Missing Data in Clinical Trials: Challenges and Recent Developments

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NOVARTIS

Outline

- Introduction
- Case Study
- Traditional Methods
- Principled Methods and Scientific Questions of Interest
- Case Study Revisited
- Remarks
- Conclusions

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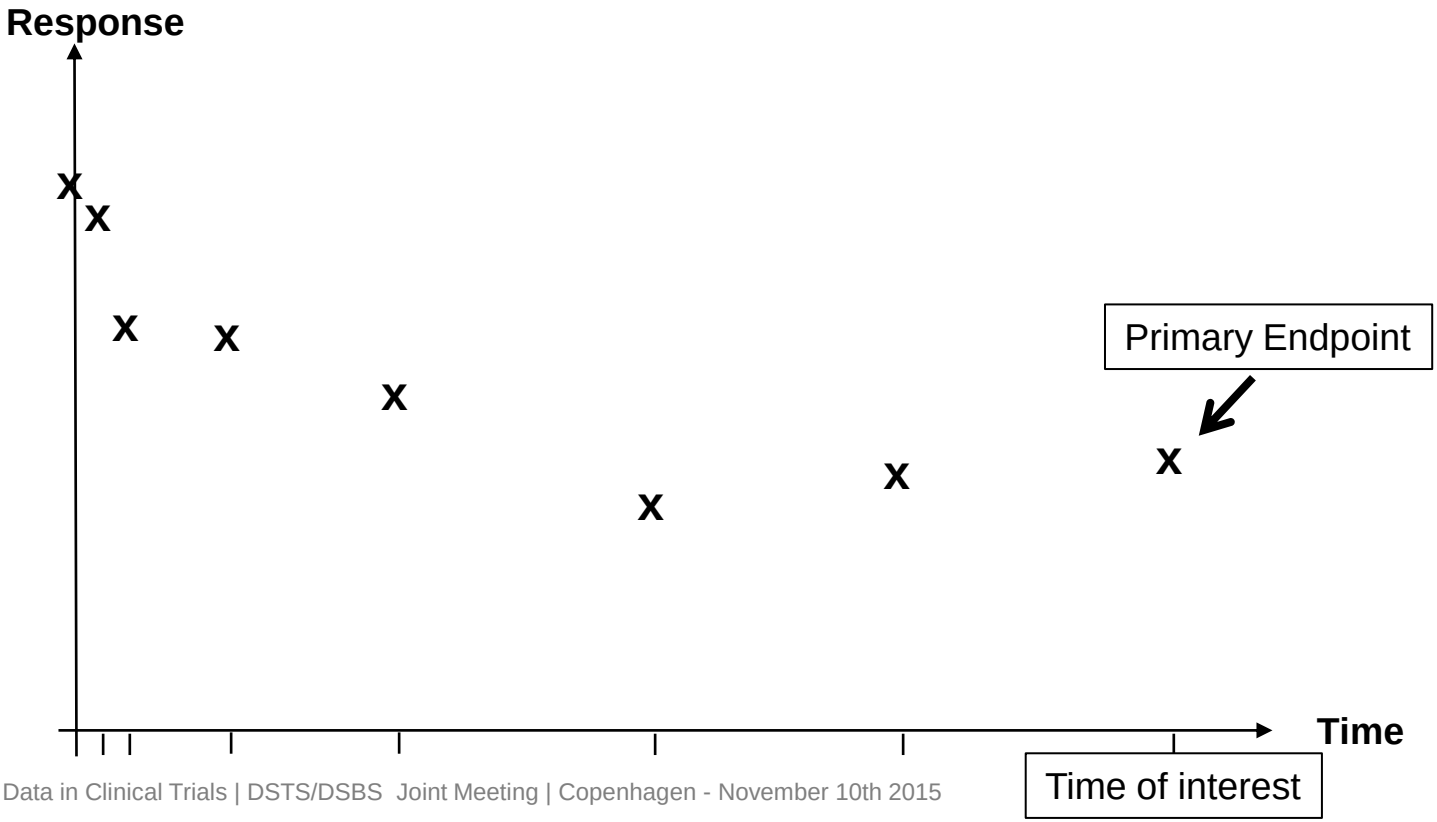
Missing Data

Frequently encountered across all development phases

In a clinical trial context, missing data are data we intended to collect, but for one reason or another did not.

Patients may skip a single visit or drop out/discontinue from the study such that the primary endpoint of interest is missing.



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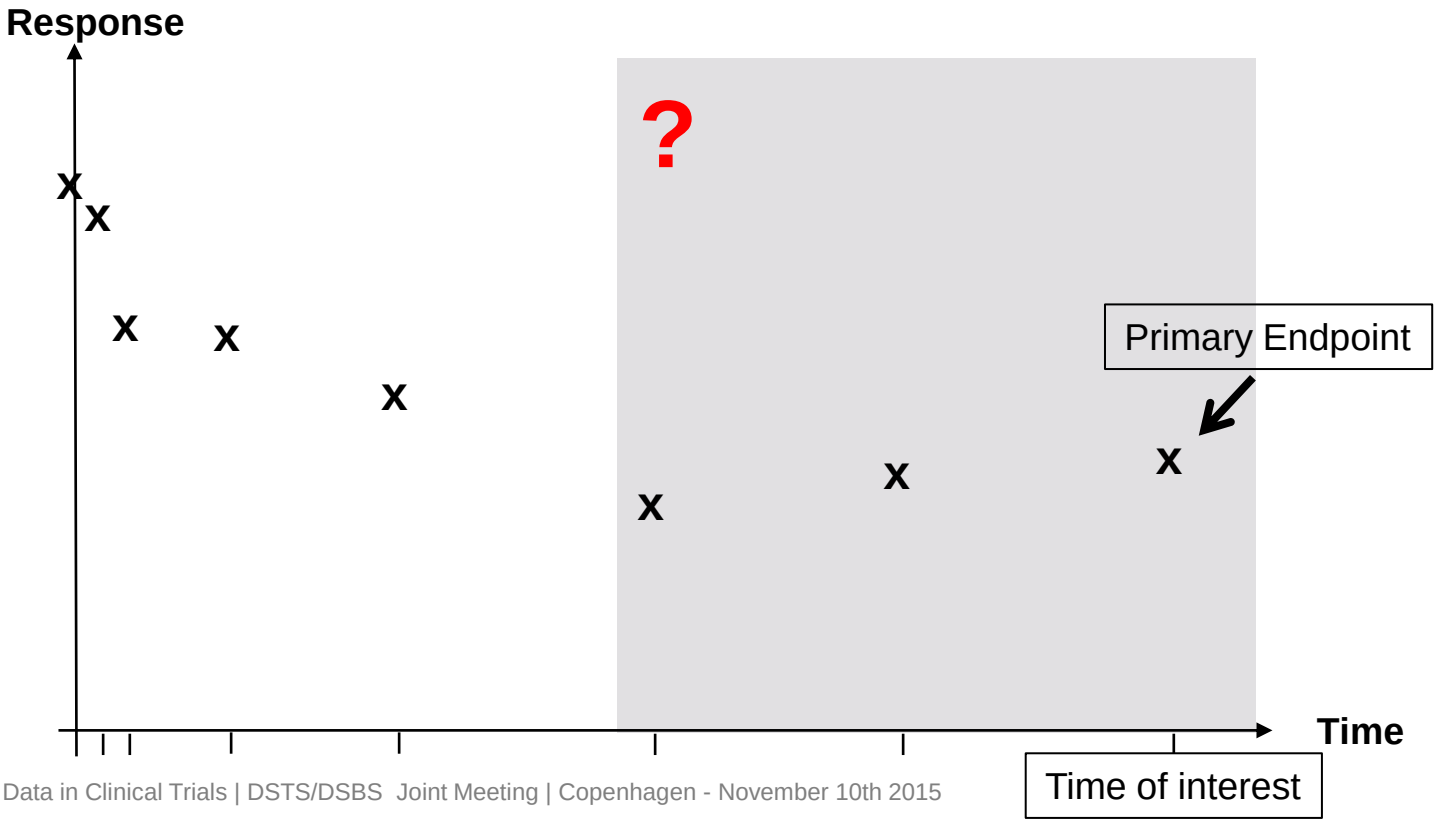

Examples for Reasons of Missing Data

Primary endpoint may be missing because of

- lack of efficacy
- patients consider themselves to have fully recovered
- unacceptable adverse event
- practical or administrative reason (e.g. patient moves away)

} Problematic as related to efficacy or safety

The following are special cases

- patients are not able to perform a test (e.g. 6 minute walking test, 6MWD)
- patients die

which should ideally be considered as components of the endpoint, e.g.

- If clinically meaningful, assign 6MWD= 0 meters for patients that cannot walk
- When patient die we may
  - Consider cause-specific death as primary endpoint (e.g. cardiovascular death)
  - Fold death into another outcome to form a composite endpoint (e.g. CV death or heart failure hospitalization)
  - Consider questions such as: “What would the outcome be, had the patient not died?”

(Indication specific)

Missing Data are a Critical Factor in the Regulatory Assessment

REUTERS

US FDA staff cite missing data for J&J's Xarelto

May 21, 2012

U.S. drug reviewers said Johnson & Johnson's blood thinner Xarelto appeared to reduce the risk of new heart attacks and strokes in people with heart problems, **but missing data raised doubts about whether the drug actually worked.**

- Drug for acute coronary syndromes (ACS)
- 12% of patients had incomplete follow-up
- Cardiovascular and Renal Drugs Advisory Committee voted against recommending approval: 6 to 4 (with one abstention) against recommending Xarelto for ACS
- FDA followed the recommendation of the advisory committee and did not approve the drug for ACS

Missing Data are a Critical Factor in the Regulatory Assessment

US FDA staff cite missing data for J&J's Xarelto

May 21, 2012

Comments by 3 advisory committee panelists:

- "Were there not questions about loss to follow-up and missing data, it would have been a yes."
- “It’s not the question about what happened with the data we have, but the bigger question is what happened in the patients with the missing data.”
- “There was enough uncertainty in the robustness and quality of the data that dissuaded me from voting yes... The 'missingness' of the data doesn’t invalidate it, but it certainly makes it hard to infer.”

Missing Data may compromise Randomization

- Randomization is needed to achieve comparable groups such that differences between groups must be due to treatment
- If subjects that drop out are excluded from the final analysis, it may create important systematic differences among groups
  → complete case analyses (CCA) are potentially biased
- For example, consider 2-arm comparison where
  - many active arm patients with poor outcomes drop out;
  - no placebo arm patients drop out;
  - treatment effect estimate based on 'completers' is larger than in reality.
- Maintain comparable groups by including every subject who is randomized regardless of drop out

Question: How to include a subject for whom the primary endpoint is missing?

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Case Study in COPD

Chronic Obstructive Pulmonary Disease

AIM: Evaluate the efficacy of an investigational treatment compared to placebo as measured by the change in 6-minute walk distance (6MWD) from baseline to 24 weeks

- Randomized, multinational, double-blind, placebo controlled study
- 200 patients with COPD were randomized
- **Measurements:**
  - 6MWD at baseline and every 4 weeks thereafter
  - Various covariates

Missing Data Pattern for Primary Endpoint

Reason for Drop-Out	Active Arm	Placebo
Adverse events	**27 (26%)**	7 (7%)
Abnormal laboratory values	1 (1%)	0
Unsatisfactory therapeutic effect	1 (1%)	**5 (5%)**
Subject withdrew consent	2 (2%)	1 (1%)
Administrative problems	0	1(1%)
Death	2 (2%)	2 (2%)
Protocol Deviation	0	1(1%)
Discontinued	34 (**33%**)	17 (**17%**)
Completers	69 (67%)	81 (83%)
Total	102	98

- Large proportion of discontinuation
- Imbalance in dropout rates
- Most patients discontinue for reasons that are associated with safety or efficacy
- **What is the impact on conclusions that can be drawn from such data?**

