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THE PER PROTOCOL PRINCIPLE

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Intention to Treat

- Randomization
- Treatment policy
- Analysis set
- What we do now

Randomization

- Comparisons of all patients randomized are valid
- Comparisons of nonrandomized subsets may be confounded
  - Epidemiologists do them all the time, but …
  - They're hard, and …
  - Results may be controversial

Treatment Policy

- Noncompliance is a fact of real life as well as of trials
- Physicians (regulators, payers, etc.) should take this into account and consider all patients to whom the drug is prescribed
- But what real life? (representativeness)
- And I'm not a physician!

Analysis Sets

- Full Analysis Set ≈ ITT
- Per protocol = something else
- In E9, but …
- Not useful
  - because analysis of PP data set is not PP analysis

What We Do Now (ITT)

- "Outcome" studies: treatment policy
- "Symptom" studies
  - Don't retrieve dropouts
  - Pretend to know what "would have" happened
  - This is …
    - An exquisite compromise, or …
    - An unholy mess

Per Protocol

- Not randomization?
- Not treatment policy?
- Not ITT analysis set?
- Not what we do now!

Not Randomization

- Obviously undesirable
- May be inevitable, but …
  - Requires addressing confounding
  - Still subject to uncertainties

Not Treatment Policy

- Maybe desirable
- Depends on
  - Disease
  - What happened

What Happened?

- Death
- Lost to follow-up
- Consent withdrawn
- Adverse event
- Lack of efficacy
  - Rescue?
    - Per protocol or
    - Pace protocol
- Violation of entry criteria

- Could be “per protocol” or not
- Could be “missing” or not

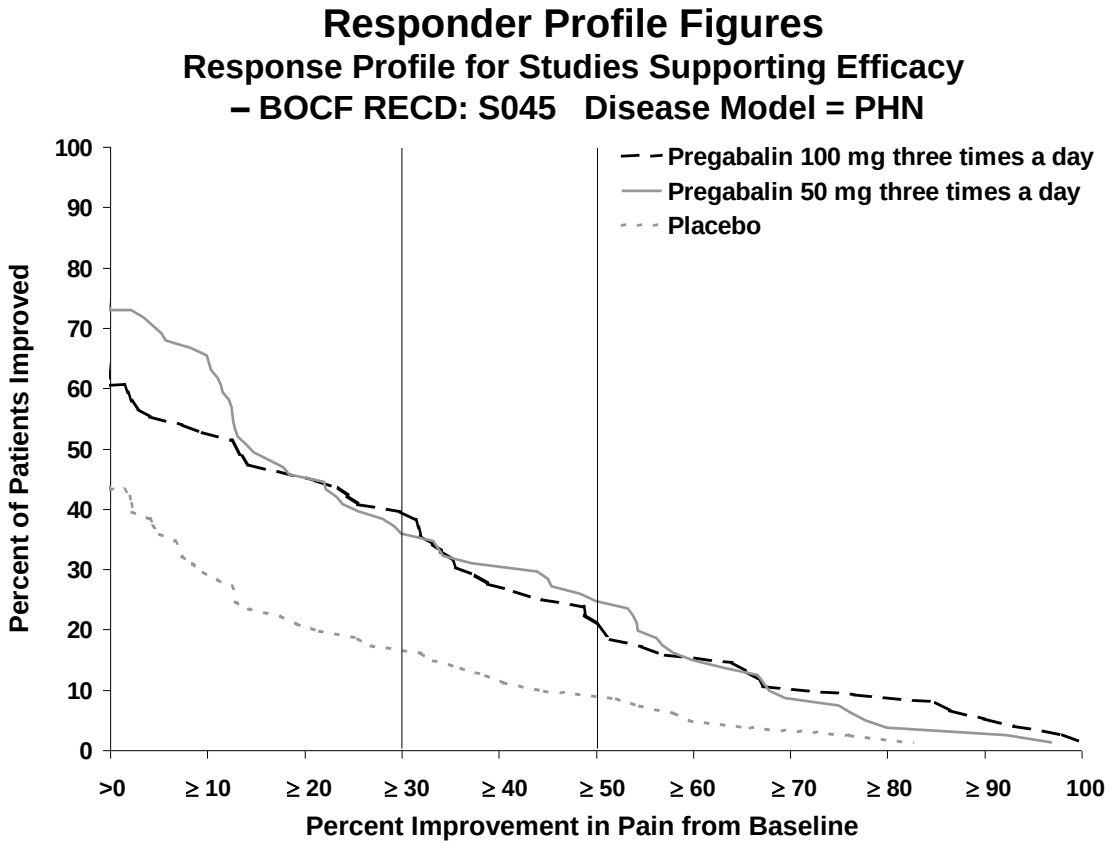
What Can We Do?

