Missing Data in Clinical Trials

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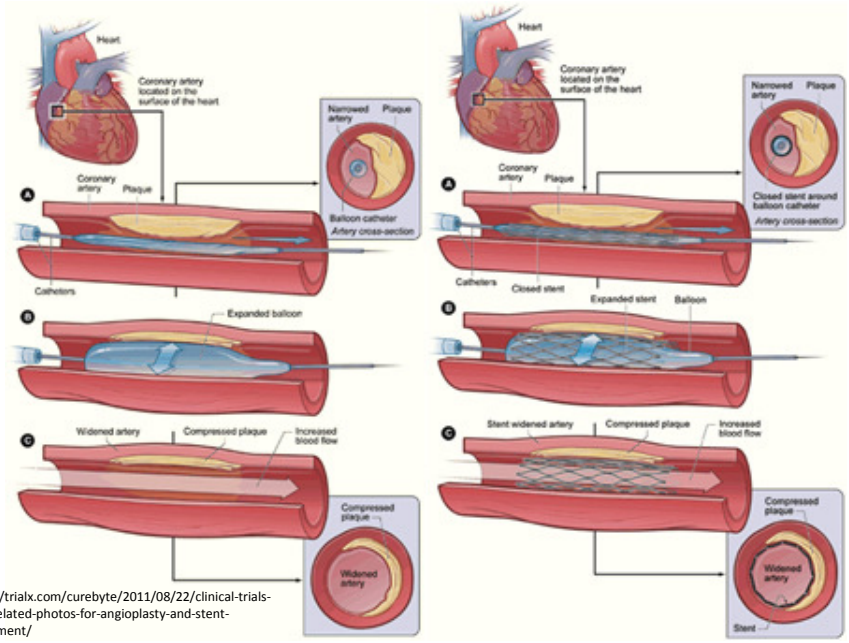
Today's content

- Missing Data
  - Regulatory guidelines
  - Brief overview of missing data methods
  - What statisticians can do



http://trialx.com/curebyte/2011/08/22/clinical-trials-and-related-photos-for-angioplasty-and-stent-placement/

Carpenter (2007) example

		Stent	Angio-plasty
Restenosis	No (Good)	54	43
	Yes (Poor)	32	37
	Unknown	24	30
Total randomised		110	110

Restenosis: Recurrence of a narrowing of blood vessels

Assumption 1 (same proportion of good results as the known results)

		Stent	Angioplasty
Restenosis	No (Good)	54	43
	Yes (Poor)	32	37
	Unknown	24	30
Total randomised		110	110

		Stent	Angioplasty
Restenosis	Good	69	59
	Poor	41	51
Total randomised		110	110

Assumption 2 (all unknown outcomes were poor)

		Stent	Angioplasty
Restenosis	No (Good)	54	43
	Yes (Poor)	32	37
	Unknown	24	30
Total randomised		110	110

		Stent	Angioplasty
Restenosis	Good	54	43
	Poor	56	67
Total randomised		110	110

Assumption 3 (all unknown outcomes were good)

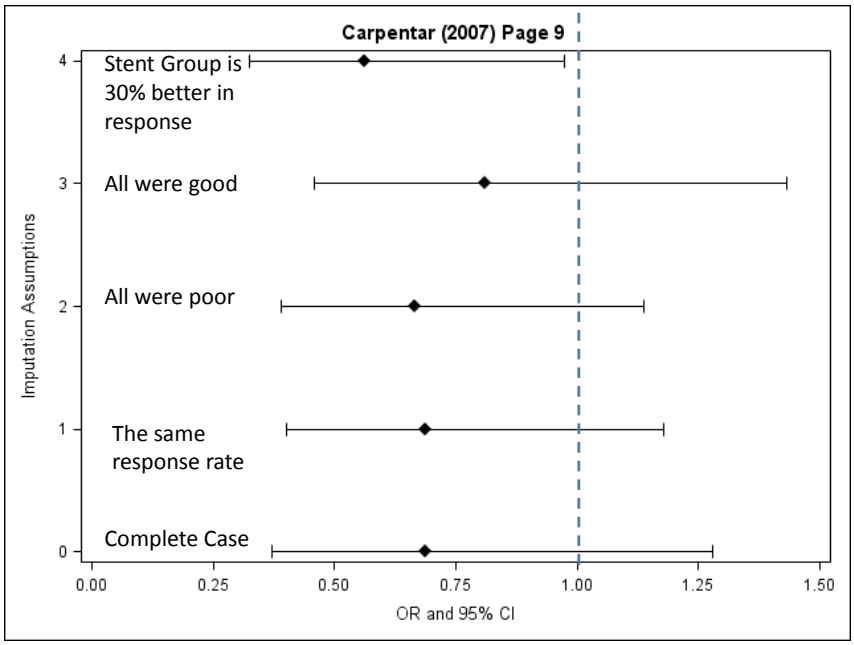
		Stent	Angioplasty
Restenosis	No (Good)	54	43
	Yes (Poor)	32	37
	Unknown	24	30
Total randomised		110	110