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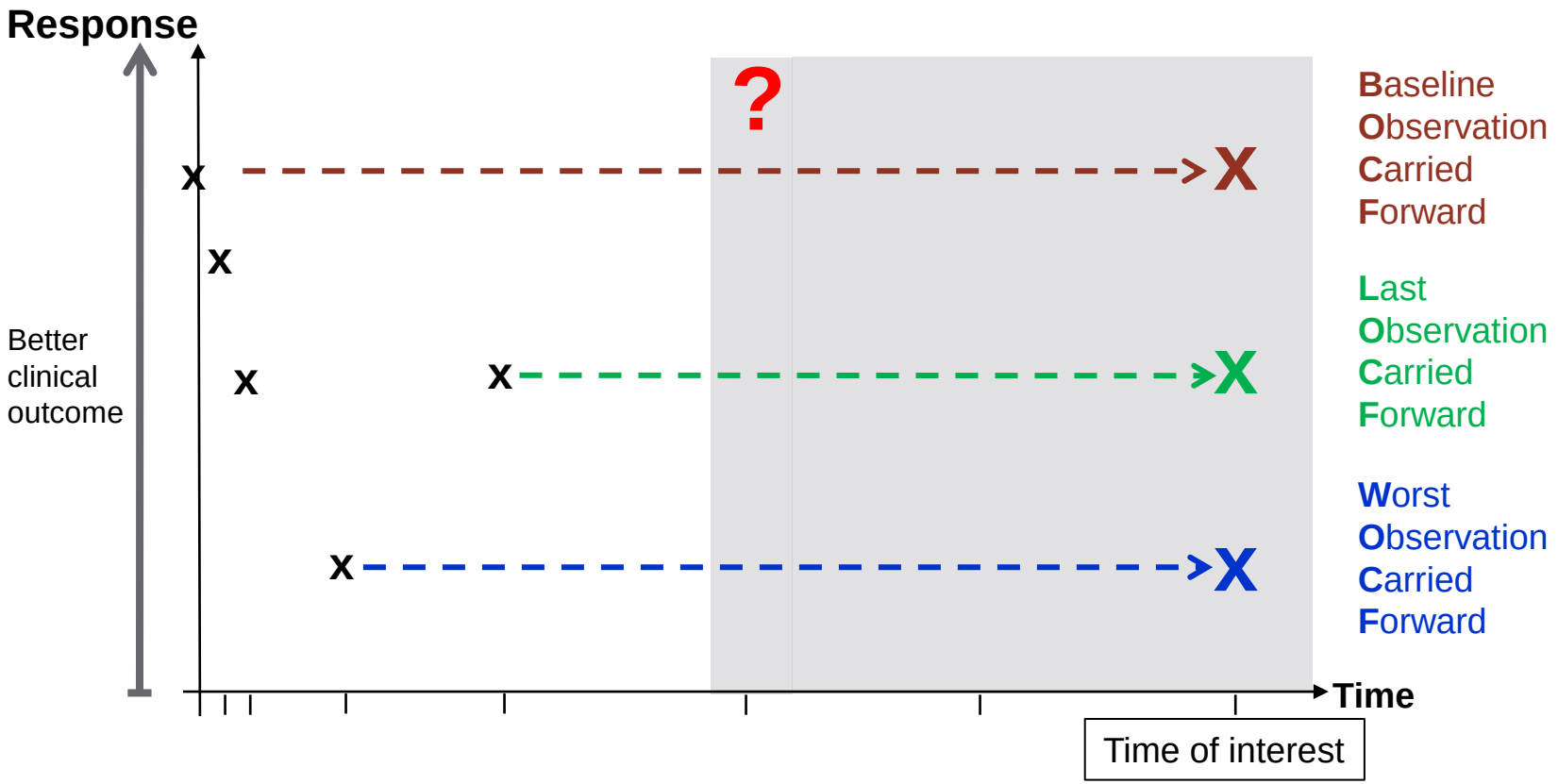
Single Imputation Techniques

AIM: Evaluate the efficacy of an investigational arm compared to placebo as measured by the change in 6-minute walk distance (6MWD) from baseline to 24 weeks



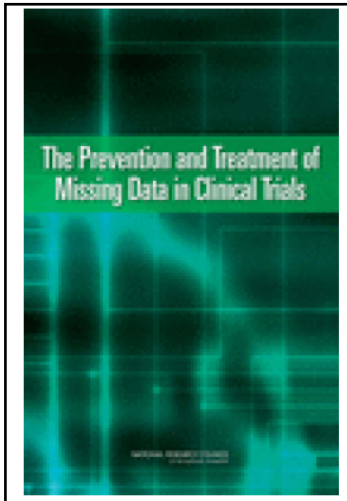
Health Agency Views

Single Imputation Techniques are no longer acceptable

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 July 2010
EMA/CPMP/EWP/1776/99 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Missing Data in Confirmatory Clinical Trials



Commissioned by the FDA

The Prevention and Treatment of Missing Data in Clinical Trials

Panel on Handling Missing Data in Clinical Trials; National Research Council

ISBN: 0-309-15815-X, 162 pages, 6 x 9, (2010)

Health Agency Comments on LOCF

Negative view on LOCF

- **FDA [2012]:** "[...] you proposed to apply LOCF approach to impute missing data. In general, this approach is not acceptable because it assumes that patient outcome does not change after dropout."
- **FDA [2013]:** "[...] using the LOCF method for dealing with missing data is no longer recommended by the Division [...], please specify a primary statistical analysis that does not rely on LOCF and that is in line with NAS recommendations."
- **CHMP [2013]:** "[...] the adequacy of the LOCF approach is particularly questionable, since [...] cannot be assumed as being stable over time, hence contradicting the LOCF assumption. Furthermore it is known that deterministic imputations may bias the variance estimates downward."

Health Agency Comments on LOCF

Negative view on LOCF

Are there alternative approaches that enable using all randomized patients and all observed data in a 'better' way?

