Does it Make Sense to Apply the Estimand Framework to Clinical Pharmacology Trials?

Sue McKendrick and Helle Lynggaard,

on behalf of the EIWG sub-team

on Estimands in Clinical Pharmacology and Early Phase Trials

12 June 2023

Estimands in Clinical Pharmacology Trials

Introductions and Disclaimer

	Presenter	Company	Job title
	**Helle Lynggaard** is a key driver in implementing estimands in Novo Nordisk studies. Helle is an active member of many EIWG sub-teams including **Estimands in Clinical Pharmacology and Early Phase Trials**.	novo nordisk®	Principal Statistician
	**Sue McKendrick** leads the cross-functional Estimand Working Group at the PPD clinical research business (part of Thermo Fisher Scientific) and currently leads the EIWG sub-team for **Estimands in Clinical Pharmacology and Early Phase Trials**. She is also a member of the EIWG training team.	PPD® Part of Thermo Fisher Scientific	Statistical Science Director

Disclaimer:

The views expressed by the presenters are not necessarily the views and practices of their employers, or of any of the EIWG member companies

Acknowledging Sponsors and Two Teams (Overlapping Membership)

Bioequivalence Publication Team

”How Estimands can be applied to Bioequivalence and Other Clinical Pharmacology Trials” (in preparation)

- Helle Lynggaard, Novo Nordisk
- Sue McKendrick, PPD
- Mark Baird, PPD
- Essam Kerwash, MHRA
- Vivian Lanius, Bayer
- Florian Lasch, EMA
- David Wright, AstraZeneca

Sponsors

of open access publication

AstraZeneca

novo nordisk®

PPD® Part of Thermo Fisher Scientific

Reviewers

Estimands in Clinical Pharmacology and Early Phase EIWG Sub-team

Agenda

Background

Applying Steps of the Estimand Thinking Process to a Bioequivalence Case Study

Summary and Conclusions

Questions and Comments

Background: Examples of Types of Clinical Pharmacology Trials

Exploratory

- Single-ascending dose (SAD)
- Multiple-ascending dose (MAD)

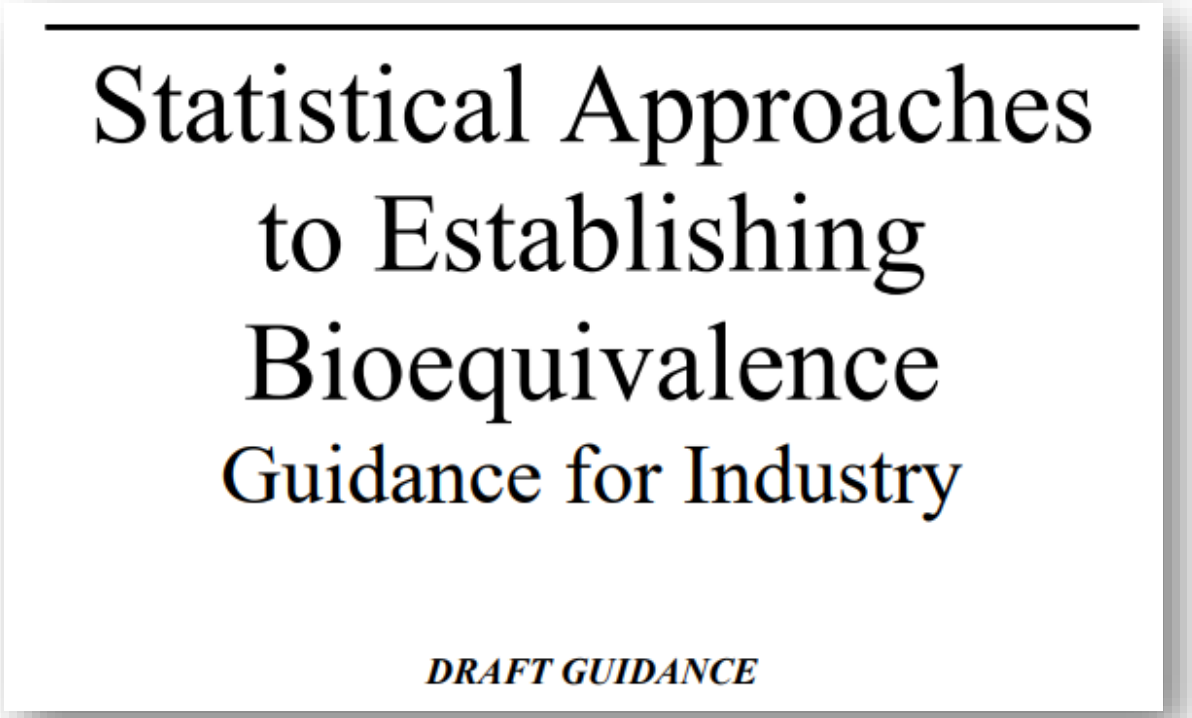
Lots of regulatory BE guidance but estimands not stated!

