Optimizing Estimands with Optimus

A Perspective on Estimands in Early Development

Presented at the 2023 Basel Biometrics Section Workshop

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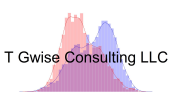
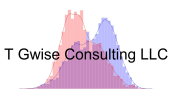
Disclaimer

This presentation is a collection of my thoughts on the utility of the estimand framework for Early Development. The opinions expressed in this presentation are mine alone.



Outline



Estimands in Early Development

Questions for Today

a. When/how to raise awareness of the topic of estimatnds also in early stage development (will it depend on disease area, patient population, endpoint?)

b. What value lies in introducing the language of estimands in protocols and analysis plans in Early Development?

c. Can estimands aid in the goal of dose optimization?

(c.) Can Estimands Aid in the Goal of Dose Optimization?

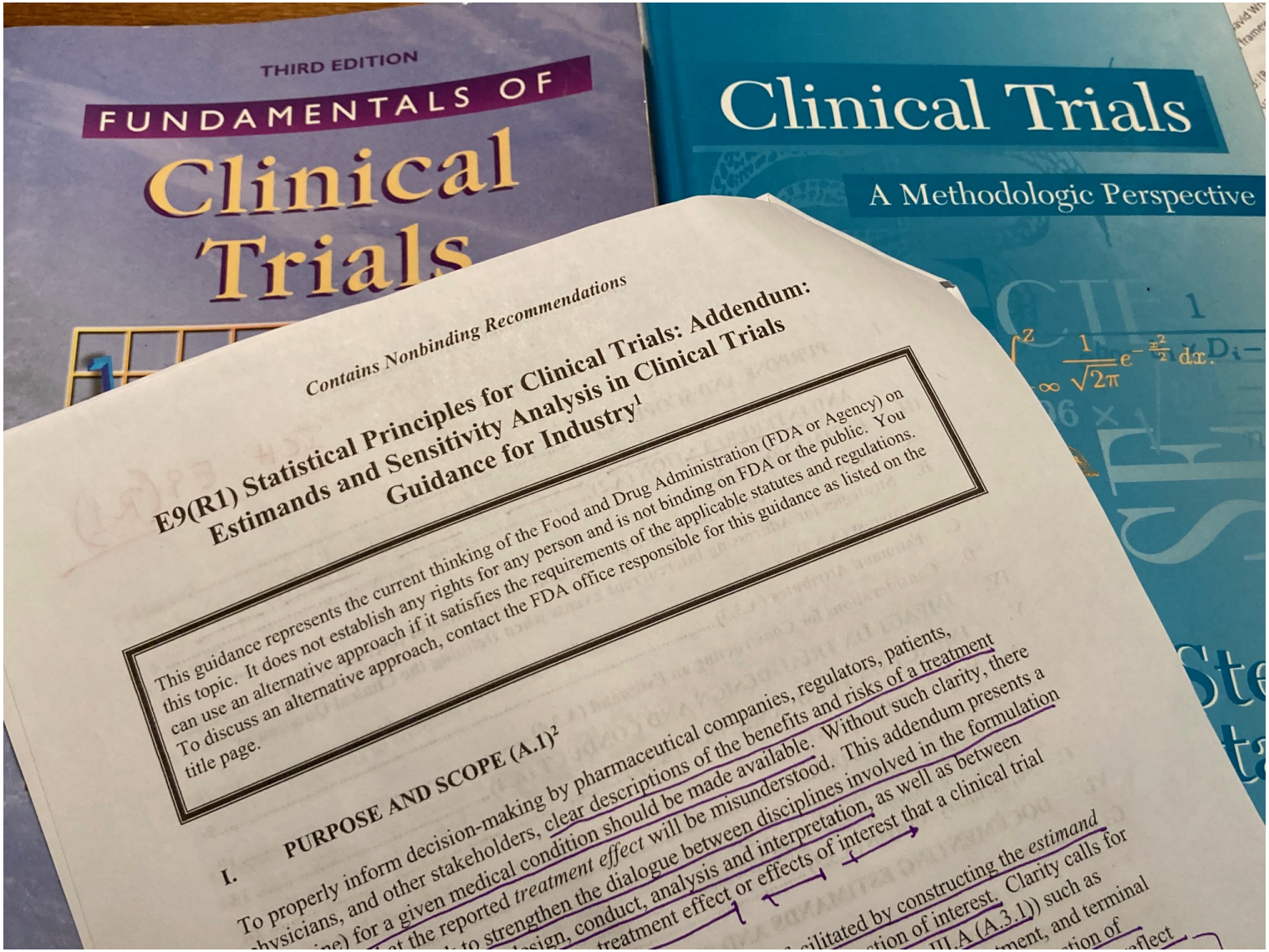
Yes

- ICH E9(R1): *"...The principles outlined in this addendum are relevant whenever a treatment effect is estimated or a hypothesis related to a treatment effect is tested, whether related to efficacy or safety. Although the main focus is on randomized clinical trials, the principles are also applicable for single-arm trials and observational studies. The framework applies to any data type, including longitudinal, time-to-first event, and recurrent event data."*
- Will applying the Estimand Framework always seem as simple as all that?... maybe not, but...

ICH E9(R1), (accessed 13 Oct 2023) https://www.fda.gov/media/148473/download

Familiar Concepts - Different Packaging

with altered statistical argot



E9(R1) Framework

New Barrels for Old Wine

Mitroiu, Rengerink, Teerenstra, Petavy and Roes compared sets of EMA Guidelines, sponsor's trial documents (protocols, SAPs, study reports,etc), and regulatory questions completed prior to the 2017 draft of ICH E9(R1)

- Out of 34 sets of sponsor documents reviewed, 100% included wording and descriptions that could be aligned with all of the estimand attributes in (R1)
- But, those didn't always align with regulators' suggestions.
  - Guidelines recommended treatment policy
  - Sponsors applied hypothetical

Elements of the E9(R1) framework were in guidelines, regulators' questions and sponsor trial documents under different descriptors