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Yes, but we will always need to make assumptions on the 'missing data' / post-discontinuation behavior

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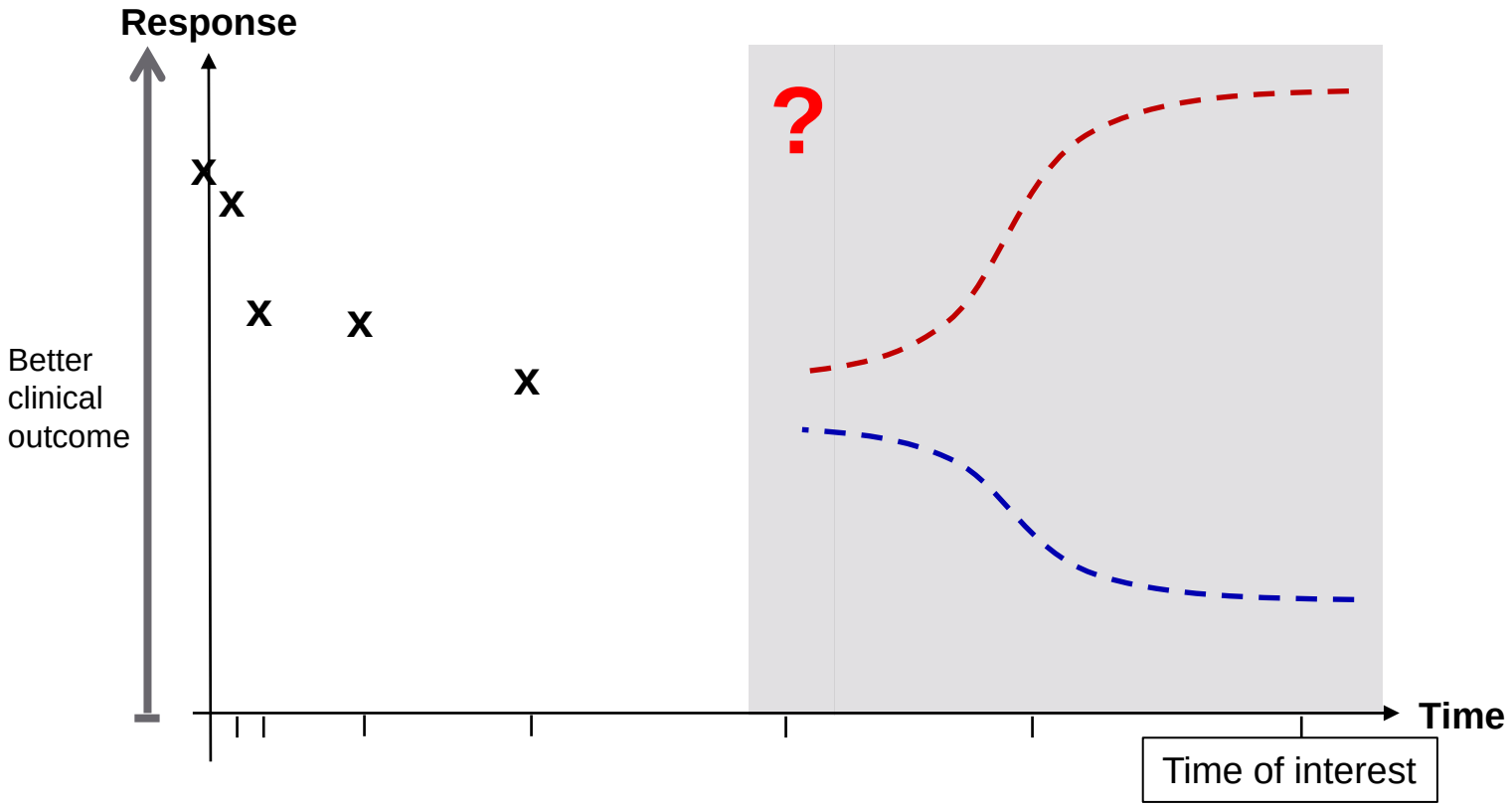


Yes, but we will always need to make assumptions on the ‘missing data’ / post-discontinuation behavior

What are plausible assumptions?

Plausible assumptions have to match the scientific question of interest!

Handling of missing data is not solely a statistical issue.

Time of interest

Scientific Question of Interest

Ambiguity in the presence of missing data

- "What would the treatment effect be, had patients that discontinued stayed in study and behaved like other similar patients in the same treatment arm?"
  - Similarly:
    - What is the effect assuming patients stay in study withstanding all the rigors (including adverse events)?
    - What is the benefit of the drug if taken as directed?
- "What would the effect seen in practice be, if this treatment were assigned to the target population?"
  - Similarly:
    - What is the benefit of the drug, taking (among others) into account that patients who cannot tolerate the drug will discontinue the drug?
    - What is the benefit of the drug as actually taken?

Scientific Question of Interest

Illustration based on the case study

Recall: 26% of patients in the active arm drop out due to adverse events. In particular, it is known that patients discontinue the study drug after dropping out from the study.

What is the benefit of the drug if taken as directed?

- Hypothetical question of effect had patients that dropped out continued taken the treatment.
  - Dependent on the reason of discontinuation this may be a more or less plausible question to ask.

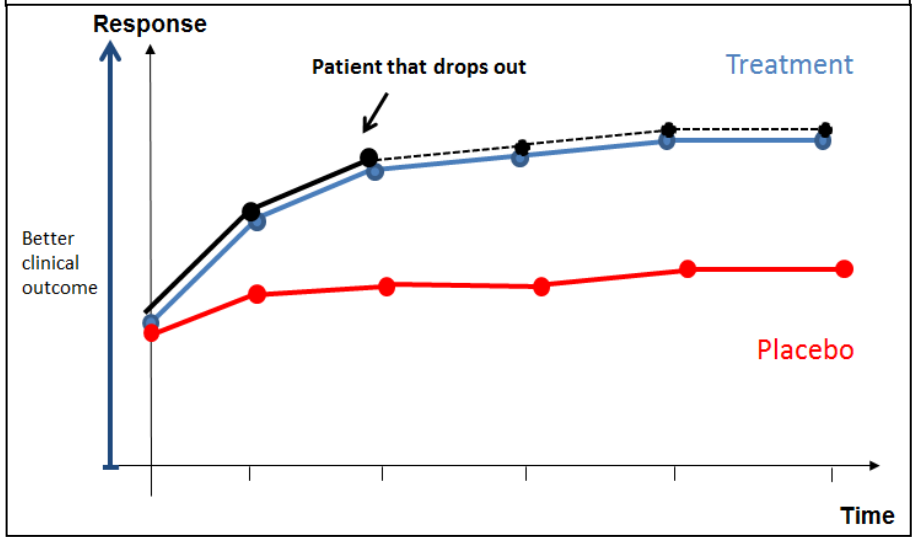
What is the benefit of the drug as actually taken?

- Question of effect taking into account that patients stop treatment after dropping out.
  - For non-disease modifying drugs, the treatment effect may be attenuated after treatment is stopped.
  - Ideally, post-treatment discontinuation data are available to assess this question.