Confirmatory

- Bioequivalence (BE)
- Drug-drug interaction
- Food effect
- Special populations
  - Renal impaired patients
  - Hepatic impaired patients
  - Pregnant and lactating women

- Concentration - QTc

New FDA Draft Guidance Requires Estimands



Statistical Approaches to Establishing Bioequivalence

Guidance for Industry

DRAFT GUIDANCE

Issued December 2022
https://www.fda.gov/media/163638/download

The ICH (Internal Council for Harmonization) E9(R1) Addendum introduces the concept of an estimand, which is a precise description of the treatment effect reflecting the clinical question posed by a particular study objective.[21] The trial protocol of a BE study should include the following components of an estimand: (1) the treatment of interest and alternative treatment(s) to which comparison will be made: e.g., test drug compared with reference drug; (2) the analysis population for BE assessment; (3) the variable (or endpoint) to be measured for each subject (e.g., AUC or C_{max}); (4) the specification of how to account for intercurrent events in assessing the scientific question of interest (for example, in a comparative clinical endpoint BE study with a binary endpoint, subjects who discontinue study treatment early due to lack of treatment effect should be included as treatment failures); and (5) the population-level summary for the variable to compare between treatment conditions, e.g., the geometric mean ratio of the test to reference drug in a PK BE study.

Bioequivalence (BE) protocols "should include the following components of an estimand"

The Thinking Process of the Estimand Framework

WHAT

1. **Therapeutic setting** and **intent of treatment** determining a **study objective**
2. Identify **intercurrent events**
3. **Discuss strategies** to address intercurrent events
4. Precisely **describe** the **treatment effect** of interest (estimand)

HOW

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 estimand(s)

Resist temptation to skip to HOW

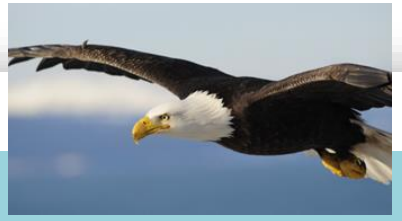
ICH E9(R1) training slides: E9(R1) Training Material - PDF_0.pdf (https://database.ich.org)

Don’t Skip like the Kangaroo, Glide like an Eagle!

The (Estimand) Eagle has sight of the (clinical) landscape and eye for detail

Glides purposefully to its target

Applying Steps of the Thinking Process to a Bioequivalence Case Study



Our "**Eagle Trial**" Case Study takes this clinical setting

Adv Ther (2017) 34:2071–2082
DOI 10.1007/s12325-017-0594-8

ORIGINAL RESEARCH

A Pharmacokinetic Bioequivalence Study Comparing Pirfenidone Tablet and Capsule Dosage Forms in Healthy Adult Volunteers

Lin Pan · Paula Belloni · Han Ting Ding · Jianshuang Wang · Christopher M. Rubino · Wendy S. Putnam

Received: June 12, 2017 / Published online: August 14, 2017

Study designed and published 2017, pre-ICH E9(R1)

Step 1. **Therapeutic Setting and Intent of Treatment Determining a Trial Objective**

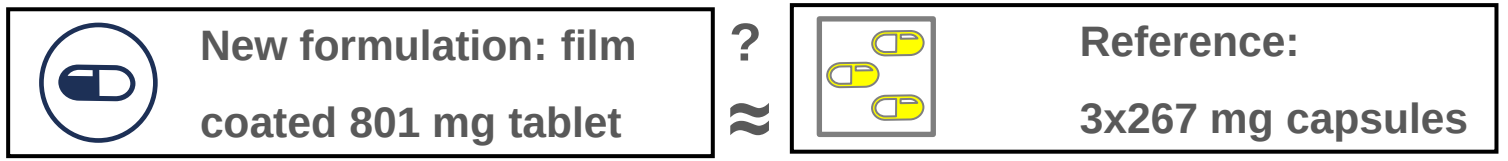
Pirfenidone: an oral anti-fibrotic agent used to treat serious condition of idiopathic pulmonary fibrosis with side effects of nausea, vomiting and rash (poor tolerability, worse when fasted)

