Does the Estimand Framework Add Value to Clinical Pharmacology Trials? YES!

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A Walk Through the Thinking Process

of ICH E9(R1)[1,2] with
a bioequivalence (BE) case study[3]

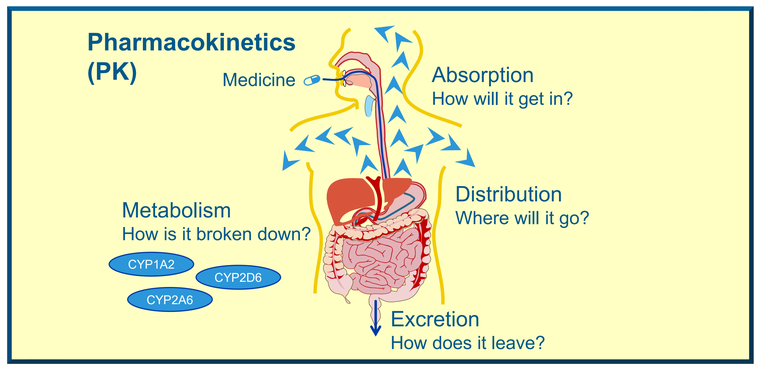
Step 1. Therapeutic Setting and Intent of Treatment Determining a Trial Objective

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)

New formulation: film coated 801 mg tablet ? ≈ **Reference:** 3x267 mg capsules

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

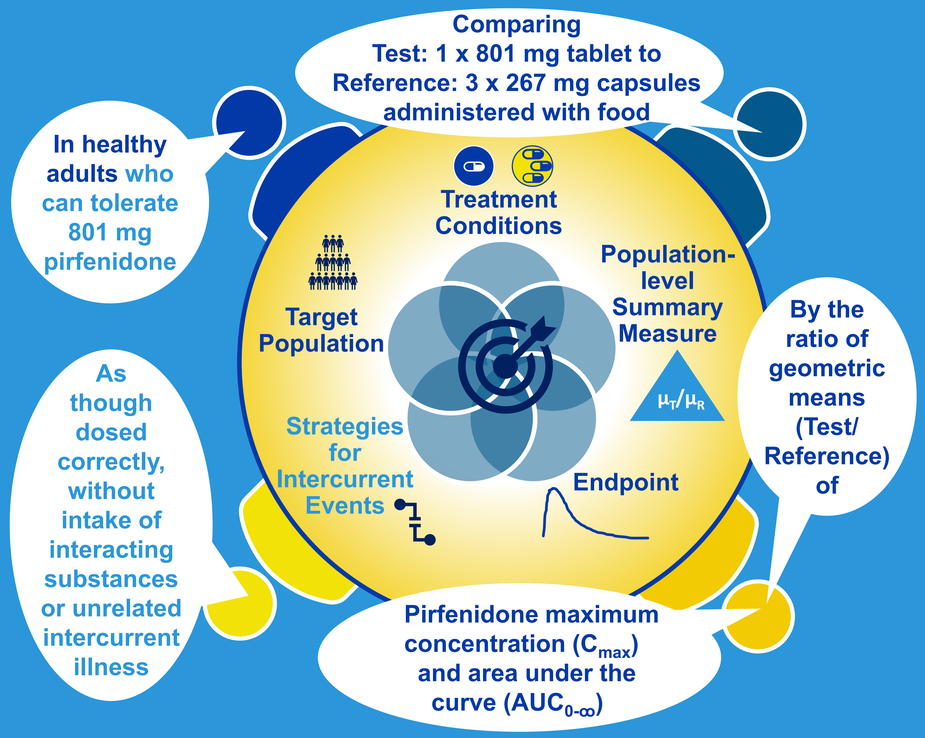
Objective: establish equivalence in the rate and extent of absorption of pirfenidone



Step 2. Identify Intercurrent Events / Step 3. Discuss Strategies to Address Intercurrent Events

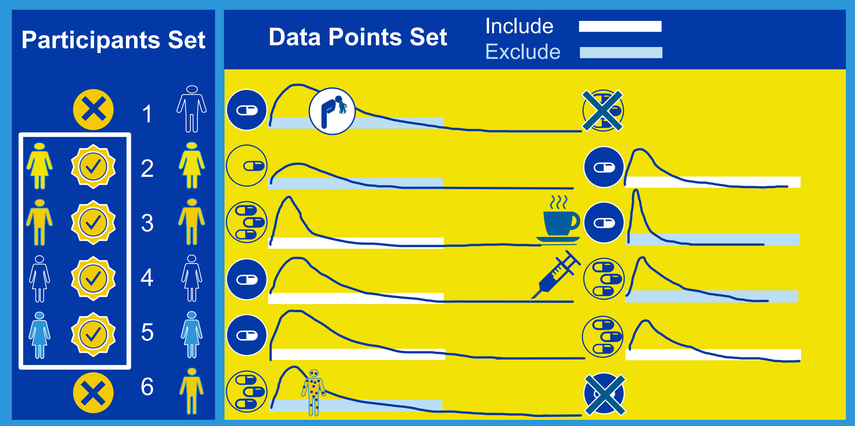
Step 2. Identify Intercurrent Events	Step 3. Discuss Strategies to Address Intercurrent Events
Discontinue due to any tolerability issue (vomiting or rash)	Principal Stratum: adults who can tolerate pirfenidone (dosed with food)
Incomplete dose due to dosing error or tummy bug (vomiting or diarrhoea)	Hypothetical: had the full dose been taken, and without illness impacting absorption
Dosing deviation (e.g. takes drug with hot drink)	Hypothetical: had the drug been taken as directed (with cold water) without impacting dissolution
Interacting drugs or substances	Hypothetical: had the drug been taken without interacting substances

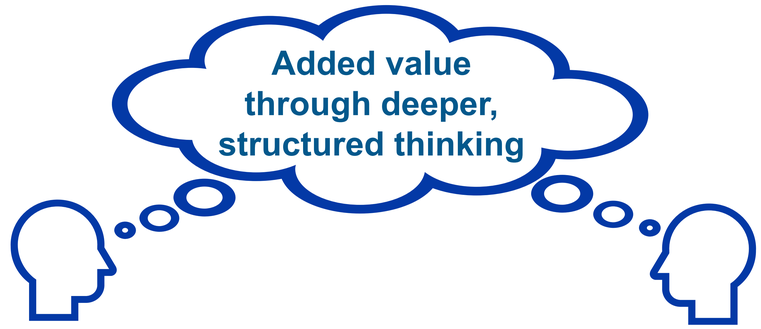
Step 4. Construct the Estimand



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

- 2x2 Cross-over with sufficient washout
- Healthy subjects without use of interacting substances
- Good study conduct: controlled conditions + minimize dosing errors
- Mixed model on log scale with sequence, treatment, period as fixed effects and subject as random effect
- Show 90% confidence interval for ratio of geometric means lies within (0.80, 1.25) BE limits





Step 6. Identify assumptions for the main analysis and suitable sensitivity analyses

- Assume missing PK profiles are missing at random
- Multiple imputation with tipping point to understand the robustness of a BE conclusion

Conclusion

Regulatory guidance in BE[4,5,6,7] would benefit from requiring estimands for clarity, particularly where decisions impact drug approval or labelling:

- Bioequivalence and biosimilarity studies
- Drug-drug interaction studies (at steady state)
- Effect of food studies

Estimand framework can help us to work together better as a team to deliver better science!

Focus on you **what you want to find out (estimand)** before planning how (design and methods)

References

Please see supplementary materials at QR code.

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EFSPI European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe