The 9th Data Science Roundtable Discussion

Practical Application of Estimands in Clinical Trials

Note: These are opinions based on the experience of the DSRT participants and are not official to each participant's organization.

Introduction

- 4 years have passed since the ICH E9(R1) guideline reached step4 in 2019, and the estimand framework has come to play an important role in clinical trial design, conduct, analysis, and interpretation.
- However, the practical application of estimand involves, for example, the following challenges.
  - How statisticians communicate with non-statisticians when defining appropriate estimand
  - Definition and use of sensitivity analysis and supplementary analysis
- About 50 young biostatisticians from industry, government, and academia separated into six tables to discuss the above two topics.

Part1: Communication

Results of discussion

- This content summarizes the results from the 6 groups that discussed the topic of estimands.

What challenges exist and what approaches are effective in promoting understanding of the estimand framework and preventing misunderstandings?

- **Challenge:**
  - Low awareness of estimands and its importance is not well understood in non-statisticians.
  - There is a misunderstanding that “statisticians take the initiative”, and collaboration among various functions is lacking.
  - Concepts such as strategy and ICEs are difficult to understand and confuse non-statisticians.
  - Statisticians lack disease knowledge and it is difficult to obtain sufficient input from a clinical perspective.
  - If requirements for estimands differ among regulatory authorities in each country, there is a burden of Japan-specific response.
- **Approach:**
  - Hold question-based or scenario-based study trainings to explain concepts in line with the needs of the field.
  - Describe the concepts in lay language, emphasizing that they are an extension of what would normally be discussed at a study planning.
  - Establish a place for industry-government-academia discussions to promote mutual understanding.
  - Develop estimand experts in each function to share and educate specialized knowledge.
  - Case studies and on-the-job training will be incorporated to deepen understanding of practical operations.
  - Ensures proactive communication with the regulatory authority to agree on estimand requirements.
  - Engage in estimand discussions and share perceptions with the entire team from study planning onwards, not just the statistician.

What kind of environment and knowledge do you think are necessary to achieve effective estimand discussions?

- It is necessary to create an environment where clinicians and statisticians can easily consult each other and provide opportunities to deepen mutual understanding.
- It helps non-statisticians naturally understand the importance of estimands by presenting in non-technical and familiar language.
- Share the meaning of estimands using case-based discussions such as specific study designs and ICEs.
- Statisticians with enhanced disease knowledge draw specific input from various stakeholders to enrich the estimand discussion.
- Prepare an explanation that is easy for clinical team (CRA, etc.) to understand regarding data collection after ICEs (e.g., treatment discontinuation).
- Establish an environment for discussion from the viewpoint of regulatory authorities, for example, to present a study plan with estimands at the meeting with regulatory authorities.
- Leverage templates that incorporate estimands into protocols and set up natural situations for discussion.
- Strengthen knowledge sharing with relevant parties including DM and strengthen common recognition by providing a place for multidisciplinary discussion from the early stage of study planning.

What processes and collaborations with other functions do you think are effective in identifying ICEs and selecting corresponding strategies?

- Preparation of checklists and guidelines that make use of the experiences and knowledge of clinicians would promote efficient discussions.
- Use historical examples and training materials to illustrate each strategy's explanation to give a concrete picture of the impact of ICEs.
- Create a project meeting and a place for multidisciplinary discussion to have a common understanding from the time of drawing up a study plan.
- When discussing potential ICEs with clinicians, the study team can deepen discussions by sharing background information based on study objectives and disease characteristics.
- Collaborates with all relevant stakeholders, including DM and programmers, to establish a process to appropriately handle ICEs in the CRF and SAP.
- Statisticians deepen basic knowledge about diseases and treatments, and clinicians understand basic statistical perspectives to facilitate mutual communication.
- In order to maintain the transparency of the setting of ICEs, the setting process and discussion will be documented.
- Even if different estimands are adopted according to the request of different regulatory authorities, the policy and strategy should be aligned in Japan team in advance.
- With reference to the Target Product Profile (TPP) and protocols for drugs in the same class, determine ICEs and strategy in a way that matches the study objectives.

What are the challenges in documenting and implementing estimands, and how can they be overcome?