Label: advises dosing with food to reduce risk of nausea [only ~60% tolerate 801 mg tid]

Intent of new formulation: convenience of 1 tablet rather than 3 capsules three times per day (similar tolerability and PK expected)

Objective: to evaluate the rate and extent of absorption of pirfenidone of a new high dose tablet formulation of pirfenidone with goal to establish equivalence to three capsules in the fed state

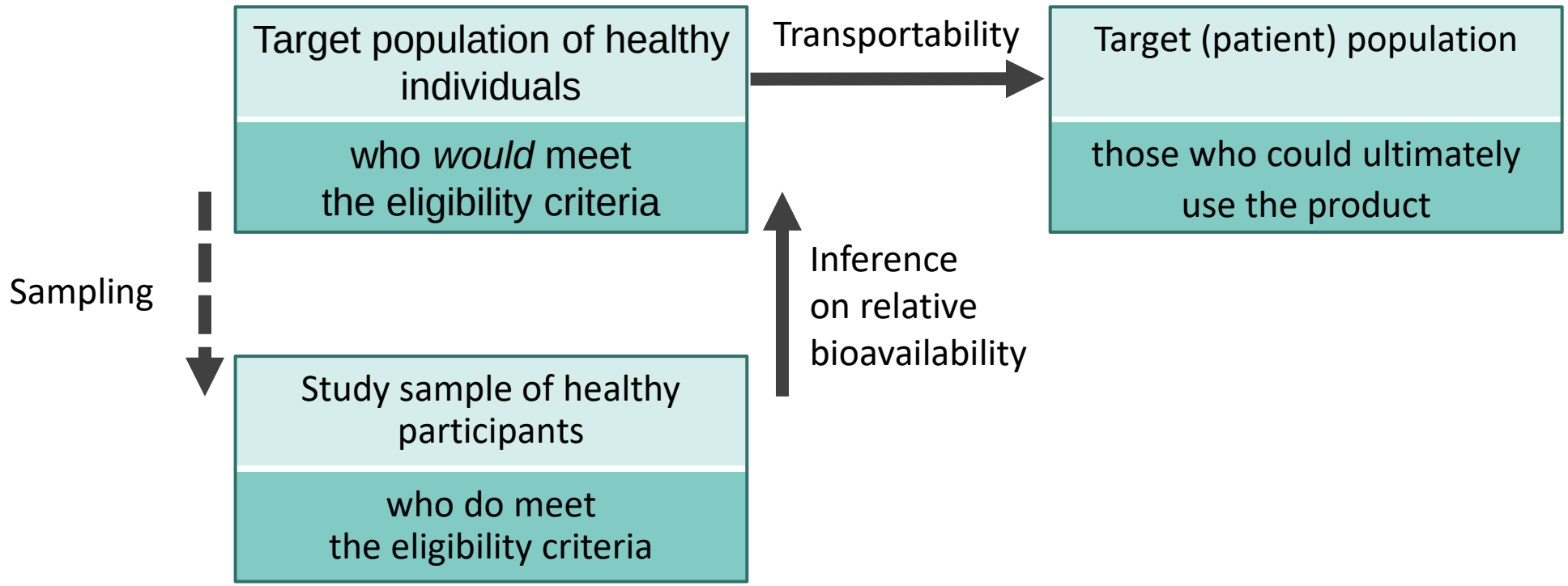
Typical endpoints: $AUC_{0-\infty}$ and C_{max} (single dose)



tid ter in die (three times daily); $AUC_{0-\infty}$ =area under the plasma pirfenidone concentration curve extrapolated to infinity; Cmax =maximum concentration

Study Objective Relates to a Single dose in Healthy Individuals **Transportability** to Multiple Dosing at Steady State in Patients?

EMA guidance: "*In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers*"



Ref: Adapted from Antonio Remiro-Azócar. Target estimands for population-adjusted indirect comparisons. Statistics in Medicine Vol 41, issue 28, December 2022, 5501-5596

Step 2 **Identify Intercurrent events**

Step 3 **Discuss Strategies for Intercurrent Events**

	Hypothetical	Principal Stratum	Treatment Policy	Composite	While on treatment
1. Dosing Deviation	✖				
2. Interacting drugs & substances	✖				
3a. Vomiting & diarrhoea (related)		✖			
3b. Vomiting & diarrhoea (unrelated)	✖				
Discontinuation of subsequent pirfenidone administration: 4a. Tolerability issues (incl. 3a)		✖			
Discontinuation of subsequent pirfenidone administration: 4b. Logistical/ Unrelated Medical incl. 3b	✖				

Step 4. **Construct the estimand**

Estimand attributes to Evaluate Equivalence of New High Dose Tablet Formulation

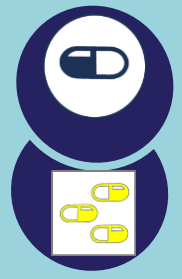
Population-Level Summary

What is the geometric mean ratio (test/reference) of the

Variable

$AUC_{0-\infty}$ (C_{max}) of plasma pirfenidone concentration-time profile

Treatment Conditions

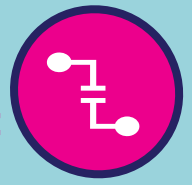


comparing **Test** (1 x 801 mg film-coated tablet) to **Reference** (3 x 267 mg capsules) both as single oral doses administered with food as though dosed correctly, without intake of interacting substances or unrelated intercurrent illness affecting absorption or elimination [1]

Target Population

in healthy adults able to tolerate 801 mg pirfenidone [2]