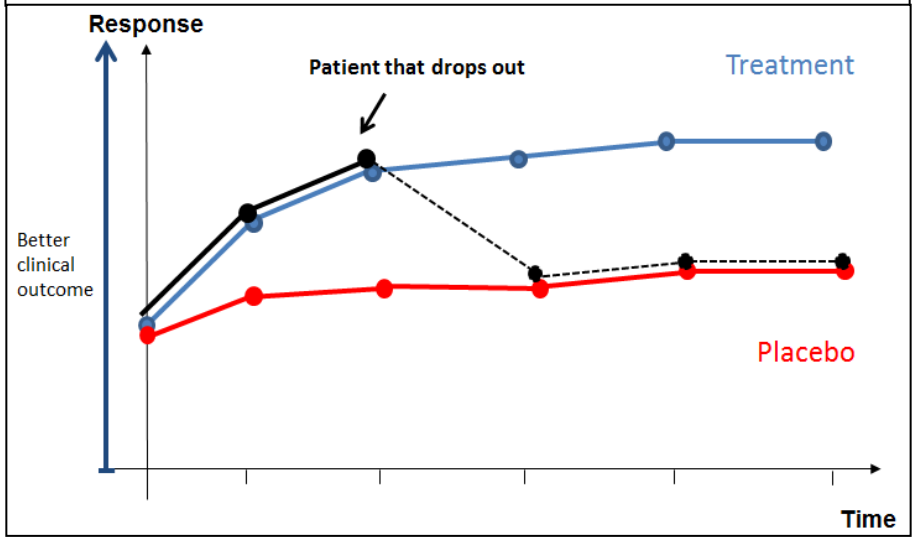
Different scientific questions require different assumptions* on post-discontinuation behavior

Recall: 26% of patients in the active arm drop out due to adverse events. In particular, it is known that patients discontinue the study drug after dropping out from the study.

What is the benefit of the drug if taken as directed?



What is the benefit of the drug as actually taken? (assume effect lost after drop out)



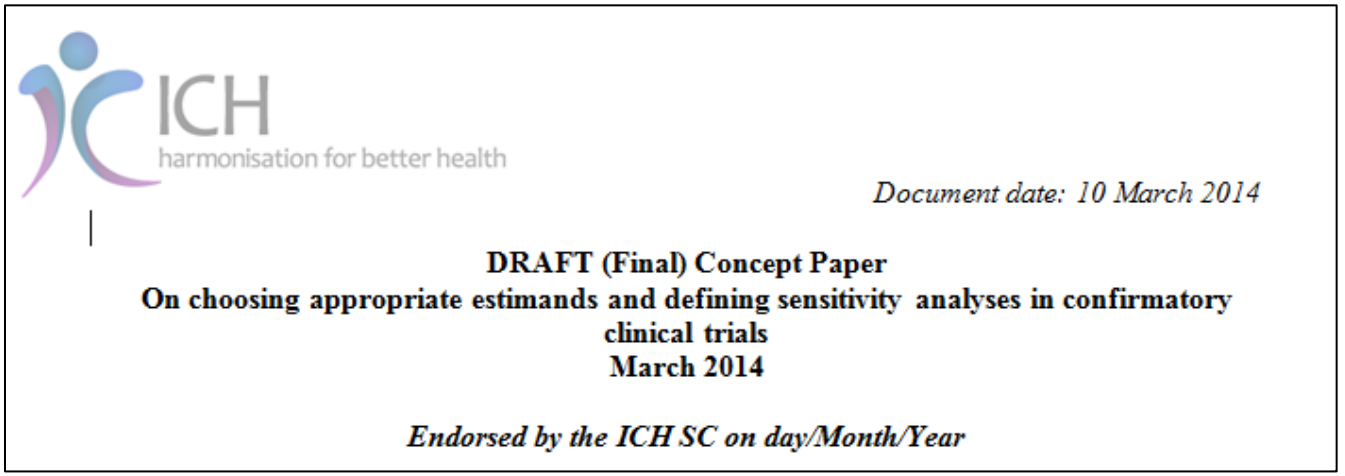
*The assumptions may vary for different reasons of discontinuation.

Scientific Question of Interest

Estimands

- Formulating the scientific question at the beginning is critical.
- This can be challenging in the presence of missing data or other post-randomization events, e.g. treatment switching.
- Currently the scientific question is often not stated very clearly
  - Primary objectives rarely state which assumptions are made if the primary outcome is not observed
- The National Academy of Science therefore introduced the concept of *Estimand* = “What is being estimated?”
- An addendum to the ICH E9 is currently being developed to introduce the estimand framework more formally in the clinical trial context.

ICH-E9 Addendum


ICH
harmonisation for better health

Document date: 10 March 2014

DRAFT (Final) Concept Paper
On choosing appropriate estimands and defining sensitivity analyses in confirmatory clinical trials
March 2014

Endorsed by the ICH SC on day/Month/Year

- A working group was tasked to create the addendum (first meeting held in Nov 2014)
- Members include representatives from the regulatory bodies and industry associations across the ICH regions
  - EMA, MHRA, EFPIA, MHLW/PMDA, JPMA, FDA, PhRMA, Health Canada
- Addendum likely to be released for public comments in 2016