		Stent	Angioplasty
Restenosis	Good	78	73
	Poor	32	37
Total randomised		110	110

Assumption 4 (+30 % better response rate in Stent)

		Stent	Angioplasty
Restenosis	No (Good)	54	43
	Yes (Poor)	32	37
	Unknown	24	30
Total randomised		110	110

		Stent	Angioplasty
Restenosis	Good	74	59
	Poor	36	51
Total randomised		110	110



Missing Data Regulatory Guidelines

Year		
1995	ICH	E3 - Structure and Content of Clinical Study Reports
1998	ICH	E9 - STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
2001	EU (EMEA)	Points to Consider On Missing Data
2007	EU (EMEA)	RECOMMENDATION FOR THE REVISION OF THE POINTS TO CONSIDER ON MISSING DATA
2010	EU (EMEA)	Guideline on Missing Data in Confirmatory Clinical Trials

What the guidelines say about missing data

1. Importance of minimizing the issue
2. Choose the appropriate analyses methods and predefine them
3. Conduct sufficient sensitivity analyses to evaluate the robustness of the results
4. Report it properly

Missing Data Mechanisms (Rubin 1976)

- Missing Completely At Random (MCAR)

$$F(M \mid Y, \phi) = F(M \mid \phi) \quad \text{for all } Y, \phi$$

- Missing At Random (MAR)

$$f(M \mid Y, \phi) = f(M \mid Y_{obs}, \phi) \quad \text{for all } Y_{miss}, \phi$$

- Missing Not At Random (MNAR) (or NMAR, informatively missing, non-ignorable)

  When data are neither MCAR nor MAR.

Approaches for Missing Data

- Complete Case Analysis or Available case analysis
- Imputation-Based Procedures
  - Single Imputation (LOCF, BOCF, WOCF etc)
  - Multiple Imputation
- Model-Based Procedures

$f(\boldsymbol{Y}_i, \boldsymbol{R}_i | X_i, \boldsymbol{\theta}, \boldsymbol{\psi})$

Selection models: $f(\boldsymbol{Y}_i | X_i, \boldsymbol{\theta}) f(\boldsymbol{R}_i | X_i, \boldsymbol{Y}_i^o, \boldsymbol{Y}_i^m, \boldsymbol{\psi})$

MCAR	→	MAR	→	MNAR
$f(\boldsymbol{R}_i \| X_i, \boldsymbol{\psi})$		$f(\boldsymbol{R}_i \| X_i, \boldsymbol{Y}_i^o, \boldsymbol{\psi})$		$f(\boldsymbol{R}_i \| X_i, \boldsymbol{Y}_i^o, \boldsymbol{Y}_i^m, \boldsymbol{\psi})$
CC?		**direct likelihood!**		joint model!?
LOCF?		EM		sensitivity analysis?!
single imputation?		**MI!**		
⋮		**WGEE!**		

Pattern-mixture models: $f(\boldsymbol{Y}_i | X_i, \boldsymbol{R}_i, \boldsymbol{\theta}) f(\boldsymbol{R}_i | X_i, \boldsymbol{\psi})$

Shared-parameter models: $f(\boldsymbol{Y}_i | X_i, \boldsymbol{b}_i, \boldsymbol{\theta}) f(\boldsymbol{R}_i | X_i, \boldsymbol{b}_i, \boldsymbol{\psi})$

From Molenberghs G. and Kenward M. G., 2007

Approaches

- No universal approach
- The appropriate approach is different
  - depending on the disease area
  - superiority study or non-inferiority study

