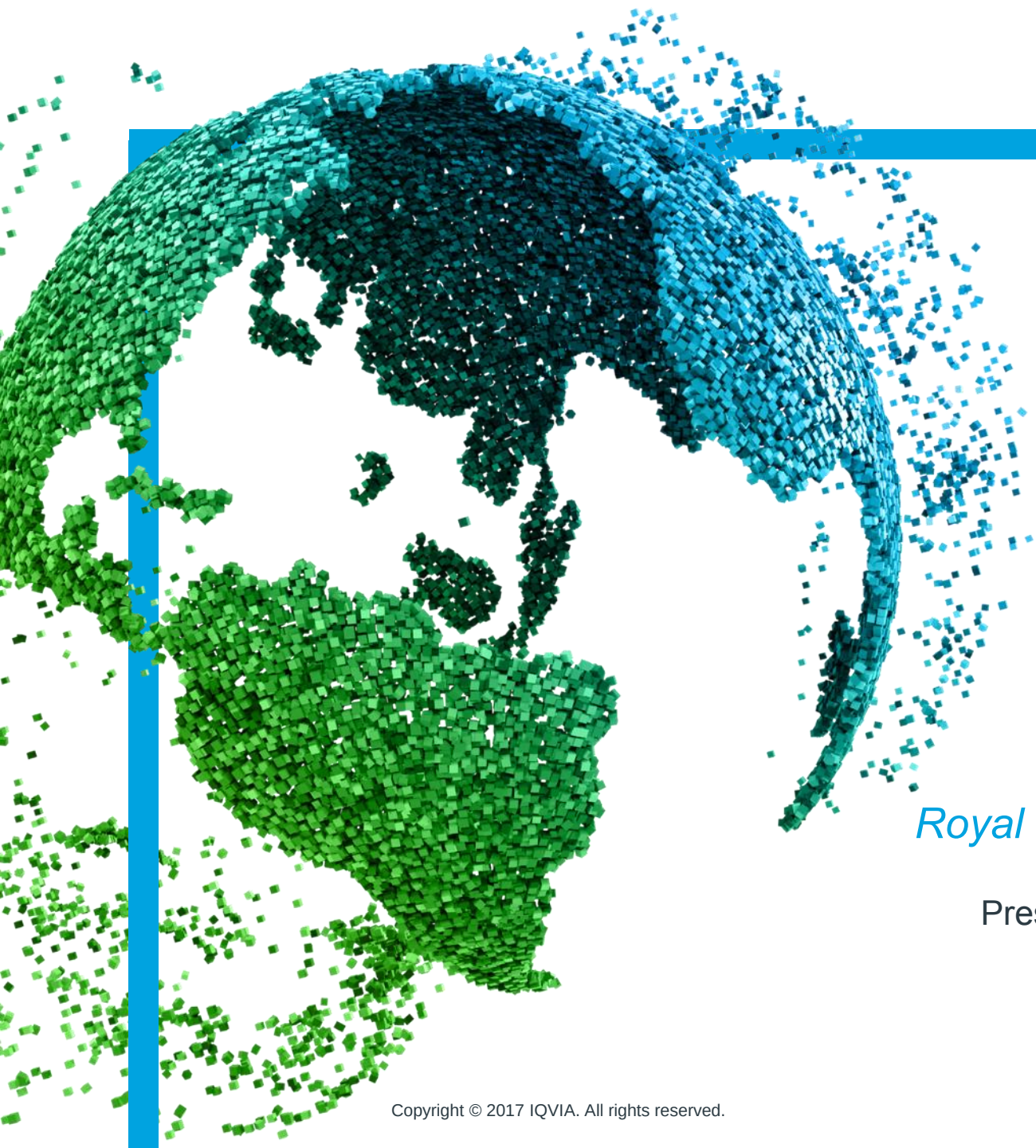

IMS Health & Quintiles are now IQVIA™

Missing data in clinical trials: making the best of what we haven't got.

Royal Statistical Society Professional Statisticians' Forum

Presentation by Michael O'Kelly, Senior Statistical Director, IQVIA

What I will cover

- The landscape of ideas about missing data in clinical trials, c. 2007-2018
- Our attempts at good practical approaches for taking account of missing data
- Resources now available for you in this area (a selection)
- Selected topics
  - Prevention
  - Use of evidence from historical data
  - Interpretability

Acknowledgements

- Bohdana Ratitch, IQVIA, co-author of *Clinical Trials With Missing Data: A Practitioner's Guide.*
- Sara Hughes, GlaxoSmithKline; Belinda Hernández, Dublin Conway Institute and IQVIA; Ilya Lipkovich, IQVIA;
  - contributors to *Clinical trials with missing data: a practitioner's guide.*

- James Roger, Livedata, and London School of Hygiene and Tropical Medicine:
  - Authored or co-authored key recent software that expands what we can estimate in clinical trials
- DIA Scientific Working Group on missing data, www.missingdata.org.uk.
- Gary Koch, regular advice.

Some early work on missing data

- Early work on missing data was done with surveys and censuses in mind.
- Donald Rubin: "…concern for problems of nonresponse in the Current Population Survey led to a working paper for the Social Security Administration (Rubin, 1977), which explicitly proposed multiple imputation"*.
- Surveys: may be able to argue that missingness is independent of the unobserved data, given the data that are observed.
  - i.e. that data are missing at random (MAR);
- Clinical trials: there is an intervention; public safety at stake; hypothesis driven; attempt causal inference; need to control rate of false positive findings;
  - stakeholders may assume that post-withdrawal data must be worse in some unknown way than data while subject was in study – i.e. that outcomes are missing NOT at random - MNAR.
  - (However, Rubin has good example of survey data that may be MNAR+).

- Important corollary of MAR: if, given the observed data, the probability of an outcome being unobserved is independent of the value of the unobserved outcome
  - then, where background data is similar, the unobserved outcome cannot be systematically distinguished from observed outcomes
  - i.e. we should be able to model the unobserved outcome using observed outcomes as a basis.

*Rubin, D (1987) *Multiple Imputation for Nonresponse in Surveys*. Wiley
+Rubin, D (1976) Inference and missing data. *Biometrika*.

The landscape of ideas about missing data in clinical trials, c. 2007

- International Conference on Harmonisation (ICH) guideline *Statistical principles for clinical trials* (1998)
  - Prevent missing data
  - "No universally applicable methods of handling missing data"
  - Investigate "sensitivity of the results…to the method of handling missing data" (p. 24)
  - "Methods of dealing with missing data…pre-defined in the protocol" (p. 24)
  - Make a record of reasons for withdrawal: "frequency and type of…missing values should be documented" (p. 22)
- Problem in clinical trials: often the last visit in a clinical trial is the one at which clinical benefit is credibly measured.
  - What if a subject drops out before that last visit?
- Practice for missing data around 2007:
  - Use the last observed value – "last observation carried forward" (LOCF), or some "poor" value, e.g., baseline observation carried forward (BOCF)
  - Use some representative values, e.g., an average for the subject or for the treatment group
  - Growing use of Mixed Models in the Repeated Measures setting (MMRM)*
  - Growing understanding that standard multiple imputation (MI) gives same results as MMRM: MI and MMRM model from observed data and thus assume MAR.

*Mallinckrodt CH, Clark WS, David SR (2001) Accounting for dropout bias using mixed effects models. *Journal of Biopharmaceutical Statistics* **11** (1–2): 9–21

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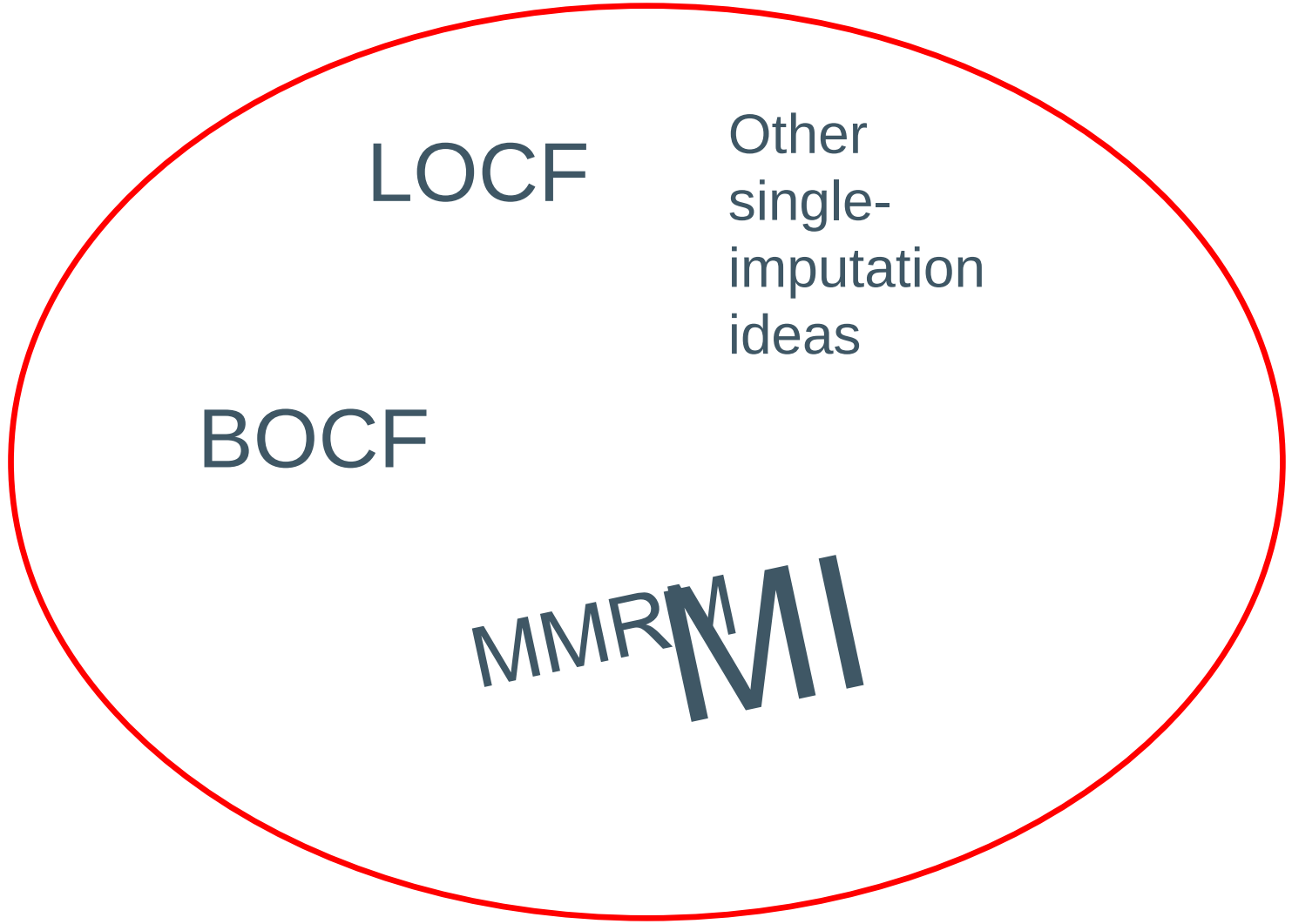
"Handling" missing outcomes



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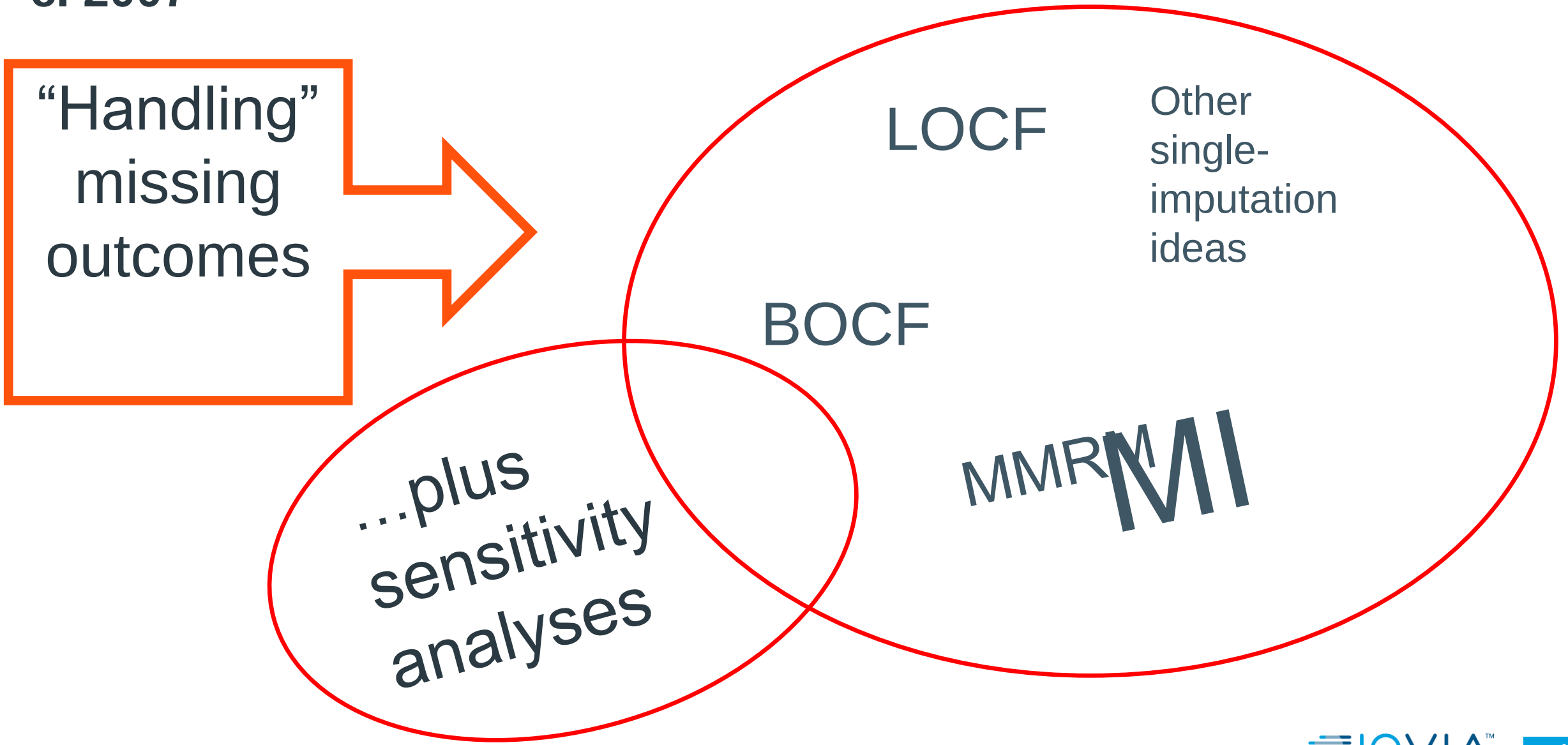

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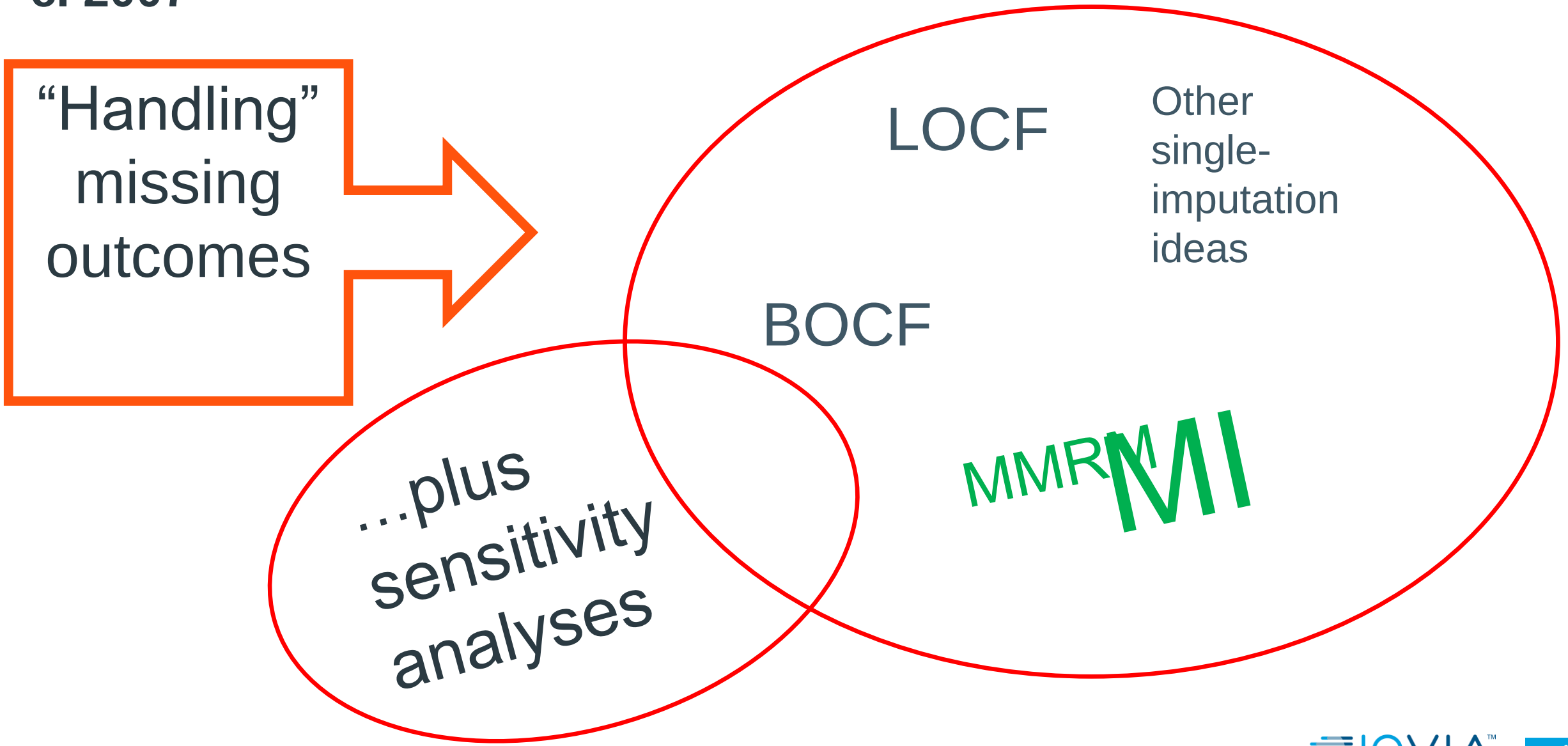
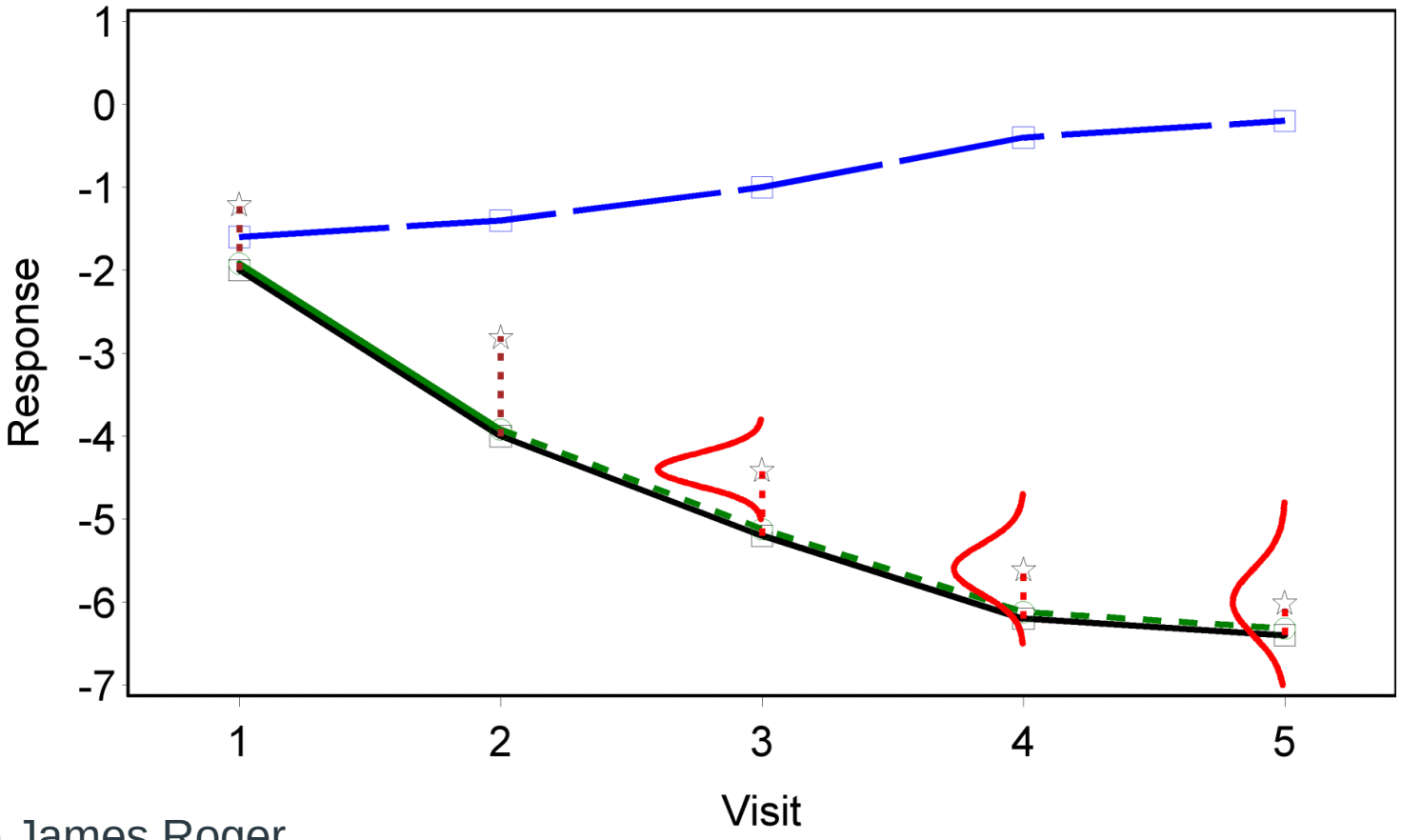


How MI implements MAR



Sketch plot due to James Roger.
Green line shows the means A_{JK} (squares), dotted after withdrawal.
Brown residuals are for two observed values (star) before withdrawal.
Red "residuals" show location of means (star) for conditional distribution.

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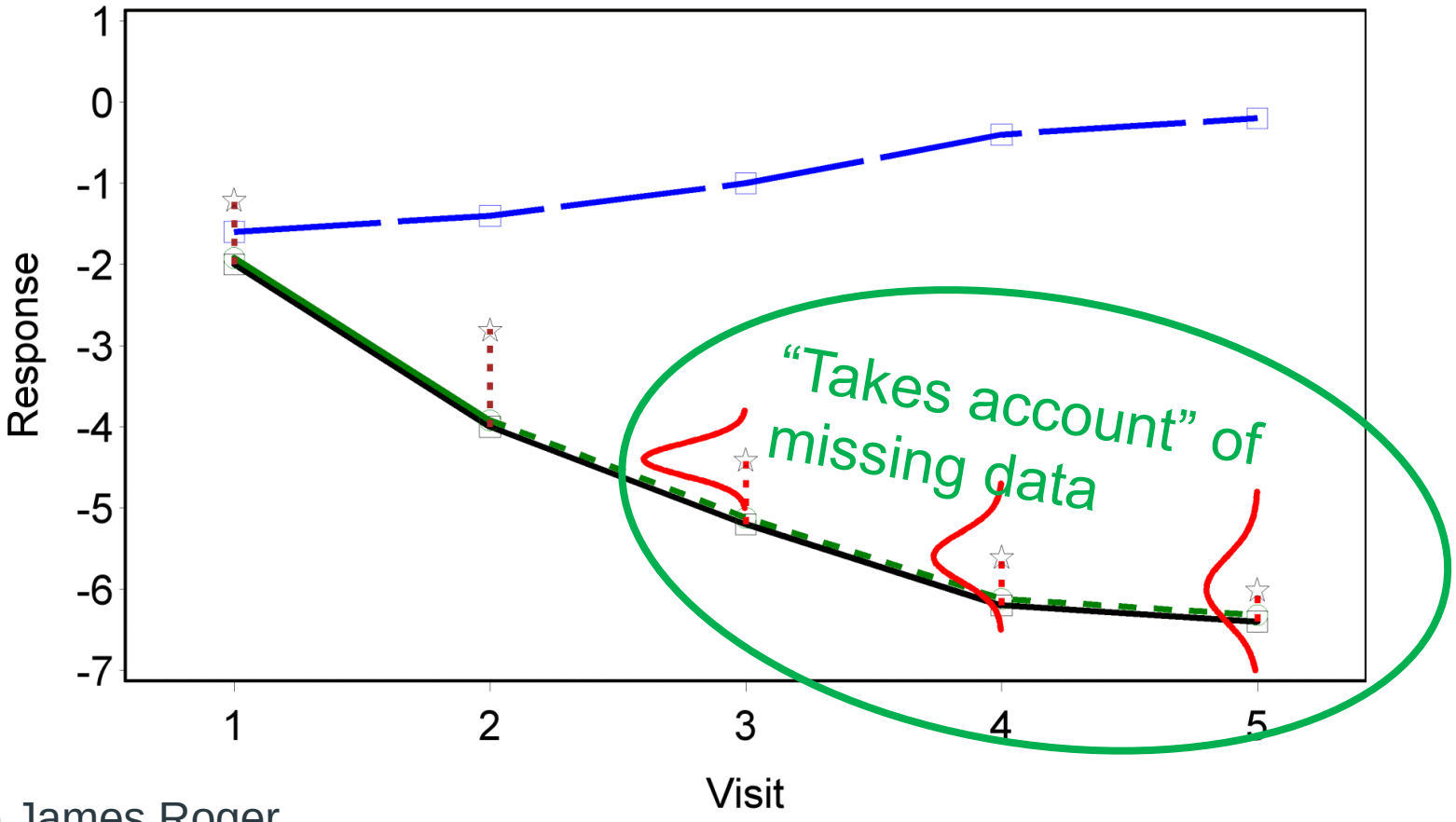

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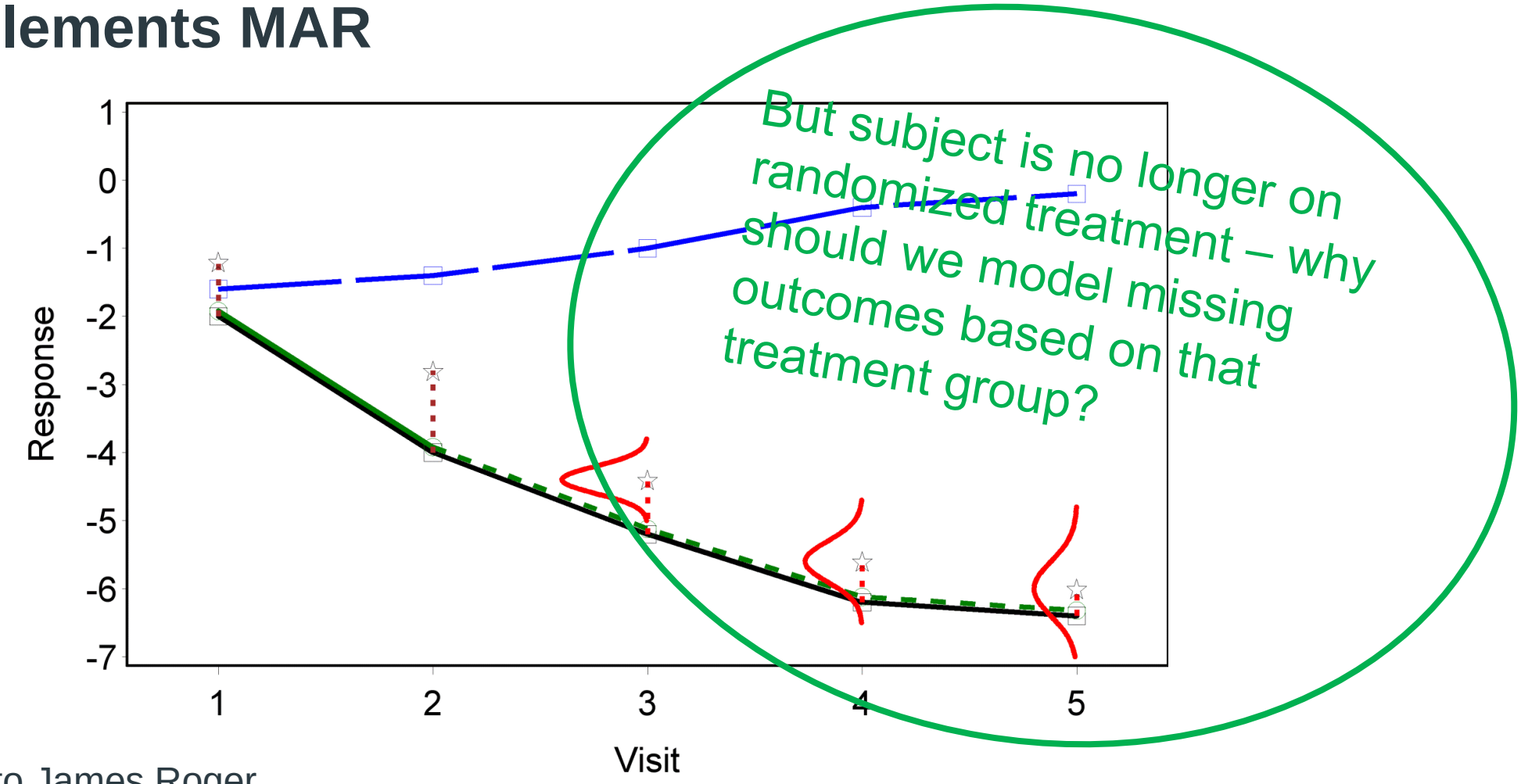

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So: “handling” missing data - even in sophisticated ways - is not enough

“Handling” missing outcomes

How could we take account of subjects who withdraw?

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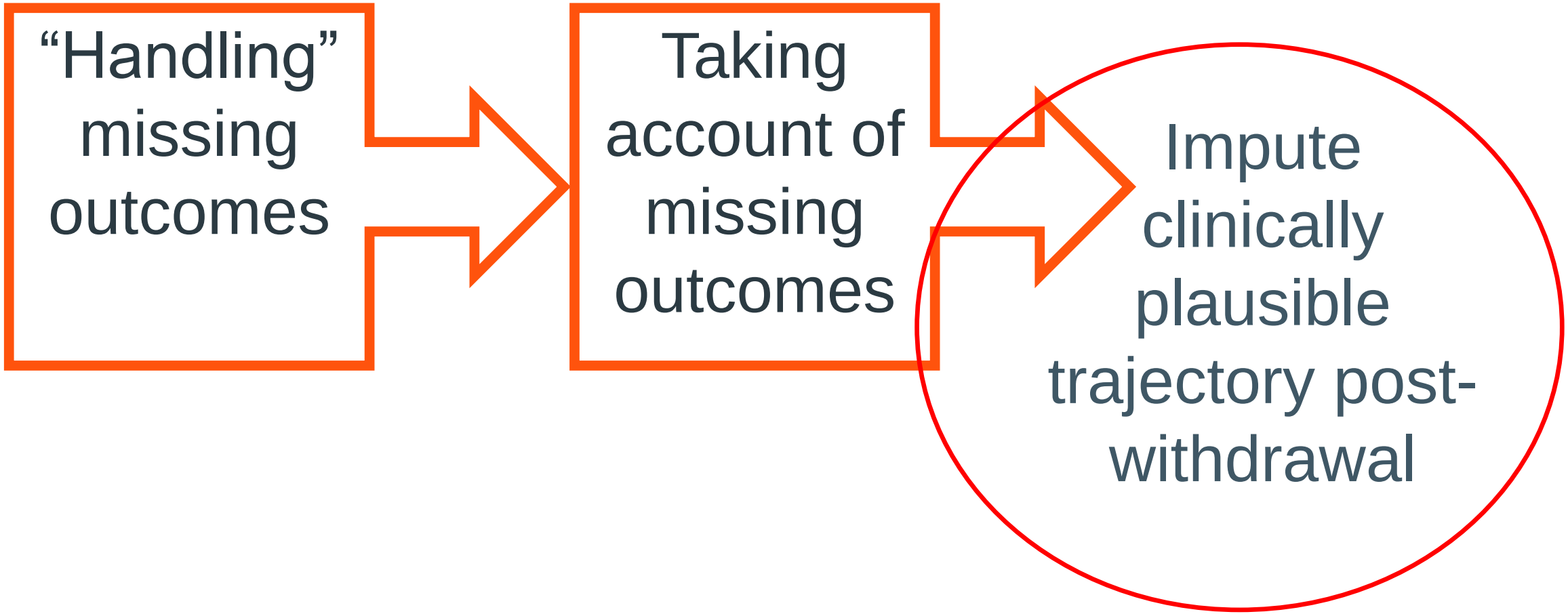
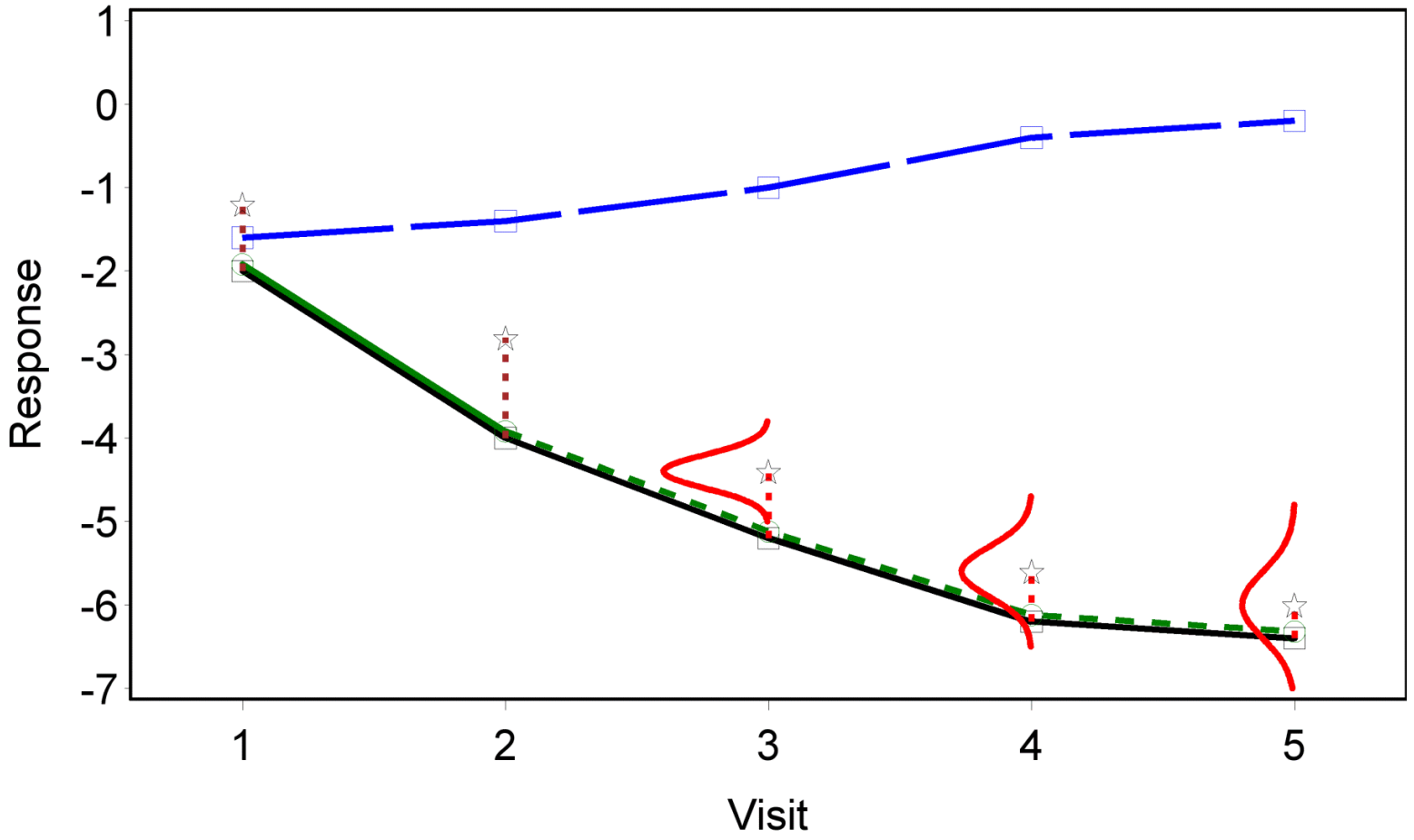
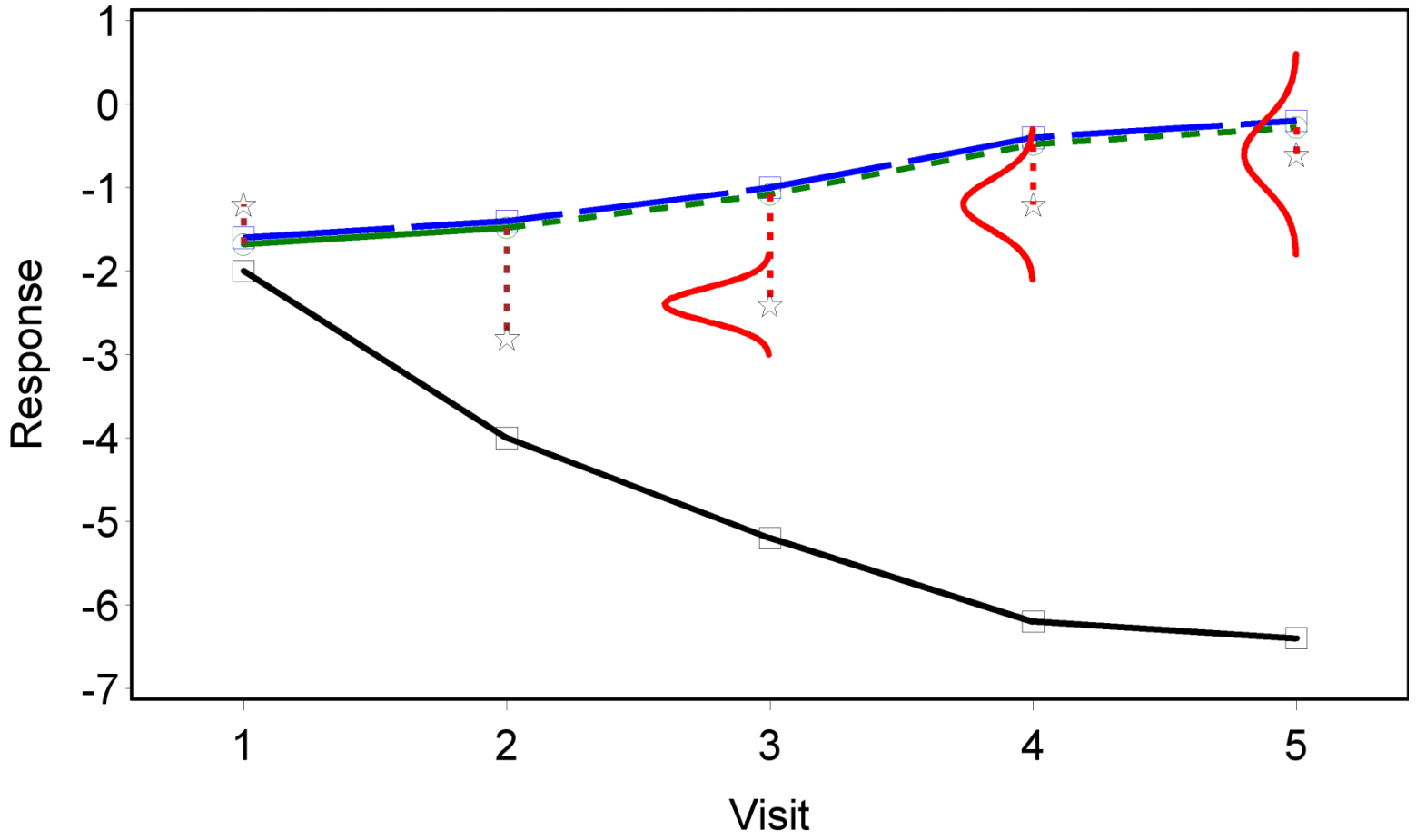


Recall: how MI implements MAR



Model outcomes after withdrawal as if subject was always member of reference group (often placebo group) (Copy Reference (CR) assumption)



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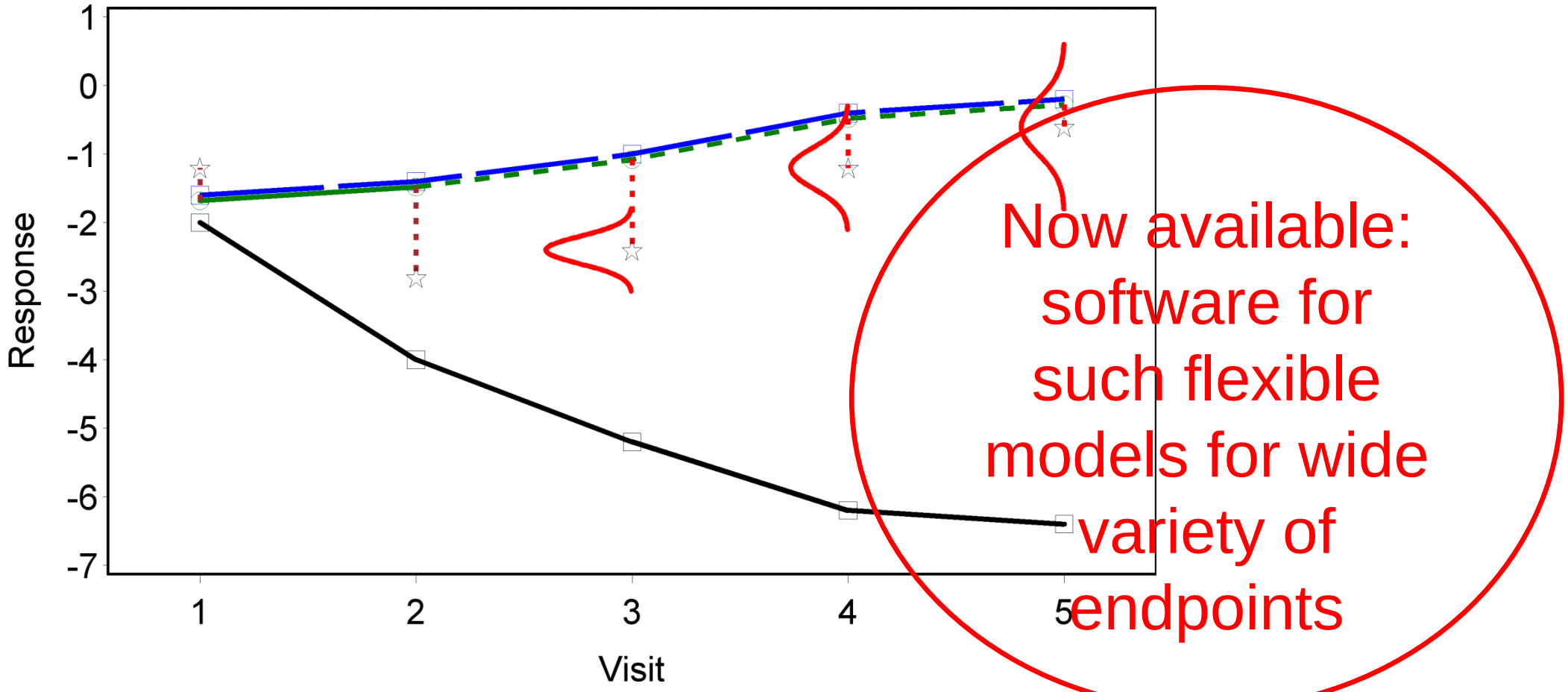

Another way of thinking about experiments where not all data is observed or not all data is usable…

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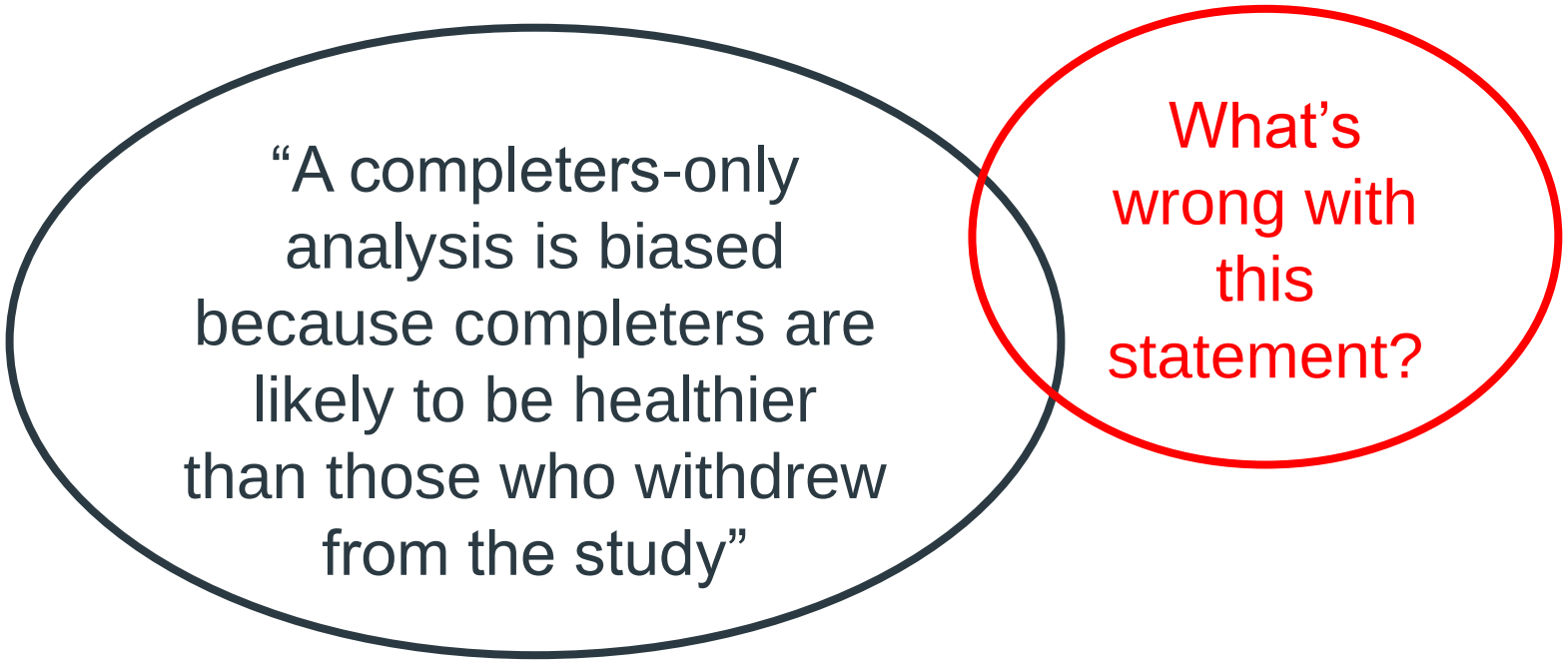
Missing data and its relation to what you want to estimate (i.e. to the estimand)

"A completers-only analysis is biased because completers are likely to be healthier than those who withdrew from the study"

Missing data and its relation to what you want to estimate (i.e. to the estimand)



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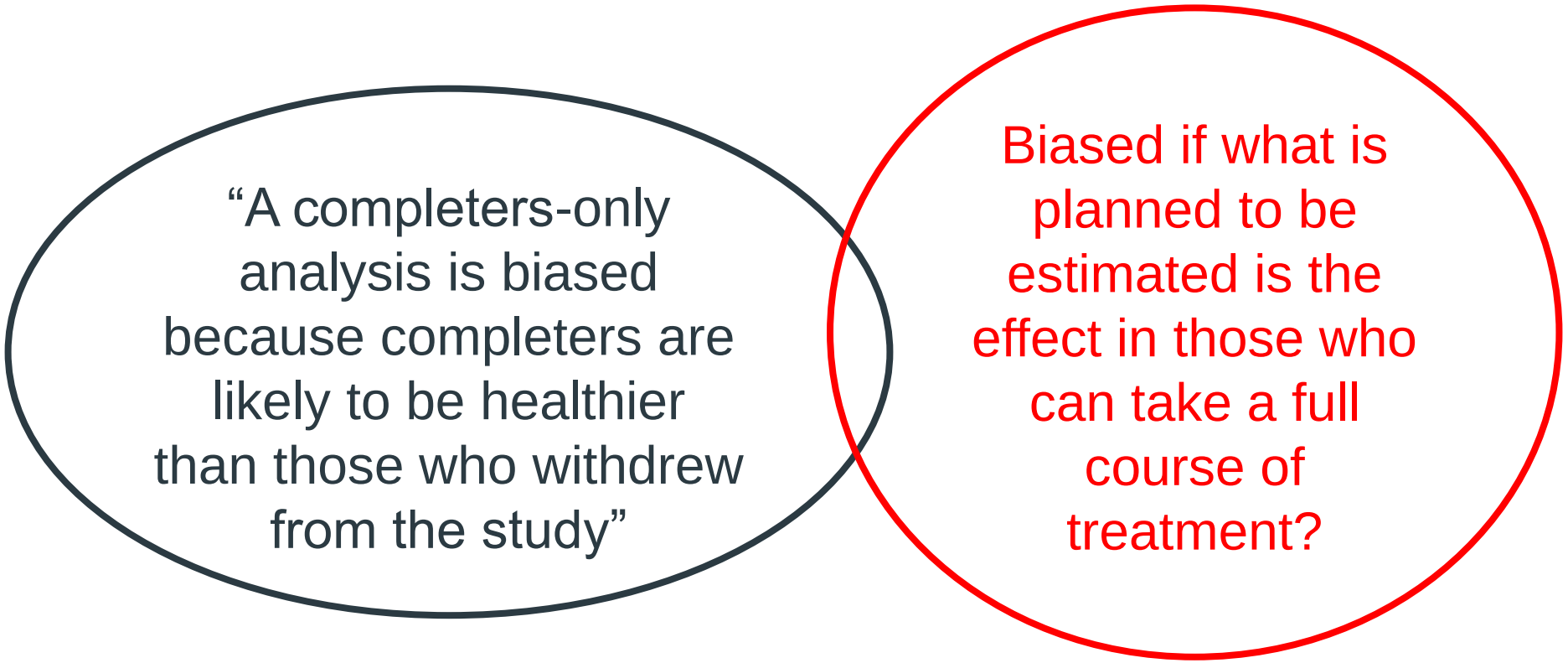

Missing data and its relation to what you want to estimate (i.e. to the estimand)

- The message
  - Is data missing?
  - Is data usable?
  - Does my approach to missing data lead to bias?
  - Depends on what you want to estimate.

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A consequence: "missing" is too small a word for missing data now. Why?

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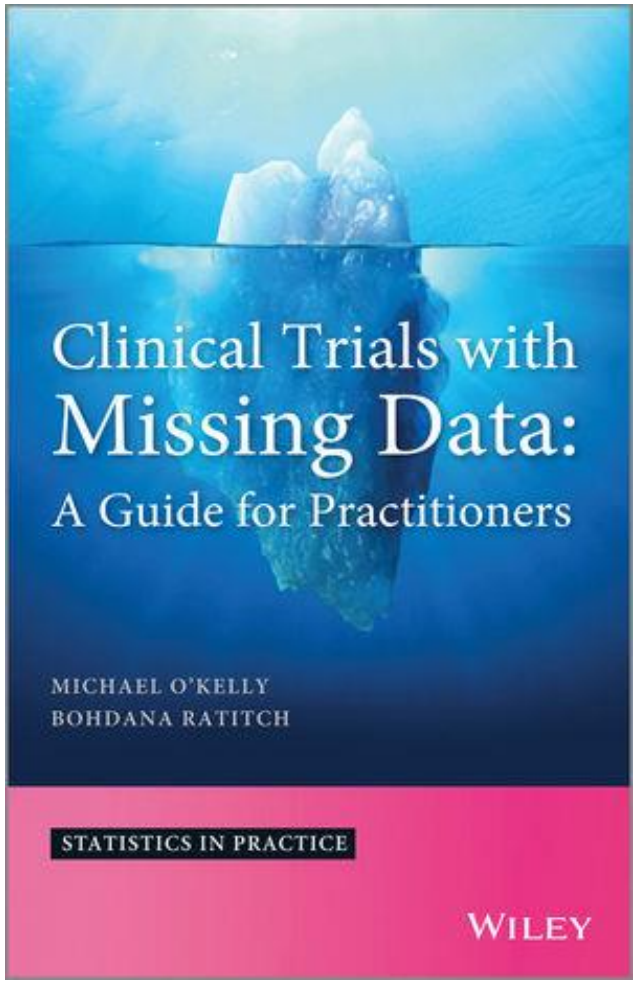
A consequence: "missing" is too small a word for missing data now. Why?

Estimand: treatment effect were no rescue taken

"Most subjects on the control arm took rescue, while few on the experimental arm did"

Our attempts at good practical approaches for taking account of missing data

- Company supported the authoring of a book on missing data



Our attempts at good practical approaches for taking account of missing data

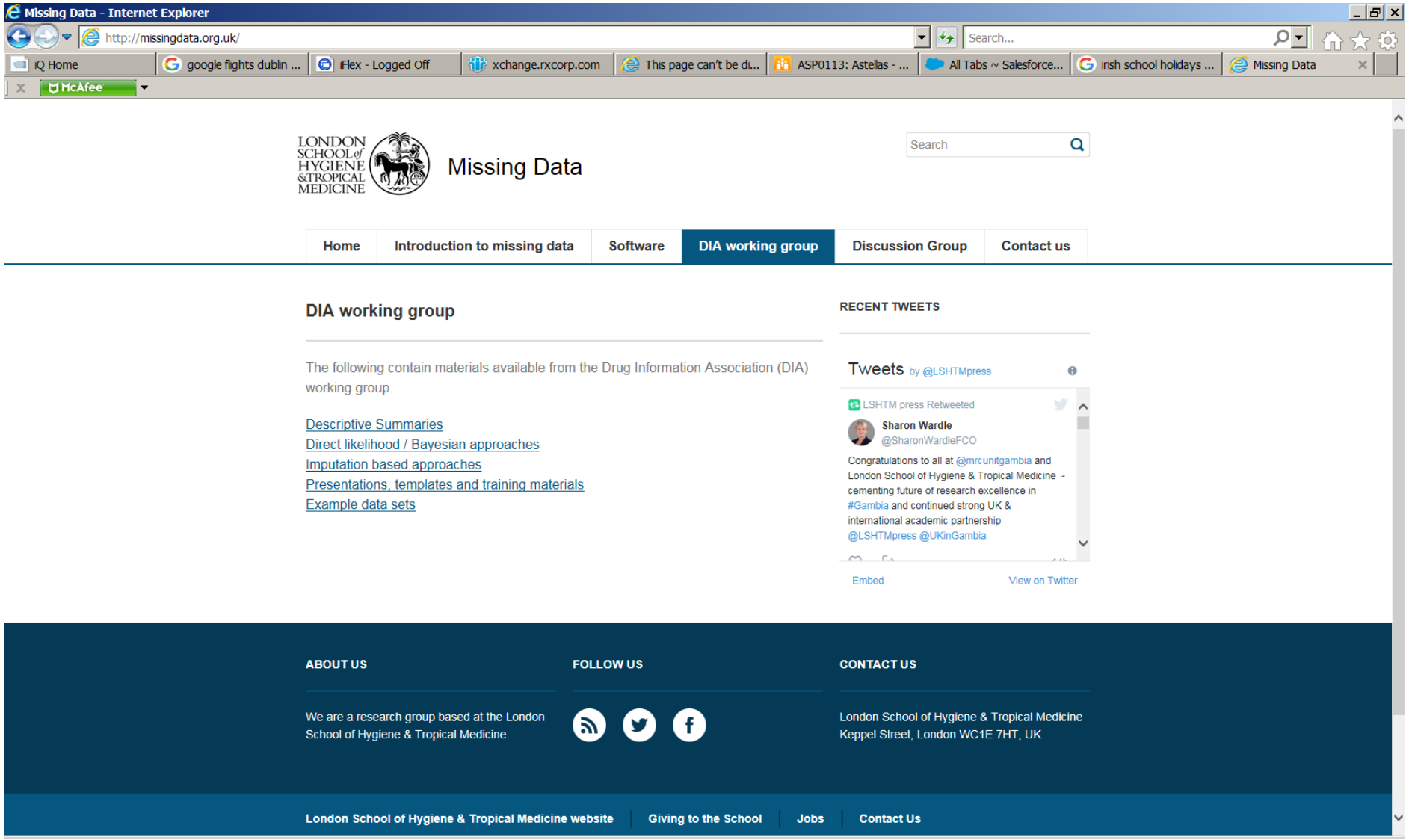
- Training – eight modules, each 1-1.5 hours – recordings available.
- Practical workshops – statisticians given clinical data – amend template code to achieve stated objective.
  - Compare and discuss how outcomes differ depending on estimand, depending on scenarios for subjects who withdraw from treatment.
- Extra training + workshops for “Missing Data Superusers”
  - Idea: a Missing Data Superuser in each physical office
  - First call for anyone in the office with a problem or question about missing data
  - Experienced consultant on call to work with Superuser as needed
    - (Needed about 60% of the time)
- Business case can be made because this issue affects almost every clinical trial with which we work

Resources for the practice of taking missing data into account, particularly in clinical trials

Resources for the practice of taking missing data into account, particularly in clinical trials

- R package: MICE (Multiple imputation by chained equations)
- Drug Information Association Scientific Working Group (DIA SWG) for Missing Data
  - Active researchers from industry and academia
  - Unprecedented collaboration and sharing of new software for missing data
  - Missingdata.org.uk hosts web page for the DIA SWG for Missing Data, includes some links to R packages but mainly SAS macros:
    - › Flexible imputation for continuous endpoints using both Markov chain Monte Carlo and regression-imputation approaches
    - › Doubly robust estimation
    - › Flexible imputation for recurrent events
    - › Imputation for time to event outcomes
    - › Sample statistical analysis plans
    - › Training slides
    - › Test data sets (widely used in papers)

Missingdata.org.uk



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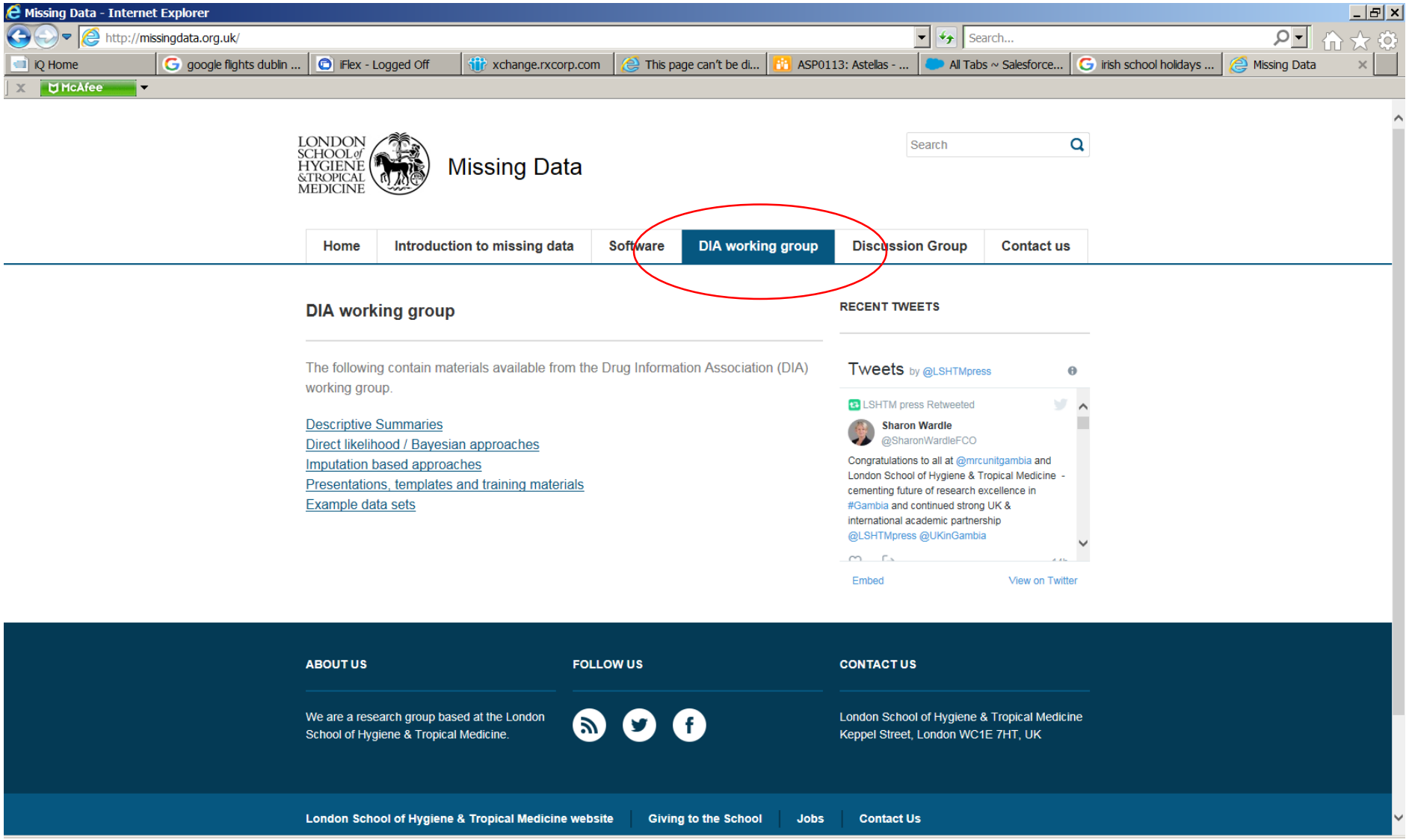


Resources for the practice of taking missing data into account, particularly in clinical trials

- Monograph by Carpenter, Kenward and Roger (2007), available online: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.468.9391&rep=rep1&type=pdf.
  - (Funded by NHS)

Where the statistician can help to prevent missing data in clinical trials

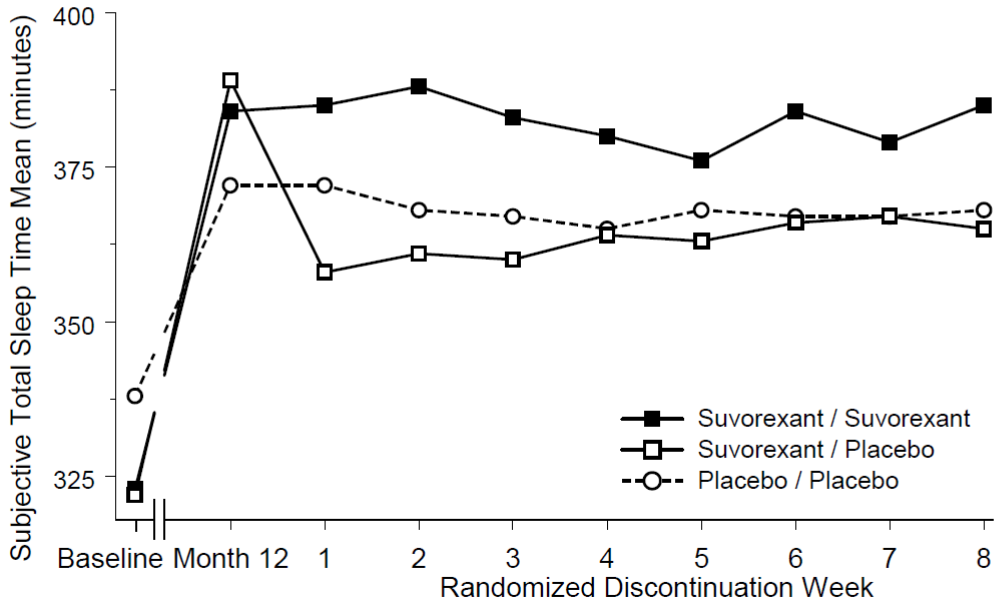
- Trial design
  - Formulate what is required to be the primary estimate (of treatment effect) so as to inform the reader of a clear and meaningful treatment outcome for all randomized, including non-adherers
  - Decide what data will be usable / meaningful for what is required to be estimated in the study
- Trial conduct
  - Patient retention strategies
  - Prevention of missing data
- Trial analysis
  - Choose analysis strategies with missing data assumptions that are consistent with what is required to be estimated
  - Conduct sensitivity analyses to demonstrate robustness of study conclusions to missing data assumptions
  - Formulate all assumptions in a manner that can be clinically interpretable and transparent
- Lessons learned
  - Examine patterns and reasons of drop-out/missingness from completed trials
  - Use acquired knowledge for design of future studies (including Phase II → Phase III).

Use of evidence from historical data: insomnia example

- Randomized, double-blind, two-arm trial vs. placebo;
- Efficacy score total sleep time (TST)
  - higher is better.
- About 20% withdrawals expected in each treatment group.
- We will suppose the experimental treatment has a mechanism of action similar to the orexin receptor antagonists (ORAs).
- Data on post-withdrawal TST in an ORA is available in recent randomized withdrawal study available as FDA Briefing Document.

Historical data: subjects on ORA suvorexant randomized to placebo

Figure 17
Observed Mean for Subjective Total Sleep Time (sTSTm; minutes) at Baseline (Month 0), Month 12, and during each week of the Randomized Discontinuation Phase (LDA / Randomized Discontinuation Set / Data-as-Observed) – P009



FDA Peripheral & Central Nervous System Drugs Advisory Committee Meeting (2013) Suvorexant Tablets Insomnia indication Advisory Committee Briefing Document for NDA 204569

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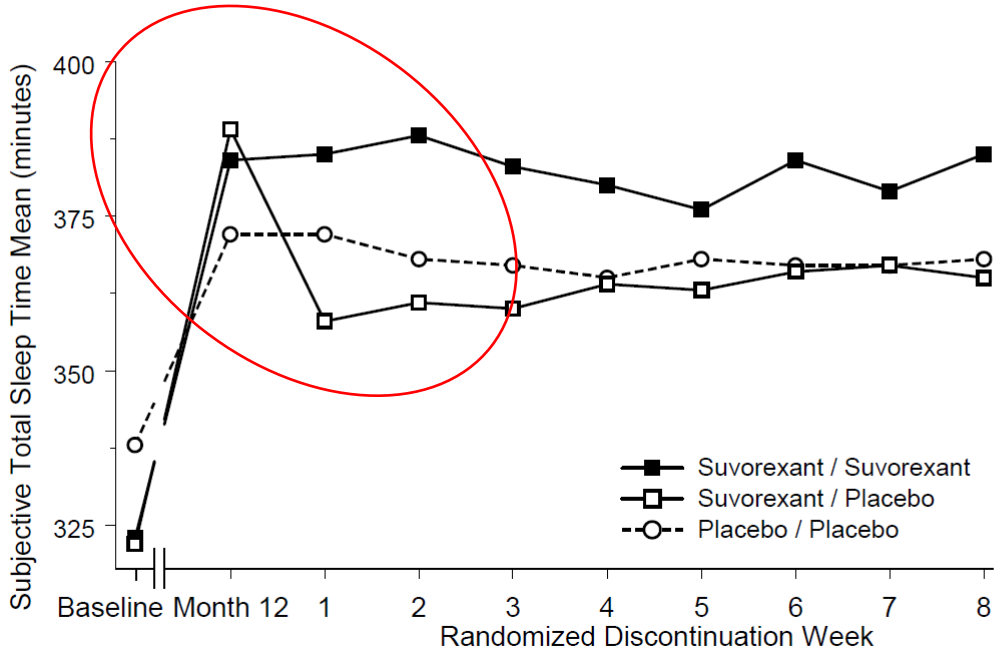

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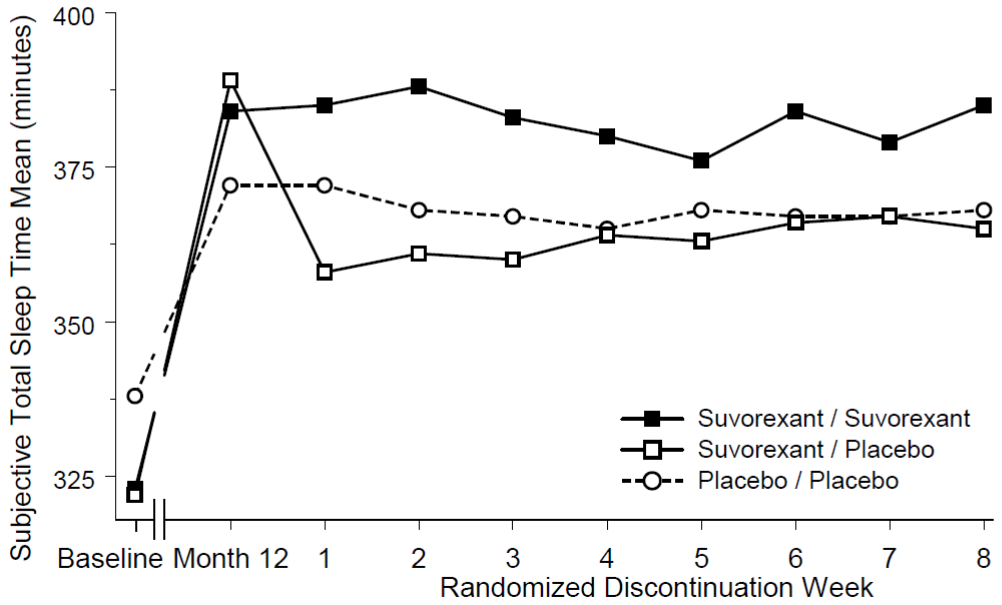

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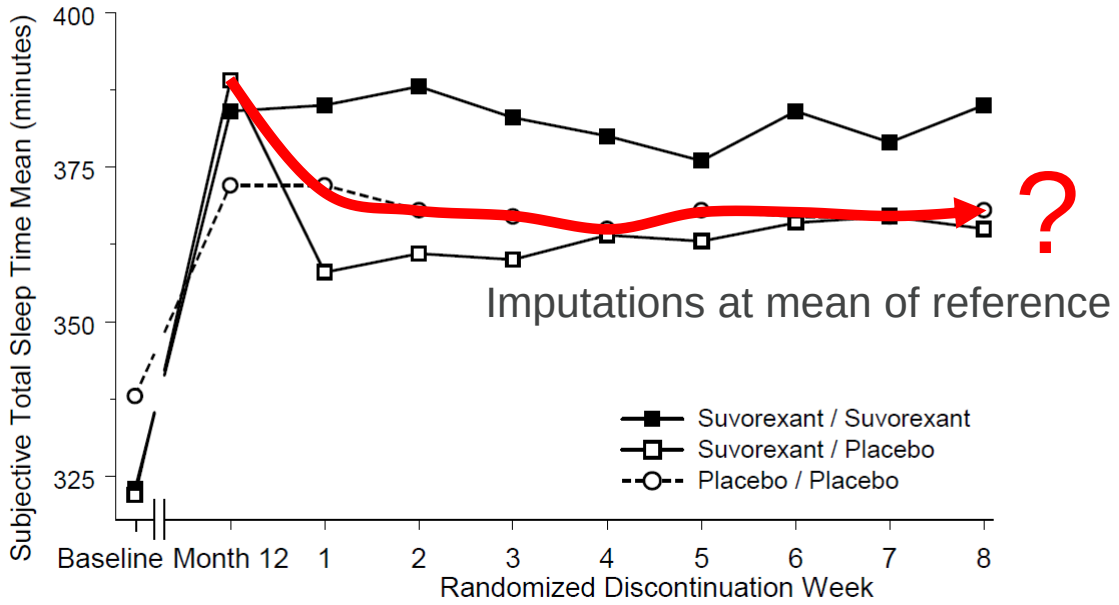

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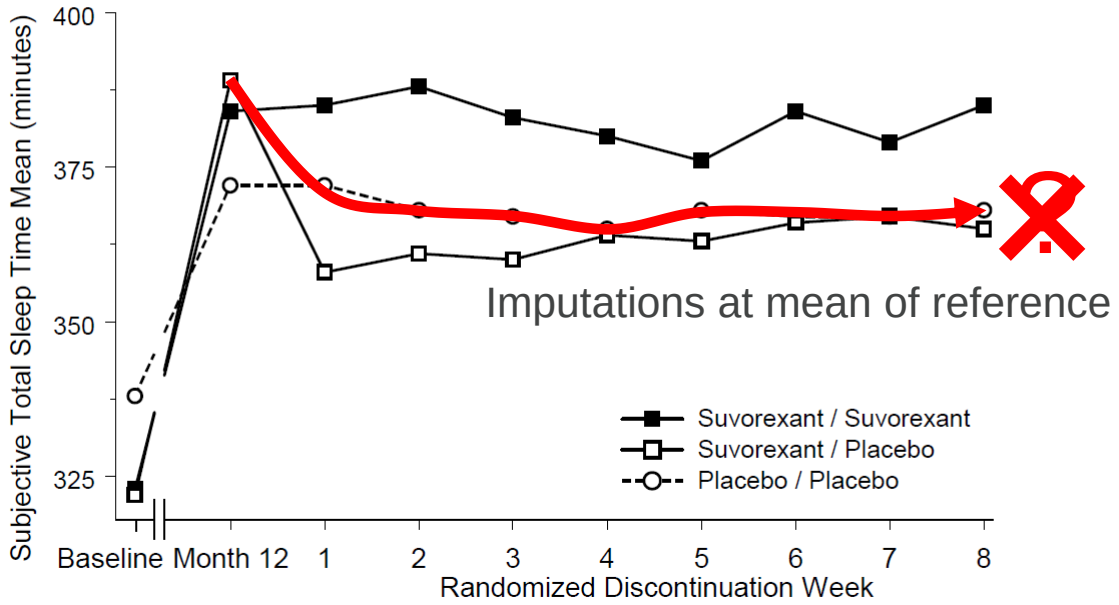

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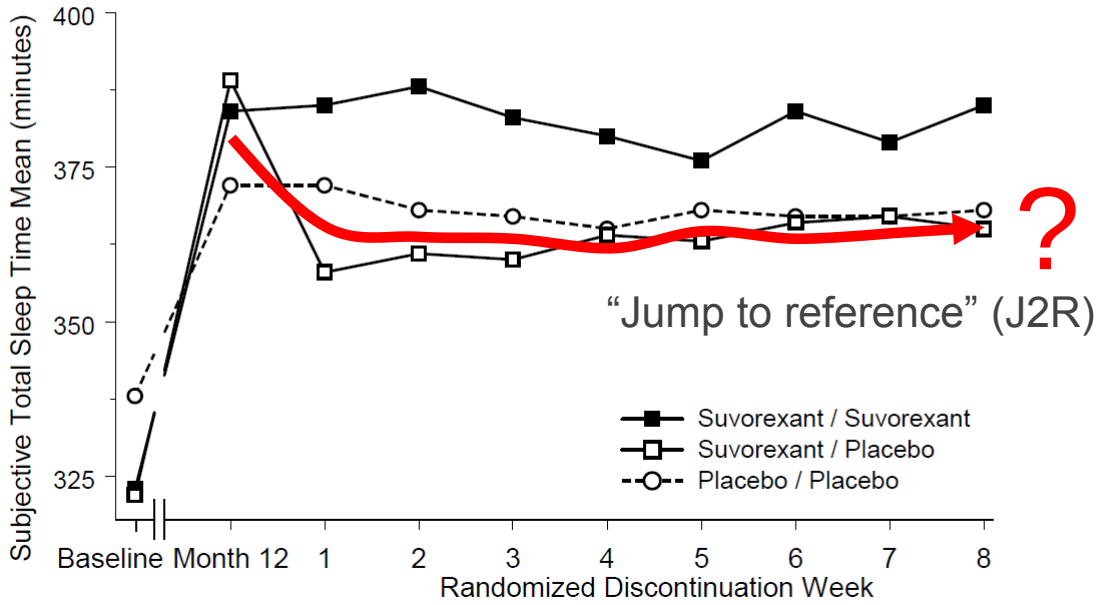

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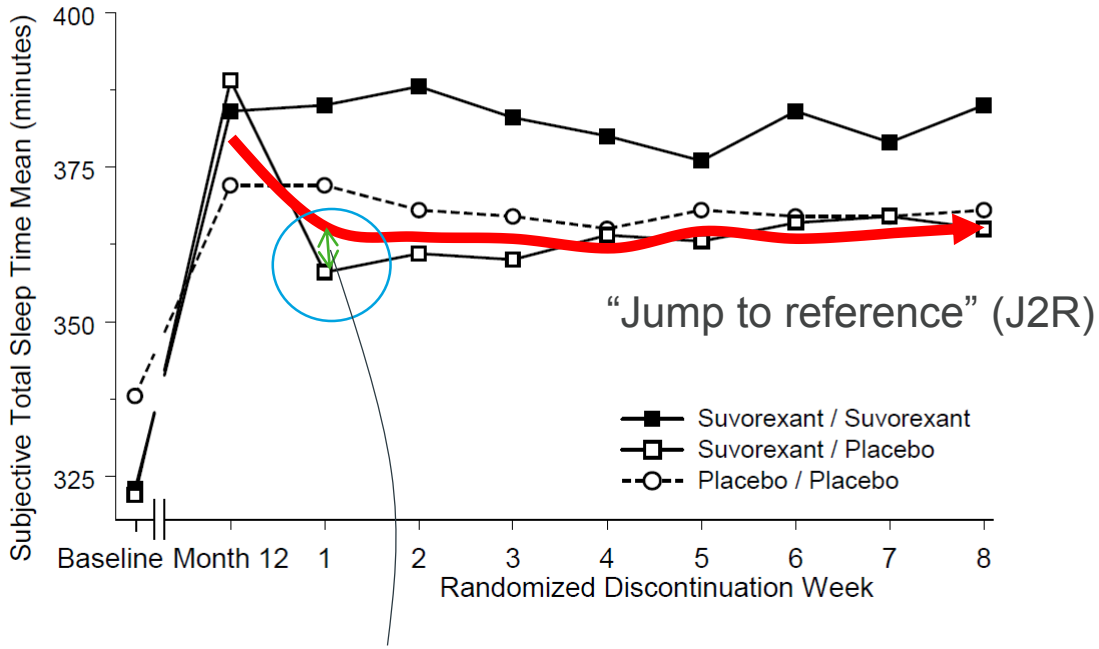

Take account of apparent early lower TST by subtracting 10 minutes here ("delta adjustment")?

FDA Peripheral & Central Nervous System Drugs Advisory Committee Meeting (2013) Suvorexant Tablets Insomnia indication Advisory Committee Briefing Document for NDA 204569

Using historical data for planning, case study: insomnia

- Based on historical data, clinically interpretable (and clinical reasonable) assumptions for missing data could be
  - Imputations for experimental arm follow the “jump to control” assumption: withdrawal from experimental arm, usually with poor TST, will be imputed to perform similarly poorly in the control arm, OR
  - As above, but subtract 10 minutes from imputed values for first post-withdrawal visit (“delta-adjust” with $\delta = 10$) to take account of apparent early lower TST in withdrawals.

Interpretability

- Assumptions about missing data will be most useful if they reflect reasonable (clinical) scenarios and result in (clinically) interpretable estimates: statisticians and subject matter experts can work together to identify these.
  - The intelligent reader will want scientific justification for missing data strategy.
  - Ask “Is what I am estimating of interest, given the data I am likely to be able to collect?”
  - Historical data are often available to help subject matter experts and statisticians identify likely outcomes dependent on events that interfere with the experiment
    - › Using historical data will encourage us to base the estimand and the corresponding strategy in scenario(s) likely to be relevant to practice.

In summary

- Thinking and practice with regard to incomplete data in clinical trials has evolved considerably in the last 10-15 years
  - “handle” it -> take it into account -> it’s bound up in what we estimate
- “Superusers” can spread good practice for missing data
  - Research is ongoing and “Superusers” will need good and ongoing expert support
- Prevention of missing data – statistician’s role
- You would be surprised at how much evidence is available from historical data to aid planning for missing/unusable data
- Where missing/unusable data are concerned, stats methodologies should not be dominant factor
  - Rather, we work with others towards an interpretable estimand that fits with a useful objective
    - › (…while helping to steer the experiment away from bias, inefficiency and false positive findings).