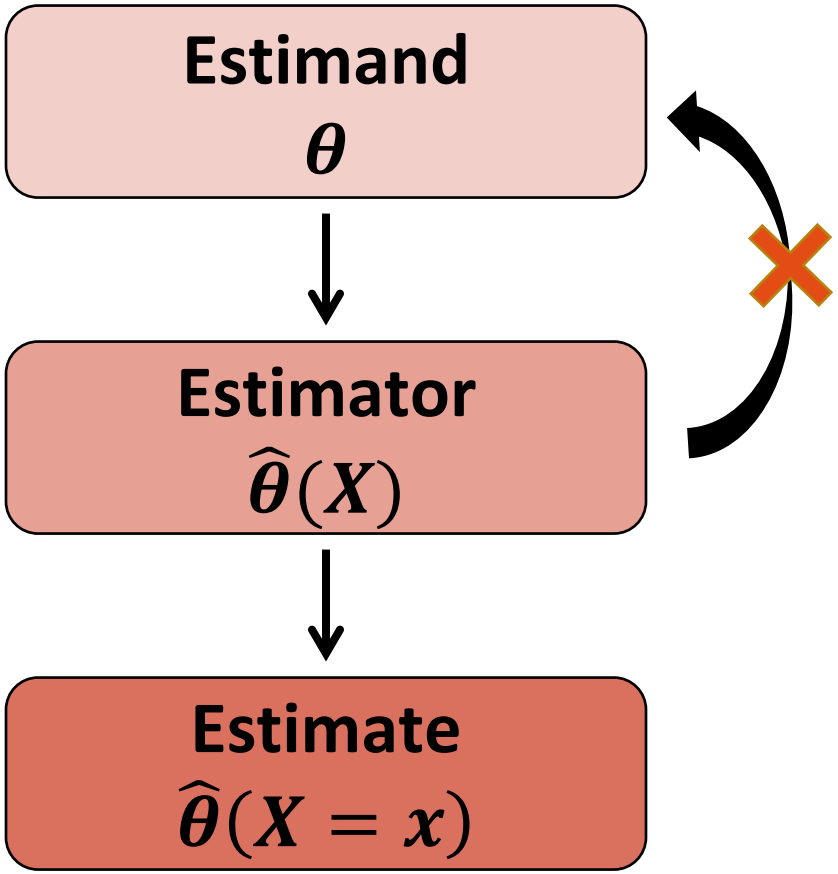
Distinguish ‘target of estimation’ and ‘method of estimation’

Estimand framework helps distinguishing between

- target of estimation (estimand)
- method of estimation (estimator)

Especially in the context of ‘missing data’ the estimand and method of estimation are often confused.

However, the estimand framework applies to a broader setting than missing data.



Scientific Questions of Interest

Commonly discussed 'estimands' in the presence of missing data

- "What would the treatment effect be, had patients stayed in study and behaved like other similar patients in the same treatment arm?"
  - Related terminology used in this context:
    - Per Protocol
    - Efficacy
    - De Jure
    - 'Missing at Random'
- "What would the effect seen in practice be, if this treatment were assigned to the target population?"
  - Related terminology used in this context:
    - Intention-to-Treat effect
    - Effectiveness
    - De Facto
    - 'Missing not at Random'

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Common Assumption underlying Principled Methods

'Missing at Random' (MAR) or more precisely 'ignorability'

"What would the treatment effect be, had patients stayed in study and behaved like other 'similar patients' in the same treatment arm?"

For a given patient,

- information from the own observed history and
- information about the future from other similar patients (same history, treatment and other covariates)

can be used to provide information about the missing data.

In particular: The future behaviour of dropouts can be modelled using future behaviour of 'similar patients' that remain in the same treatment arm, i.e. also treatment behaviour is borrowed.

Principled Methods under MAR / ignorability

Use all available measurements (history and relevant covariates) for a given patient and account for the added uncertainty due to missing data.

- Direct Likelihood Approaches
  - Repeated measures analysis which jointly models the repeated measurements on a given subject
  - Missing data are not explicitly imputed
- Multiple Imputation (MI)
  - Same as above but missing data are explicitly imputed
  - In contrast to single imputations, each missing value is replaced by several imputations thus accounting for uncertainty due to missing data
  - Auxiliary information can be incorporated more naturally than with direct likelihood approaches

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Principled Methods

'Missing not at Random' (MNAR)

"What would the effect seen in practice be, if this treatment were assigned to the target population?"

For a given patient,

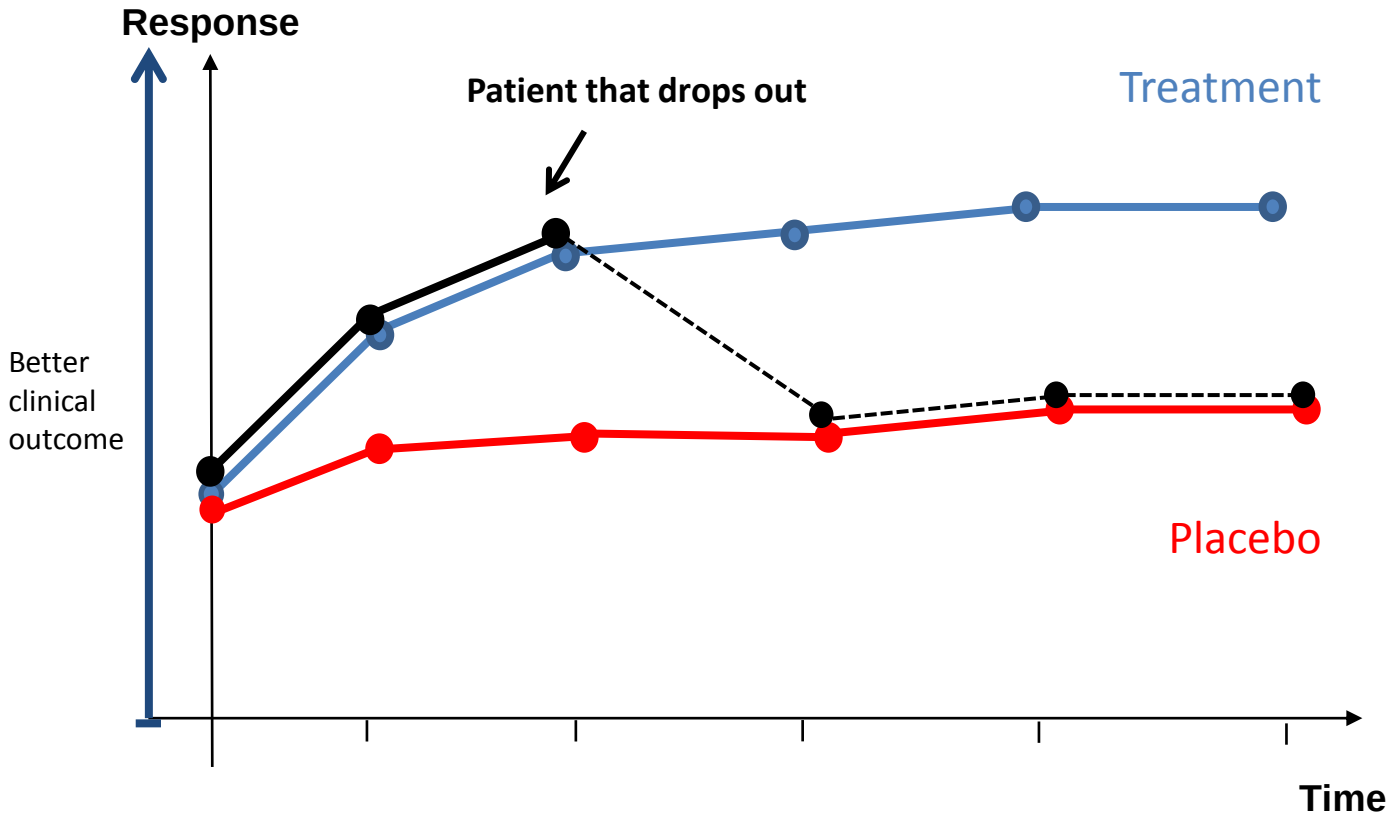
- information from the own observed history and
- information about the future from other similar patients (same history, treatment and other covariates)

