Impact of proposed study development framework on clinical trial practice

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Outline

- **A brief look at current trends / issues in each of the study development steps**
  - **Objectives – driven by decisions**
  - **Estimands**
  - **Design**
  - **Analysis**
  - **Sensitivity**

Different Decisions & Perspectives

Stakeholders	Types of Clinical Trials
• Regulators • Payers • Physicians • Patients • Sponsors	• Exploratory vs. confirmatory vs. post-approval • Short-term vs. long-term treatment • Symptomatic treatment vs. disease modification • Efficacy vs. safety • In-patient vs out-patient

General Categories of Objectives

- **Compare treatment A vs treatment B**
- **Compare treatment policy A vs policy B**
  - **Begin with treatment A vs begin with treatment B**
  - **Treatment A + rescue vs Treatment B + rescue**

Current ICH E9 Recommends ITT

"The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given.

It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment."

Intention to Treat

- **Primary focus of ITT in ICH E9 was on which patients to include, not as a means of dealing with missing data**
  - **Including post-rescue data does reduce the number of missing values**
- **ICH E10 states that need for rescue is an endpoint**
- **Today's more nuanced discussion of estimands compelled an update to E9**
- **That is a sign of significant progress!!!**

Rescue Medication Considerations

- **Post-rescue data in an ITT analysis can mask or exaggerate effect of originally assigned med**
  - **Post rescue data not included for treatment objectives**
  - **When data after rescue are included inference is on treatment policy / regimen**
- **Availability of rescue should not influence adherence to initial treatments - but this is a concern in placebo controlled / blinded trials**
  - **On blinded med X% chance on placebo**
  - **On rescue med 0% chance on placebo**

General Trends

- **Objectives**
  - **ITT should not be followed blindly, but deviations should not be taken lightly**
  - **Pre-approval**
    - **Symptomatic endpoints: treatment objectives often more relevant**
    - **Hard endpoints: treatment policy more prevalent – ethical need for rescue**
  - **Post-approval, policy objectives increase in relevance**

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General Categories of Estimands

- **Efficacy**
  - **Benefit of the drug when taken as directed**
- **Effectiveness**
  - **Benefit of the drug as actually taken**
  - **Conceptually, a composite of efficacy and adherence**
- **More general categorization (safety outcomes)**
  - **De-jure: When taken as directed**
  - **De-facto: As actually taken**

Fundamental Considerations

- **De-jure estimands**
  - **What to expect if patient hadn't stopped / switched**
  - **Counterfactual for group; assess as if all patients adhere when in fact some do not**
  - **Valid estimate of what to expect if patients adhere – the majority**
  - **In order to give proper directions, must assess what happens if taken as directed**
  - **Regulators generally do not accept as primary**

Pharmaceutical Statistics; DOI: 10.1002/pst.1765

Fundamental Considerations

- **De-facto estimands**
  - **Counterfactual for individual patients**
  - **Mixture of adherent and non-adherent – each patient is one OR the other, not a mix**
  - **Valid estimate of what to expect for the group**

- **Strengths and limitations for each category**

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General Trends

- **Estimands**
  - **Diverse stake holders. Often Important to assess multiple estimands in a trial**
  - **Greater focus on de-jure early (Ph2), shifting to de-facto later (ph3)**
  - **Those making decisions about groups favor de-facto, those making decisions about individuals favor de-jure**
  - **Discussing estimands can be cumbersome, we risk over-complicating things**

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Design Considerations

- For de-jure estimands, maximizing adherence
  - Improves sensitivity – reduces probability plausible departures from MAR overturn result
  - Does not influence parameter values
- For de-facto estimands, maximizing adherence
  - Influences parameter values
    - With NRI, If dropout reduced by design, fewer fail & treatment is more effective
  - If means to maximize adherence in trial are not feasible in practice, generalizability of results may suffer

Design considerations

- **Missing data can be minimized via design and / or conduct**
- **NRC guidance provided designs to minimize missing data, often entail trade-offs (e.g., patient population)**
- **Altering trial conduct to minimize missing data - especially loss to follow up – may involve fewer trade-offs**

General Trends

- **Design**
  - **Minimizing loss to follow up and capturing detailed reasons for discontinuation are key**
  - **Pragmatic / real world estimands best evaluated from pragmatic real world designs where adherence decisions are generalizable to clinical practice**
    - **Placebo and blinding**

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Common Analyses – dealing with intercurrent events

- **1) Treatment policy – So-called ITT**
- **2) Composite - modified definition of the variable (or the summary measure) with inter-current event(s) a component of the outcome**
- **3) Hypothetical - specific hypothetical conditions of interest; e.g.,**
  - **Outcome if no inter-current events**
  - **Outcome if patients could be followed without treatment after discontinuation of randomized treatment**

Other Analyses of Interest

- **Principal strata - restrict population of interest to the stratum of patients in which an inter-current event would not have happened.**
- **While on treatment - values of the variable up to the time of the inter-current event**

Considerations for Composite Analyses

- Unifying principle: if patients don't adhere they don't benefit
- Implicitly assumes adherence decisions approximate clinical practice
- Key is how to quantify "no benefit"
- Dropout = failure: NRI, mNRI, BOCF
  - No missing data
  - Assumes no spontaneous improvement
- Controlled imputation approaches
  - Use placebo as definition for no benefit

General Trends

- **Analyses**
  - **For composite endpoints,**
    - **mNRI and controlled imputation approaches gaining popularity**
    - **Handle different reasons for dropout differently**
      - **Bad outcome for LOE, AE, L/fu**
      - **MAR for administrative reasons**
    - **If dropout is informative, it may convey different information depending on the reasons for dropout**

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General Approaches for Assessing Sensitivity to Departures From MAR

- **Compare results from multiple (MNAR) models**
  - **Inferences difficult because results may differ because both models wrong, 1 wrong, chance differences** (Statist Med. DOI: 10.1002/sim.6753
- **Add a sensitivity component or parameter(s) to the primary analysis** Ther Innov & Reg Sci 48(1): 68-80.
  - **Vary sensitivity (MNAR) parameter(s) within the primary analysis model**
  - **Tipping point and plausible worst case approaches**

“Controlled Imputation” Family

- **MI and likelihood-based approaches**
- **General idea is to use knowledge from dropout to create relevant departures from MAR**
  - **Reference based – Plausible worst case**
    - **Jump to reference, copy reference, copy increment from reference** J Bio pharm Stat 23:1352-1371
  - **Delta adjustment – Tipping point or plausible worst case** Clinical Trials with Missing Data. (2014). Wiley, Chichester
    - **Conditional (sequential)**
    - **Marginal**

Delta Adjustment Methods

- **Conditional (sequential, visit-by-visit)**
  - **Subtract a constant (delta) from visit X imputed value that then further influences imputed values at visit > X**
    - **First missing visit only** **(diminishing effect)**
    - **All missing visits** **(accumulating effect)**
- **Marginal**
  - **Complete all imputations then add delta** **(constant effect)**

Delta Adjustment Frameworks

- **Plausible worst case**
  - **Choose a meaningful delta (e.g., average treatment effect)**
  - **If results significant after delta adjustment, conclude results are robust**
- **Tipping point**
  - **Progressively increase delta until primary analysis is overturned**
  - **If value required to overturn significance is not plausible results are robust**

General Trends

- **Sensitivity**
  - **Key is to assess departures from assumptions – typically MAR**
  - **Delta adjustment and reference-based imputation are useful sensitivity analyses**
  - **Incorporate sensitivity into sample size determination**

Summary

- **The study development framework is**
  - **useful**
  - **influencing practice**
- **We have made a lot of progress!!!**