[Mitroiu M, Oude Rengerink K, Teerenstra S, Pétavy F, Roes KCB. A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels? Trials. 2020 Jul 23;21(1):671.]

E9(R1) Framework

Promotes Good Design Through Communication

"... a structured framework to **strengthen the dialogue** between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect or effects of interest that a clinical trial should address."

ICH E9(R1), (accessed 13 Oct 2023) https://www.fda.gov/media/148473/download

E9(R1) Framework

What's new *(at time of introduction)*

Defining Estimand as having a set of attributes

- Treatment(s)
- Population
- Variable
- **Strategies for anticipated intercurrent events**
- Population summary

E9(R1) Framework

What's new *(at time of introduction)*

Explicitly Addressing Intercurrent Events

- Declaring what intercurrent events are anticipated and selecting strategies to address them should motivate cross-disciplinary discussions and improve trial quality

E9(R1) Framework

What's new *(at time of introduction)*

Clarifying the Roles of Sensitivity Analysis and Supplementary Analysis

Attempts to motivate more useful sensitivity analyses

- Sensitivity analyses investigate robustness to departure from assumptions for main estimator
- Supplementary analyses investigate different perspectives

Estimand Framework

The **Journey** is [most of] the **Destination**

Project Optimus

Purpose:

"The Oncology Center of Excellence (OCE) Project Optimus is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development. Too often, the current paradigm for dose selection—based on cytotoxic chemotherapeutics—leads to doses and schedules of molecularly targeted therapies that are inadequately characterized before initiating registration trials."

FDA Webpage (accessed 11 Oct 2023)

https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

Project Optimus

Goals include:

- Communicate expectations for dose-finding / -optimization
- Provide opportunities for and encourage drug developers to meet with FDA Oncology Review Divisions early in their development programs to discuss dose-finding and dose optimization.
- Develop strategies for dose finding and dose optimization that **leverage nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials**.
  - An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible.