- **Challenge:**
  - Even if estimands are described in the protocol, there are cases where non-statisticians do not understand them without additional explanations.
  - Template format is not uniform within the company or industry and lacks flexibility.
  - There are cases where estimands have not been sufficiently discussed during study planning.
  - There is a concern may prioritize the results of sensitivity and supplementary analyses over the study objectives.
  - Each element of the estimand may not be easily conveyed to non-statisticians, and as a result, there is a risk of misalignment with the objective and interpretation.
  - Because of inconsistent criteria for describing estimands for secondary endpoints, appropriate documentation balance is challenging.
  - Study team may not adequately communicate study objectives or analysis plans to investigators, increasing the likelihood of loss to follow-up in the study.
- **How to overcome:**
  - When describing estimands in the protocol or SAP, explain them in plain language so that they can be understood by non-statisticians, and add notes as necessary.
  - Based on ICH M11, a simple and uniform format for describing estimands is introduced from the study planning stage.
  - Initiates estimand discussion early in protocol development and mandates discussion in the work instruction to ensure that all parties have a common understanding of the study objectives and strategy.
  - Make use of seminars or trainings to have people involved correctly understand the significance of sensitivity and supplementary analyses and their impact on the study objectives.
  - Provides transparency by documenting the rationale and process for setting the strategy and sharing the big picture with stakeholders.
  - Internally align the benefits and criteria for inclusion of estimands in secondary endpoints to improve predictability in study conduct.
  - Concretely explain the study objectives and the analysis plan to clinicians, and establish a system that allows smooth responses to questions. Increase close collaboration with study sites to reduce the risk of loss to follow-up.

In setting estimands, what roles do statisticians and other functions play, and what are they expected to do for each other?

- **Role of Statistician:**
  - Leads the setting of estimands and SAP including ICEs from a scientific and statistical perspective.
  - Evaluate the content proposed by clinicians or other experts from an analytical perspective and propose an appropriate implementation method.
  - Act as facilitator within the team to facilitate discussion.
  - Considers implementability of estimands and ensures transparency, such as specifying example programs (e.g. SAS) in SAP.
- **Role of other experts:**
  - Clarify study objectives and organize clinical components including ICEs with statistician.
  - Provides regulatory authority requirements and therapeutic area specific context to supplement the required context for setting the estimand.
  - Propose a framework for study design and strategy based on epidemiological and development background.
  - Serves as a communication hub to coordinate input among stakeholders on study plans and ICEs (may be better served by PMs and clinicians).
- **Expectations for statistician:**
  - Describes the concept of ICEs and estimands in a clear way to help ensure that all team members have a common understanding.
  - Provide scientifically based analysis methods to support study design.
  - Conduct appropriate facilitation to create an environment where it is easy to discuss the study objectives and analysis plan with the entire team.
- **Expectations for others:**
  - Explain clinical knowledge in lay language and support statisticians to get the most out of the information provided.
  - Proactively provide input on ICEs and study objectives, and share elements necessary to achieve study objectives.
  - Act to facilitate communication of objectives and constraints to facilitate discussions across the team.

Part2: Sensitivity and Supplementary Analyses

Results of discussion

- This content summarizes the results from the 6 groups that discussed the topic of estimands.
- However, for the discussion based on case study, results from each group are presented (Only one case was discussed in each group: Tirzepatide in Groups 1, 3, and 6; Inavolisib in Groups 2, 4, and 5).

Is there any unclear part about the definition of sensitivity analysis/supplementary analysis in ICH E9 (R1)? Is there any opinion that “this definition is easier to understand ”? Share and discuss any examples of agonizing over ”either sensitivity analysis or supplementary analysis” with the definition in ICH E9 (R1) in mind.

1. Is there any ambiguity in the definition of sensitivity/supplementary analysis in ICH E9 (R1)?

- Definitions and interpretations of sensitivity and supplementary analyses vary by person, making unified understanding difficult.
  - The definition of sensitivity analysis is different between ICH E9 (R1) and observational studies.
  - The guideline do not provide sufficient specific explanations for sensitivity analysis except for the change in the imputation method for missing data, so it is necessary to sort on a case-by-case basis.
- It is difficult to delineate to what extent assumed deviations should be included in sensitivity analyses.
- For supplementary analyses, the definition of “different estimands” is also not specific and there is a range of interpretations.
- Direction of handling of data limitations and measurement precision (e.g., obvious data errors such as ePRO) is unclear.
  - This must be distinguished from addressing data issues that should be addressed by Quality Management.

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2. Is there any opinion that “this definition is easier to understand ”?

- There is an opinion that it is not necessary to strictly separate sensitivity analysis and supplementary analysis.
  - There is no problem if the purpose and positioning of the analysis are clear.
  - It is important to predefine the description of analysis categories and clarify the objectives.
- A suggested definition for clarity on sensitivity analyses:
  - Discussion is required if the results are different from the primary analysis.
  - To be performed when the estimation target remains the same and the assumption of the missing mechanism is different (e.g. Primary Analysis (MAR) vs. Sensitivity analysis (MNAR)).
  - Associated with the evaluation of robustness of analytical results.
- A suggested definition for clarity on supplementary analyses:
  - Even if the results differ from those of the primary analysis, there will be no problem if correct interpretation is possible.
  - To be performed when the estimation target is changed.
  - Analyses including the secondary estimand are part of supplementary analyses.
- Suggestions to complement the definition:
  - Addendum with examples: Understanding is enhanced by providing examples of the sensitivity and supplementary analyses presented in E9 (R1).
  - Explanation of “Positioning of Analysis” and “Objectives” will be added.