Strategies for Intercurrent Events

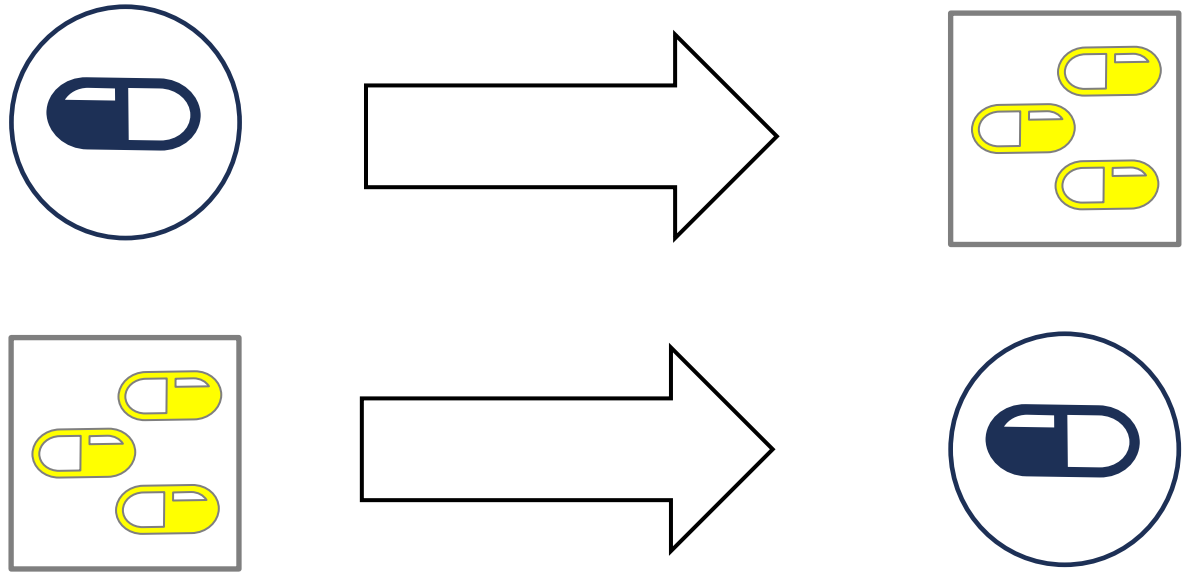


[1] Hypothetical strategy
[2] Principal stratum

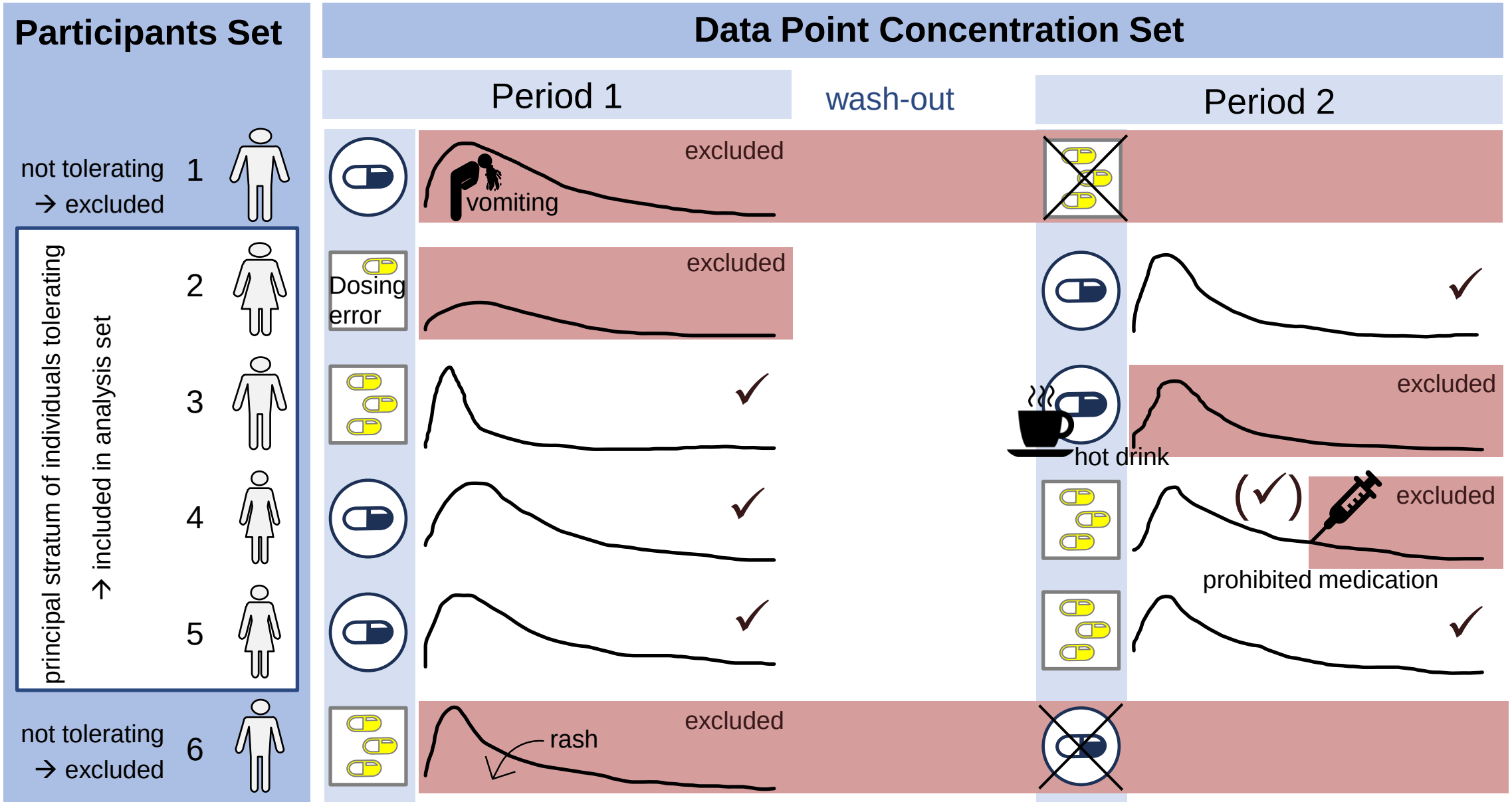
Step 5. **Align Choices on Trial Design, Data Collection and Method of Estimation**

Trial Design

- 2x2 Cross-over in fed state with sufficient washout
- Good trial conduct: controlled conditions + minimize intercurrent events