is NOT sufficient to provide information about the missing data.

For example CHMP [2013]: "[...] is requested to perform an analysis where missing data following discontinuation of the randomized drug would be imputed under the assumption of a similar evolution than observed in untreated patients."

Principled Methods under MNAR

Example – 'Jump to Placebo' after Drop Out



Pattern-mixture model based imputation approaches, where different post- discontinuation behaviors can be implied - e.g. 'jump to placebo' arm after discontinuation.

See also: Little, Yau (1996, Biometrics); Carpenter, Roger, Kenward (2013, Journal of Biopharmaceutical Statistics)

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Reminder: Case Study

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Total	**102**	**98**

Different Scientific Questions for the Case Study

Traditional / Naive Methods

- **Complete case analysis**

  "What is the effect seen in patients that complete the study?"

- **Last Observation Carried Forward (LOCF)**

  "What would the effect be, had all randomized patients stayed in study and patients that discontinued had sustained their last observed measurement until the end of the study?"

- **Baseline Observation Carried Forward (BOCF)**

  "What would the effect be, had all randomized patients stayed in study and patients that discontinued had returned to their baseline value by the end of the study?"

Different Scientific Questions for the Case Study

Principled Methods

- **Missing At Random (MAR)**

  "What would the effect be, had all randomized patients stayed in study and patients that discontinued had behaved like other 'similar patients' that remained in the same treatment arm?"

- **Missing Not At Random (MNAR) - 1**

  What is the effect based on all randomized patients, accounting for the potential reduction or loss of effect after discontinuation of the randomized treatment and the study due to AE, lack of efficacy or death?

- **Missing Not At Random (MNAR) - 2**

  What is the effect based on all randomized patients, accounting for the potential reduction or loss of effect after discontinuation of the randomized treatment and the study?

Case Study

Methods & Results

Traditional / Simple / Naive Methods:

- Complete case analysis (CCA)
- Single Imputation (SI) LOCF
- Single Imputation (SI) BOCF

Principled Methods:

MAR: MMRM

- borrow information from the same treatment arm to 'impute' missing data

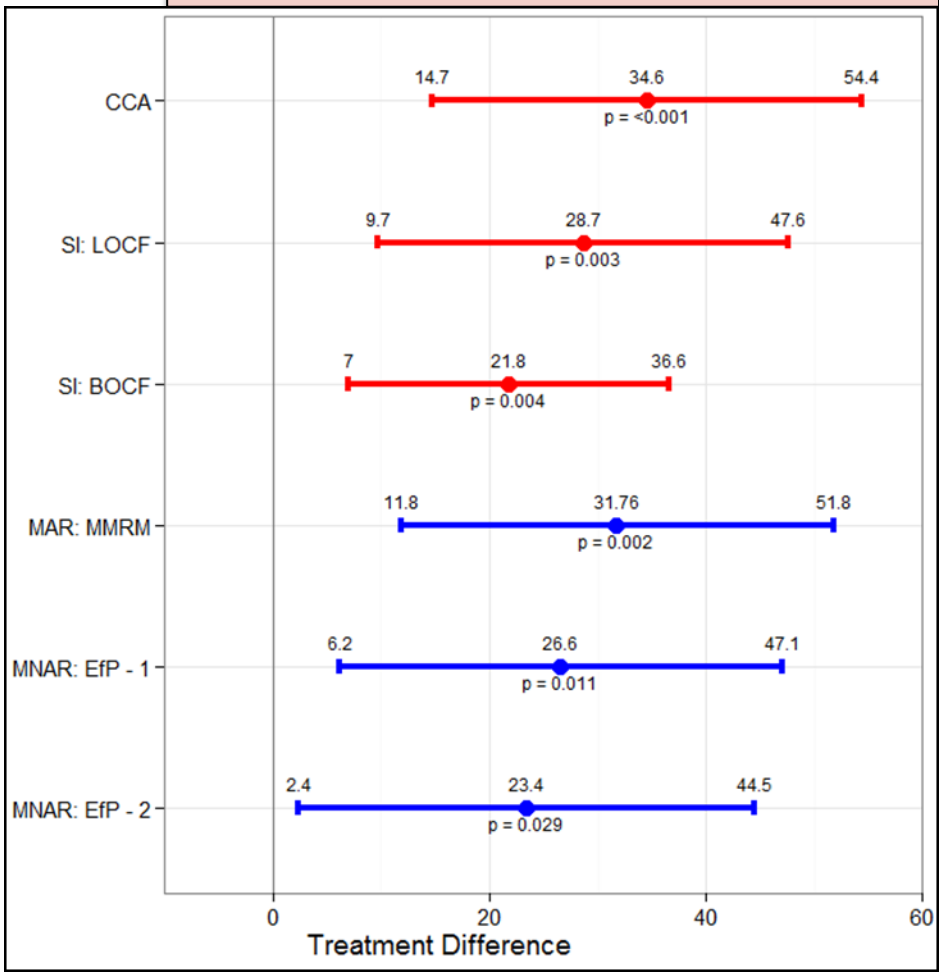
MNAR: Experimental follows Placebo (EfP) -1

- experimental arm slowly decays back to placebo response for patients that discontinue due to AE, lack of efficacy, death
- borrow information from same treatment arm for all other patients

MNAR: EfP -2

- experimental arm slowly decays back to placebo response for patients that discontinue for any reason
- for placebo patients that drop out borrow information from same arm

95% Confidence Intervals



Case Study

Comments & Results

Traditional / Simple / Naive Methods:

- **CCA** excludes 25% of patients
- **Single Imputations** yield confidence intervals which are too narrow, thus give an artificial impression of precision that does not exist.

