from purely statistical topics (variable definitions, sensitivity analyses)?

Some thoughts on Q3

- Based on our accumulating experience, the addendum is already having a noticeable impact on important study aspects beyond the expected impact on purely statistical considerations
  - The impact seen is being driven by more clarity on the clinical question of interest which is now reflected in the target of estimation (the estimand) as per the addendum to ICH E9
  - In the past, the clinical question was not typically clearly articulated in clinical trial protocols

Some thoughts on Q3

- In particular, in the past:
  - clinically relevant intercurrent events that could impact either the occurrence or the interpretation of the endpoint of interest have not always been given the careful consideration they deserve at the trial planning stage

- With the development and implementation of the addendum to ICH E9:
  - clearly articulating the treatment effect of interest at the trial planning stage “requires a thoughtful envisioning of “intercurrent events”, and this is having a direct impact on choices made with regard to study design and conduct (as well as analysis)

Some thoughts on Q3

- For example:
  - targeting a treatment effect disregarding the initiation of subsequent therapies is different from targeting a treatment effect assuming that subsequent therapies had not been initiated
  - the magnitude of the treatment effect is likely different under the two scenarios, and collection of data after the initiation of subsequent therapies is not necessary in the second case

Q4: Current Perceptions?

On a spectrum between pure burden (addendum adds more protocol text and more sensitivity analyses to accomplish the same thing) and strategic opportunities (door to new strategies leading to approvability in previously un-approvable situations, or use of previously inacceptable estimators), where do you think the addendum is currently perceived?

Question #5

What are experiences from industry with health authorities and HTA bodies, and vice versa?

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Ask to put trial setups in the estimand framework for new studies
- Use estimand language for submission inquiries and COVID inquires for ongoing studies

- Different estimand are often requested
- Comparative evidence

Your Turn

- QUESTIONS?
  - Please use the “Ask the Presenter a Question” box to send your questions to the chair.

End

- THANK YOU!