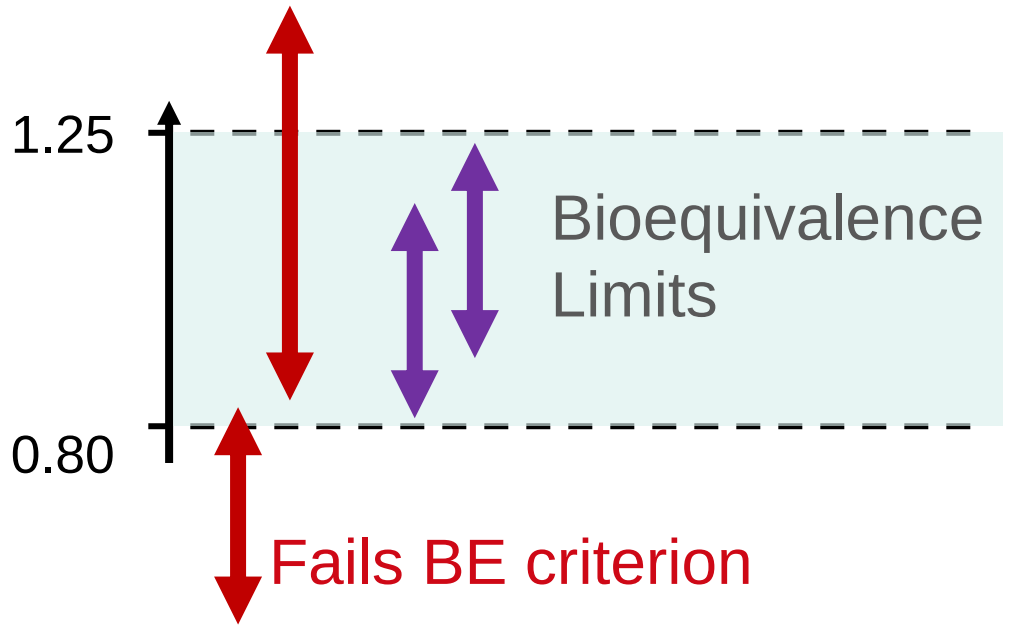


Step 5. continued
Defining Analysis Sets (Participant and Data Point Levels)



Step 5. continued
Method of Estimation

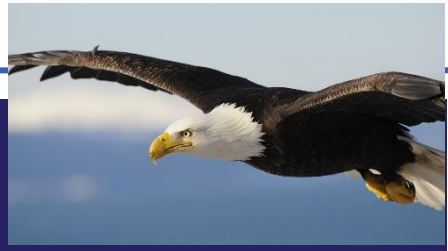
Linear mixed model on log scale with sequence, treatment, period as fixed effects and subject as random effect



Conclude bioequivalent if 90% confidence interval for the geometric mean ratio lies within (0.80, 1.25) BE limits

for both C_{max} and $AUC_{0-\infty}$

Summary and Conclusions
Comparison of Trials



	2017 Trial	"Eagle" Trial
Strategies for Intercurrent Events	Unclear, not considered	Mitigation => controlled trial conduct [1] Hypothetical strategy [2] Principal stratum (can tolerate)
Treatment Conditions	Test and reference formulations administered with food and also fasted	Administered with food only (as per label to improve tolerability)
Design	4-period cross-over	2-period cross-over
Main Estimator	2 Fixed effects ANOVA for fed and fasted separately ("completers")	Mixed model on those who can tolerate (use of more data)
Estimate	90% CI for geometric mean ratio Cmax just missed (0.80, 1.25) limits	Our geometric mean ratios might be different Improved precision (narrower 90% CI)?

Conclusions

Glide like an eagle!

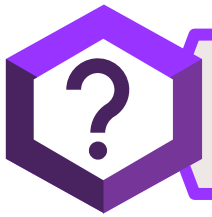
- Regulators place emphasis of ICH E9(R1) guidance on questions which impact labels (includes bioequivalence, drug-drug interactions, food effect…)

- The thinking process adds value to all trials and may impact the proposed design
- Justify transportability: healthy to patient population

- Identify **what** you want to find out before **how**

References

- ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (Effective in EMA 30 July 2020)
- ICH E9(R1) training slides: E9(R1) Training Material - PDF_0.pdf (https://database.ich.org) (accessed 1 November 2022)
- FDA draft guidance: Statistical Approaches to Establishing Bioequivalence (December 2022), https://www.fda.gov/media/163638/download
- Lin Pan, Paula Belloni, Han Ting Ding, Jianshuang Wang, Christopher M. Rubino, Wendy S. Putnam. et al. A Pharmacokinetic Bioequivalence Study Comparing Pirfenidone Tablet and Capsule Dosage Forms in Healthy Adult Volunteers. Adv Ther (2017) 34(9):2071-2082, doi: 10.1007/s12325-017-0594-8



Questions and Comments