Is there any unclear part about the definition of sensitivity analysis/supplementary analysis in ICH E9 (R1)? Is there any opinion that “this definition is easier to understand ”? Share and discuss any examples of agonizing over ”either sensitivity analysis or supplementary analysis” with the definition in ICH E9 (R1) in mind.

3. With the definition in ICH E9 (R1) in mind, are there any examples of situations in which you wonder whether to perform “sensitivity” or “supplementary” analyses?

- Change in strategy in the primary estimand:
  - For example, Case where treatment discontinuation is changed from hypothetical strategy to composite variable strategy.
  - If the estimand changes as the strategy changes, should this be classified as a supplementary analysis?
  - When the handling of ICEs changes, it is difficult to determine the analysis classification.
- Analysis to evaluate the magnitude of unmeasured confoundings in observational studies:
  - It is a difficult point whether the degree of change that effects the conclusion should be a sensitivity analysis or a supplementary analysis.
- Tipping point analysis:
  - Generally utilized as sensitivity analysis but difficult to interpret. It can depend on how regulatory authority assesses.
- Stratified analysis of endpoints with noncollapsible:
  - When the estimand is interpreted as different in the analysis by stratum, sometimes wonder whether it is a sensitivity analysis or a supplementary analysis.
- Changing the analysis set from FAS to PPS is considered to be supplementary analysis.

When major analyses, sensitivity analyses, and supplementary analyses are considered, are there any points that you struggle with and points to note from the viewpoint of analysis and data collection (including points to note in communication with other functions)?

1. Concerns and points to consider in analysis and data collection

- Data collection when treatment policy strategy is applied:
  - If ICEs such as treatment discontinuation are applied, whether related data up to the evaluation time point (e.g., Week 52) can be collected will be assessed in advance.
  - Share clear policies with clinicians and DM regarding required data collection.
  - It is necessary to adjust the range of data collection in consideration of the burden on clinical practice.
- Handling of ICEs and reasons for missing data:
  - Need to enable collection of missing reason.
  - The handling of data outside the acceptable range needs to be specified in advance.
- Securing a data collection system:
  - Considers variability in data collectability due to region, cultural context and study environment.
  - It is required to establish a data collection system based on the characteristics of each trial environment.
- Explanation based on differences in sensitivity analysis/supplementary analysis:
  - If ”primary analysis: hypothetical strategy” or ”supplementary analysis: treatment policy strategy” is set, data collection after treatment discontinuation is required.
  - The explanation of “for supplementary analysis” may be more acceptable than the explanation of “for sensitivity analysis because it gives the impression of acquisition of new information.

When major analyses, sensitivity analyses, and supplementary analyses are considered, are there any points that you struggle with and points to note from the viewpoint of analysis and data collection (including points to note in communication with other funcions)?

2. Points to consider for communication with other functions

- When explaining to non-statisticians, avoid technical terms and carefully communicate the necessity of data collection.
- Use a simple structure to explain that analysis and collection are linked.
- When collecting ICEs on EDC, how to design the form should be discussed with the DM in advance.
- Balances motivation to collect data for additional future analyses with realistic effort.
- The necessary scope will be narrowed down, and the burden of collecting data in clinical practice when additional analyses are required will be considered.

3. Balance between trial design and estimand estimability

- Consistency between target estimand setting and collected data. For example, the hypothetical strategy does not require data after ICEs, whereas the treatment policy strategy need to collect it.
- Since the amount of data to be collected is limited for rare diseases, the data collection of specified events such as ICEs and treatment discontinuation will be prioritized.
- Since overall survival (OS) data are generally collected in the oncology field, there are relatively few concerns regarding data collection through selection of strategy. Designs with follow-up often result in additional required data.

Are you aware of stakeholders (regulators, patients, internal decision makers ･･･) when considering estimands? For example, the primary estimand for continuous data is for regulatory authorities, but the responder analysis performed as a supplementary analysis is for patients.

1. Planning and analysis with awareness of regulatory authorities

- For development intended for the approval, regulatory requirements should be considered first when setting the estimand.
- Specific estimands may be required by regulatory authorities and will need to be addressed through adjustments to the protocol.
- Taking into account differences in strategy between Japan and overseas and analysis required by each regulatory authority.
- Alternative strategies may be used as preliminary options, and agreement with the regulatory authorities is an important part of the study design.