Principled Methods:

MAR: MMRM

- Assumes **on-treatment future** for 26% of patients that discontinued due to AE
- **'Hypothetical effect'**: effect seen in practice may be smaller unless tolerability is improved

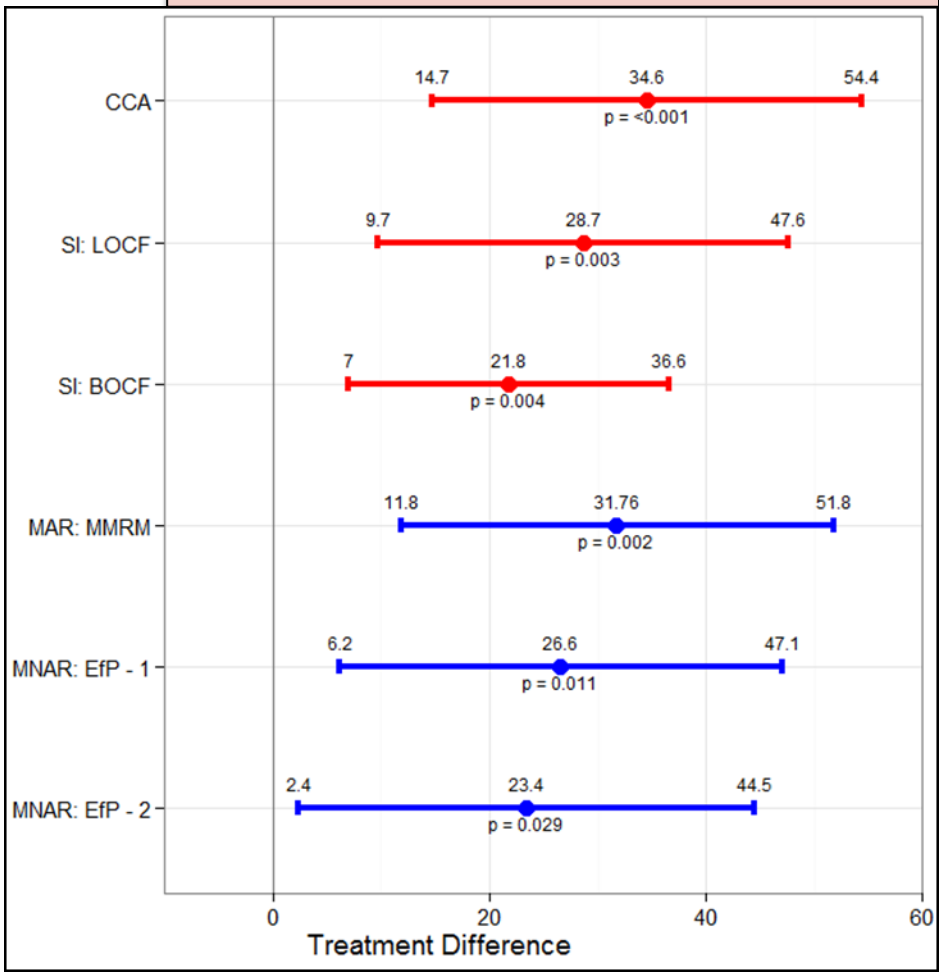
MNAR: EfP -1

- Takes into account that patients that discontinue due AE, lack of efficacy, death will discontinue their treatment
- Attempts to estimate the **effect seen in practice** under the assumption that the drug effect will be lost slowly after discontinuation from treatment

MNAR: EfP -2

- Same as EfP-1, only that loss of drug effect is implied for all active arm patients that drop out

95% Confidence Intervals



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Remarks – 1

- Different missing data techniques imply different scientific questions of interest that are answered.
- Sometimes this is not clearly communicated or understood.
- In particular, a missing data mechanism may be MAR (even deterministic MAR) - however - one is not interested in a MAR based estimator which assumes an on-treatment future.
- Important aspects to consider: patients discontinue for different reasons and the experimental conditions change after a patient drops out, e.g. the patient
  - stops taking the treatment;
  - starts taking another medication;
  - dies; ...

Remarks – 2

What should the estimand be in the presence of 'missing data'/discontinuation?

- In the presence of study discontinuation - and hence missing data - the observed data at the time point of interest consists of two components:
  - Discontinuation event information (yes/no, event time, reason etc.)
  - Endpoint data (only observed if patient did not discontinue)
- Current practice: One creates a difficult to interpret composite endpoint that combines information on discontinuation patterns and efficacy in adherers – the 'ITT' / 'effectiveness' estimand.
  - E.g. worst case or 'jump to placebo' imputations for patients that drop out due to AEs
- Disentangling discontinuation and the efficacy of treatment in patients that adhere appears more transparent and meaningful.

Overarching Questions of Interest

+ Statistical Considerations

The scientific questions of interest in drug development can broadly be classified into those addressing

a) lack of adherence to treatment due to different reasons (safety/efficacy)

b) efficacy and safety profile when patients, in fact, are able to adhere to the treatment.

a)

- May tabulate (exposure-adjusted) proportions;
- compare proportions (e.g. Fishers Exact Test);
- perform regression analyses (logistic / probit regressions)

b)

- Difficult estimation problem which may require causal inference framework;
- targeted designs such as randomized withdrawal designs may simplify the problem;
- complete case analysis with rich covariate models or methods involving inverse probability of 'adherence' weights may be suitable estimators (?)

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Conclusions

- Missing data can undermine the trial integrity as failed submissions have shown
- Regulatory landscape has changed over the last 3 years
  - Traditional methods such as LOCF are no longer accepted
- Different ways of handling missing data usually imply different underlying scientific questions / estimands
  - Missing data is therefore not solely a statistical issue
- Disentangling adherence to treatment and the efficacy and safety of treatment in patients that adhere appears to be more transparent and meaningful to all stakeholders.
- Admittedly, effect in adherers is not easy to estimate – however – if this is really of interest to all stakeholders then research and resources should be spent on adequate methods.