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 \approx 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- Consent withdrawn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)

Resonder Profile Figures
Response Profile for Studies Supporting Efficacy
– BOCF RECD: S045  Disease Model = PHN

- Pregabalin 100 mg three times a day
- Pregabalin 50 mg three times a day
- Placebo

Percent Improvement in Pain from Baseline

Percent of Patients Improved
Difference in Trimmed Means

- Pregabalin 100 mg three times a day
- Pregabalin 50 mg three times a day
- Placebo
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