2. Study design considering the patient's (clinical site's) perspective

- Some data collection may be omitted to reduce the burden on patients. It is important to collect necessary and sufficient data in consideration of the status of use in actual clinical practice.
- Include endpoints of QOL and PROs (patient-reported outcomes) will promote patient- and site-focused design.
- For certain diseases (e.g., neurologic diseases), analyses reflecting the patient voice may also be important.
- Supplimentary analyses for clinical practice may be planned and pre-specified to review critical data.
- It may be necessary to design the drug considering the actual use status in actual clinical practice to contribute to treatment selection by physicians.

Are you aware of stakeholders (regulators, patients, internal decision makers ･･･) when considering estimands? For example, the primary estimand for continuous data is for regulatory authorities, but the responder analysis performed as a supplementary analysis is for patients.

3. Study strategy with internal decision makers in mind

- In development, estimands that are acceptable to regulators are often prioritized from the perspective of internal decision makers.
- Consideration is given to incorporating multiple strategies to increase the possibility for future analyses and submissions.
- Someimes there is a gap between the data and analysis needed internally and the needs of clinical practice and regulatory authorities.
- A design is required to clarify the positioning of primary analysis and supplementary analysis and is convincing to multiple stakeholders.

4. Initiatives for balance among stakeholders

- In global studies, the strategy would be unified in Japan and overseas, but complicated adjustments are required in association with it.
- While analyses for regulatory authorities are prioritized, supplementary analyses in consideration of patients and actual clinical use have not been sufficiently considered yet.
- In the case of academia, the goal may be a creation of a published paper, it may not be able to say that aware of stakeholders is enough.

Case study - Background information

	①Tirzepatide	②Inavolisib
Target disease	Obesity (with type 2 diabetes mellitus)	HR+/HER2-/PIK3CA-mutant Endocrine-resistant, advanced or metastatic breast cancer
Design	randomized, double blind, placebo controlled, parallel group	randomized, double blind, placebo controlled, parallel group
Allocation factors	country, sex, type of hypoglycemic agent (classified according to the effect on body weight)	presence or absence of visceral disease, endocrine resistance, and region
Treatment arms	15 mg, 10 mg, and placebo (weekly SC for each)	Inavolisib, Placebo
Primary Endpoint	• Percent change in body weight from baseline to Week 72(focus of discussion) • Achievement of ≥ 5% weight loss at Week 72	PFS (investigator-assessed)
Intercurrent events	• Discontinue investigational drug • (Rescue administration of hypoglycemic agent)	• Anticancer therapies not specified in the protocol before disease progression • Discontinue investigational drug
collecting data	Scheduled visits to collect data after the occurrence of the ICE	Scheduled visits to collect data after the occurrence of the ICE
Example link	https://clinicaltrials.gov/study/NCT04657003	https://clinicaltrials.gov/study/NCT04191499

Case study - Discussion points

①Tirzepatide

No sensitivity analyses have been pre-specified for the key estimand for non-FDA regulatory authorities, if so what are the possible sensitivity analyses?

- Since MMRM is based on the assumption of MAR, an analysis based on the assumption of MNAR as the missing mechanism may be a sensitivity analysis.
- What to think about change of covariates, variance structure of MMRM, the logic of maximum likelihood estimation, the model like ranked ANCOVA ?

For some of the items set out as additional secondary/exploratory endpoints, will the discussion be clearer if they are positioned as supplementary analyses in consideration of their relationship with the primary endpoint?

- Since the primary endpoint is the percentage of weight loss of 5%, the percentage of weight loss of 10%, 15%, 20% may be better positioned as supplementary analysis.
- Is there any disadvantage of using secondary endpoints as the supplementary analysis?

②Inavolisib

What happens if each analysis is reclassified according to the definitions of sensitivity and supplementary analyses in ICH E9 (R1)? There is an opinion from the perspective that "the classification before the change is easier to discuss in papers, CSRs, etc." Also, will reconsideration of the analysis classification affect the discussion/conclusion?

- In this case study, the sensitivity and supplementary analysis for PFS(investigator-assessed) were classified as follows:
  - Sensitivity analysis
    - PFS assessed by BICR
    - Unstratified PFS
    - PFS in patients with *PIK3CA* mutation-positive status
    - Handling of missing scheduled tumor assessments
  - Supplementary analysis
    - PFS based on hypothetical strategy for use of any non-protocol anti-cancer therapy(NPT)
    - PFS based on composite strategy for use of any NPT
- Sensitivity analyses are interpreted for "robustness". How should supplementary analyses be interpreted?