FDA Webpage (accessed 11 Oct 2023)

https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

Project Optimus

2023 American Society of Clinical Oncology Ann Meeting Poster

FDA Reviewed 13 Years of New Drug Approvals for DO PMRs

- 01 Jan 2010 to 31 Dec 2022
- 138 new molecular entities or original biologics applications
- 24 PMRs were issued to 21 (15%) drugs for dose optimization
  - 18 randomized dose-comparison trials
    - N: ranged from < 100 to > 500, with $11 > 200$ and $4 > 500$
  - 2 non-randomized dose-finding trials
  - food effects and exposure response studies
- Median time to fulfill PMR: 6 years

Dosage optimization in drug development: An FDA Project Optimus analysis of postmarketing requirements issued to repair the cracks. Brian Heiss, Lili Pan, Alemayehu Akalu, Jonathon Vallejo, Joyce Cheng, Pamela Balcazar, Nam Atiqur Rahman, Stacy Shifflett Shord, Mirat Shah, Richard Pazdur, and Marc Theoret Journal of Clinical Oncology 2023 41:16 suppl, 1598-1598 (accessed 13 Oct 2023)

Project Optimus

Recent activity illustrating its importance

A non small cell lung cancer treatment targeting KRAS G12C mutation had received accelerated approval

Data showing similar PK, target saturation, and tumor response rates among patients treated at the dose used in the registration trial and patients treated at lower doses motivated FDA to require a postmarket trial to evaluate lower doses

[Shah M, Rahman A, Theoret MR, Pazdur R. The Drug-Dosing Conundrum in Oncology - When Less Is More. N Engl J Med. 2021 Oct 14;385(16):1445-1447.]

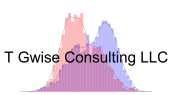
Project Optimus

Recent activity illustrating its importance

PI3Kδ Inhibitors

- 4 drugs approved for relapsed or refractory indolent non-Hodgkin lymphoma or chronic lymphocytic leukemia
- Most indication approvals based on response rate or progression free survival, although several indications were approved based on overall survival
- Ongoing studies produced concerning overall survival data
- FDA brought their concerns to the Oncologic Drug Advisory Committee

Richardson NC, Kasamon Y, Pazdur R, Gormley N. The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint. Lancet Oncol. 2022 May;23(5):563-566.



Project Optimus

Recent activity illustrating its importance

PI3Kδ Inhibitors

"The optimal dose that maximizes efficacy and minimizes safety [concerns] may not have been identified. Across their class, there's been limited dose exploration. Many doses were determined using a maximum tolerated dose, or MTD, approach, with limited exploration of lower dose levels. For each of the approved PI3-kinase inhibitors, there are exposure-response relationships for safety, but exposure-response relationships for efficacy have not been consistently observed. High rates of discontinuation, interruption, and modification also suggest the approved doses may be poorly tolerated. There have been voluntary withdrawal[s] of approval of three PI3-kinase inhibitor indications to date..."
Dr. Nicole Gormely, FDA

21 Apr 2022 ODAC Transcript (accessed 13 Oct 2023) https://www.fda.gov/media/159920/download

Project Optimus

Steps Forward

FDA authors recommend:

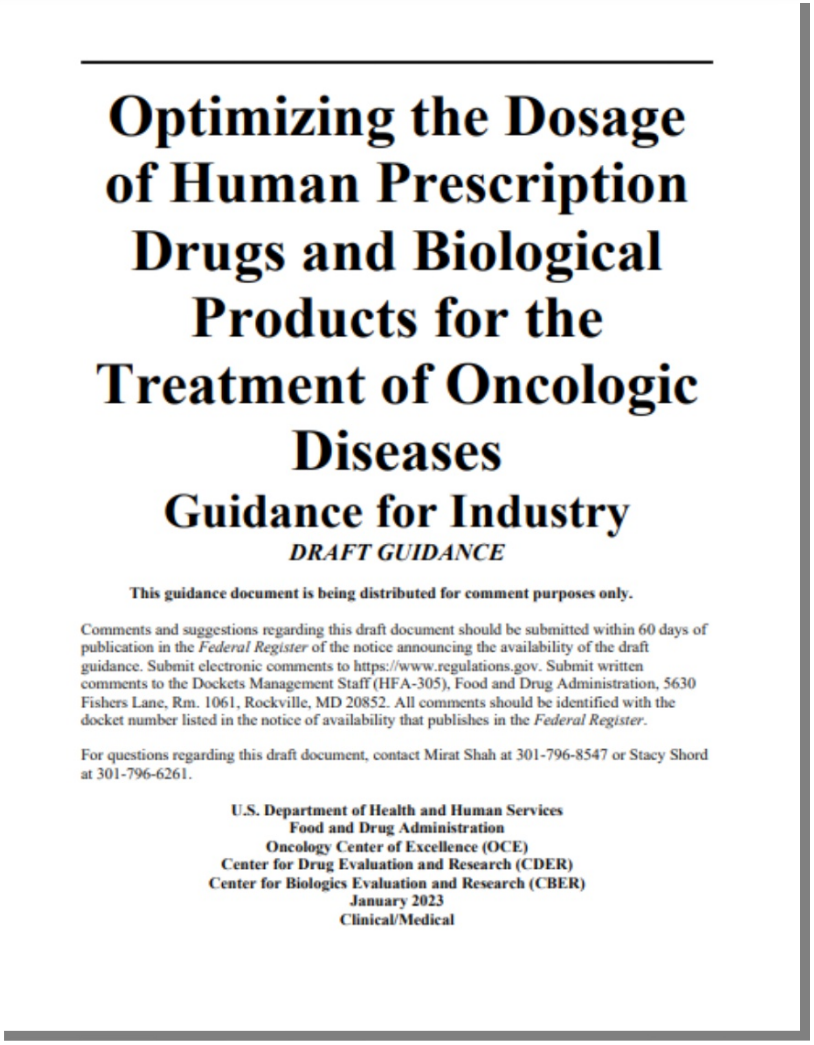
- Early planning for dose optimization strategy
- Endeavor to identify a range of doses for further evaluation after initial dose escalation
- Leverage exposure response modeling for both efficacy and safety
- Consider PD biomarkers as intermediate endpoints
- Use randomized dose trials to evaluate multiple doses
- Leverage adaptive design; Consider seamless development program

Jeanne Fourie Zirkelbach, et al. 2022 Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients Journal of Clinical Oncology 40:30, 3489-3500

Mirat Shah, MD, Atiqur Rahman, PhD, Marc R. Theoret, MD, and Richard Pazdur, MD 2020 How to Get the Dose Right (accessed 12 Oct 2023) https://ascopost.com/issues/may-10-2022/how-to-get-the-dose-right/

Project Optimus

Steps Forward



Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

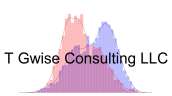
For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

(accessed 13 Oct 2023) https://www.fda.gov/media/164555/download

(b.) What value lies in introducing the language of estimands in protocols and analysis plans in Early Development?

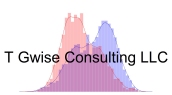
The value of thorough, rigorous pre-study planning...



Conclusion

Estimands to Optimize Optimus

Project Optimus is asking for more thorough dose optimization studies
The estimand framework provides useful tools that can be applied to that end.



(a.) When/how to raise awareness of the topic of estimands also in early stage development (will it depend on disease area, patient population, endpoint?)

Use and Reference ICH E9(R1)...

- ...Whenever an opportunity avails itself
- After all, E9(R1) is published guidance
- The destination is [most of] the journey

-The End-

Thank You

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