- Treatment policy
- Transformed or composite endpoint
- Counterfactual
- Stratification

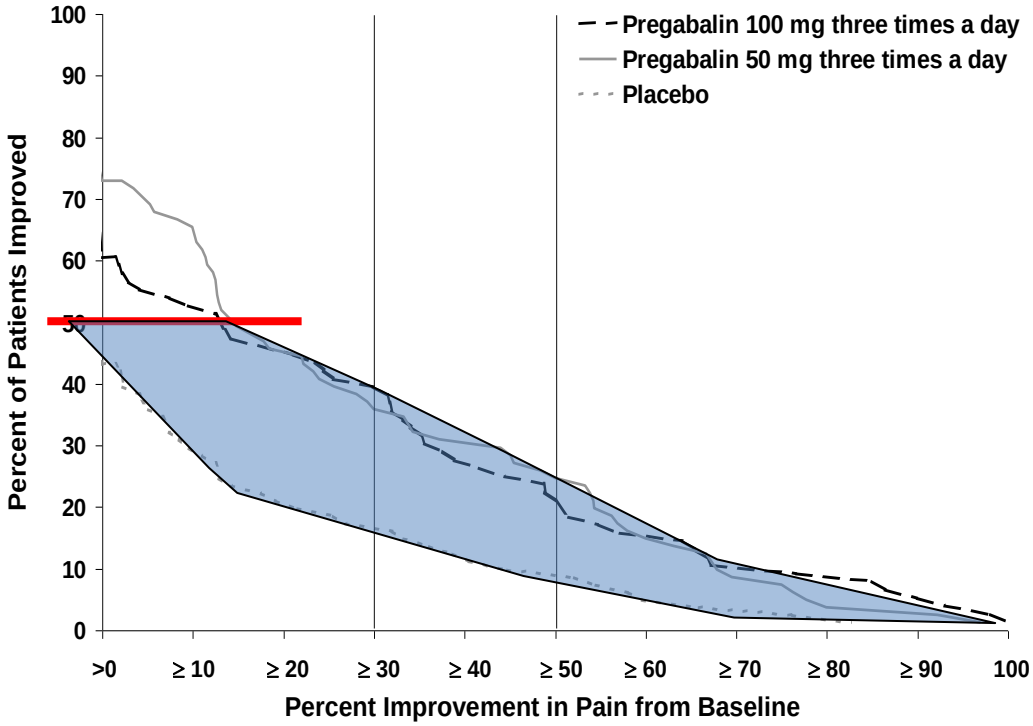
Transformed/Composite

- While on treatment
  - "Endpoint" is not endpoint
    - Palliation at end of life
  - Be careful with surrogates for long-term use
    - Smoking cessation
- Median or trimmed mean

Cumulative Responders (ECDF)



Difference in Trimmed Means



Median or Trimmed Mean

- Uses all data
  - Including the fact of dropout!
- But finds effect among tolerators
- Does not “dilute” treatment effect
  - But does follow randomization principle!

Counterfactuals

- If all patients tolerated the drug
- If my grandmother had wheels
- If we hadn't given rescue medication
  - Hard but meaningful
  - Reference-based imputation is promising
    - I.e., unrescued patients would be like *placebo* patients
    - But not like placebo *completers*

Stratification

- What is the effect in completers?
- There is no such thing
- Because the effect is both
  - To change the outcome in some completers
  - To change who is a completer
- That is, completer analysis is subject to confounding, even in randomized trials

Confounding

- Can be dealt with (epidemiology!)
- But it's hard
- Even in randomized trials
- More important than prespecification
  - But that's important

Summary

- What happened?
- Death
- Lost to follow-up
- Consent withdrawn
- Adverse event
- Lack of efficacy
  - Rescue?
- Violation of entry criteria

- What can we do?
  - Treatment policy
  - Transformed or composite endpoint
  - Counterfactual
  - Stratification