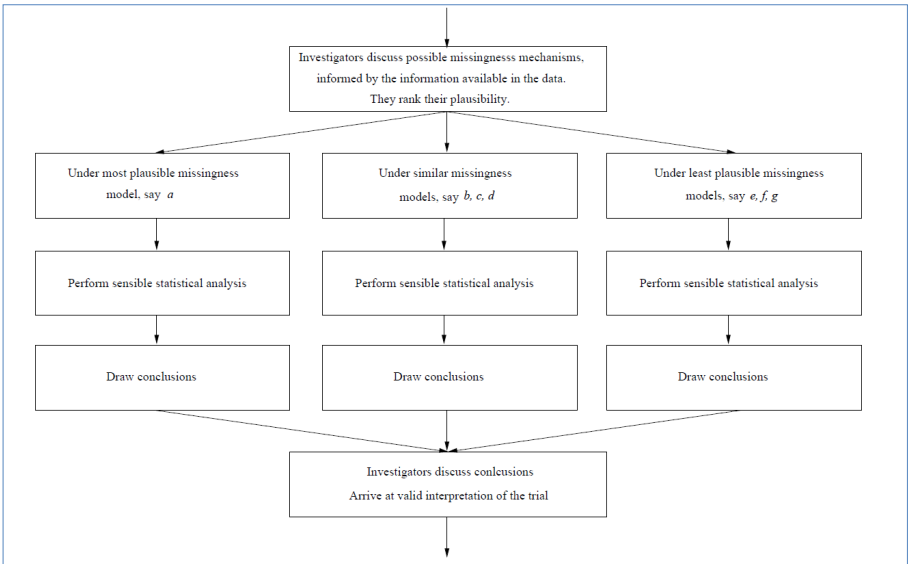


Figure 1.1: A systematic approach for analysing a trial with missing data

Carpentar J. R., Kenward M. G. 2007

ICH Statistical Guideline (E9)

- Minimize bias
- Maximize precision (accuracy)

EMEA Points to consider (2001)
Bias is the most important concern

- The estimation of the treatment effect
- The comparability of the treatment groups
- The representativeness of the study sample in relation to the target population

Validity
Rothman (1986)

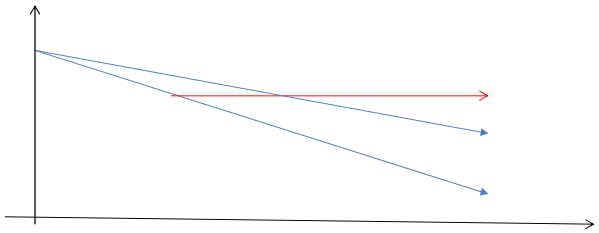
- Internal Validity – The validity of the inferences drawn as they pertain to the actual subjects
- External Validity – The validity of the inferences as they pertain to the people outside the study population

Factors which can influence results (EMEA 2010)

- Differences between the treatment groups in the proportion of patient withdrawals
- Differences between the treatment groups in the timing of withdrawals
- The reason for the patient withdrawals
- The direction of any spontaneous changes over time

EMA (2010) Guideline on Missing Data in Confirmatory Clinical Trials

- Mention the limitations of different approaches of handling missing data
- E.g. LOCF – when timing of the withdrawals are different between groups and the disease state is known to deteriorate over time



Planning

- Predefine the approaches on missing data handling in the study protocol or in analysis plan.
- Re-evaluate the approaches at the blinded data review.

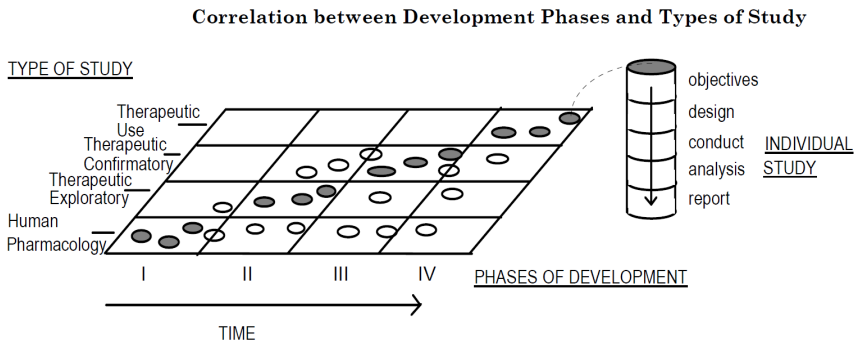
What to report

- In general, the quality of submissions would be greatly improved, and fewer requests for additional analyses would result, if the pattern of dropouts (timing and reasons) was clearly summarized and their influence discussed. (Brown (MHRA) 2008)
- Explore reasons for, and timings of, withdrawals in different treatment groups to further consider whether the planned analyses can be considered a comprehensive exploration of the problem and reliable for inference. (Hemmings (MHRA) 2012)
- Measure of robustness needs to be prespecified (Soon (FDA) 2008)

Prevention is the key

- Proper planning of the study
  - Protocol (schedule of assessment)
  - CRF
  - Raising awareness of missing data issue in the beginning of the study to the study team and sites
  - Brain storm with the team on what we can do
    - Time window
    - How much to follow
    - Clarify which assessments are more important
- Continuous improvement across studies and across projects (Toyota-way, ISO9001)

ICH E8 General Consideration for Clinical Trials (1997)



We can keep on learning from the previous experiences and improve the next step forward.

What the guidelines say about missing data

1. Do your best to prevent the issue!
2. Choose the appropriate analyses methods and predefine them
3. Conduct sufficient sensitivity analyses to evaluate the robustness of the results
4. Report it properly

References

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