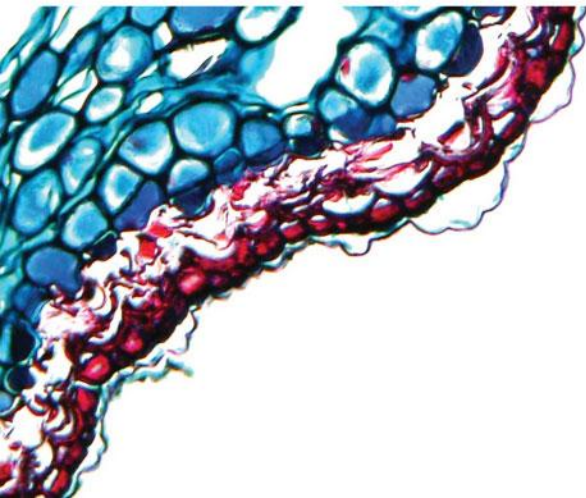


Planning for missing data: case studies

*Michael O'Kelly, Senior Director, Centre for
Statistics in Drug Development, Innovation,
Quintiles*



Acknowledgements

- SAS implementation of many key sensitivity analyses based on work by James Roger, (GlaxoSmithKline and London School of Hygiene and Tropical Medicine), with James Carpenter and Mike Kenward
- Dana Ratitch, Quintiles, co-research on missing data
- Sonia Davis, Quintiles, co-developing training in missing data
- Gary Koch, University of North Carolina

Summary

- Two helpful regulatory documents
- What is our objective when we “handle missing data”?
- How to plan an approach for missing data - help from the guidance docs
- Plan what?
- Primary analysis
- Sensitivity analyses
- Cases
 - Parkinson’s disease: patients expected to worsen, side effects expected
 - CNS indication: use of control-based sensitivity analysis approved
 - Dropouts expected to take alternative treatment: primary analysis MNAR
 - Study objective is non-inferiority: a case for MAR?
 - Using evidence on withdrawals in manic depression
 - Using auxiliary data to improve MAR
 - Extra case study, insomnia: patients expected to improve

Two helpful regulatory documents

- *The prevention and treatment of missing data in clinical trials*
 - FDA-sponsored report by the National Research Council, published by the National Academy of Sciences (hereafter “FDA report”)
- *Guideline on missing data in confirmatory trials*
 - European Medicines Agency (EMA)

What is our objective when we “handle missing data”?

- “Reduce the amount of missing data” (FDA report)
- “Elucidation of the missing data pattern” (EMA *Guideline*)
 - “helps to understand the likely direction of any bias in the analyses”
 - “empirical evidence lacking” (FDA report)
- “sample size calculations” (FDA report)
- **Render study results credible in the presence of missing data**
 - “Reduce the potential for lack of robustness of final estimates” (FDA report)

Regulatory hints about how to plan

- Factors that affect the acceptability of individual method (EMA *Guideline*)
 - **expected differences between treatment groups in the proportion and timing of patient withdrawals**
 - (e.g. Rheumatoid arthritis (RA): control groups have more withdrawals those treated with biologics)
 - **expected reasons for withdrawal**
 - (e.g. more AEs may be expected in the experimental treatment group)
 - **expected direction of spontaneous changes over time**
 - (e.g. decline in Parkinson's disease; improvement in insomnia, reversion in pain)

- to which we can add
 - **expected post-study treatment after early withdrawal**

- Assumptions about the missing data mechanism **must be transparent and accessible to clinicians** (FDA report)

How to plan, continued

- also relevant
 - study objective
 - primary estimand and statistical test
 - (estimand = that which is to be estimated)
 - potential auxiliary data

Plan what?

- Primary analysis
 - “unlikely to be biased in favour of experimental treatment to an important degree” (EMA *Guideline*)
- Sensitivity analyses
 - “assess the degree to which the treatment effects rely on the assumptions used (by the primary analysis)” (FDA report)

Primary analysis

- “Unlikely to be biased to an important degree”
- Last observation carried forward?
 - potential bias depends upon relative position on efficacy trajectory when withdrawn
- Missing at random (MAR)?
 - Often an assumption of MAR can be justified as “unlikely to be biased to an important degree”
- Potential weaknesses that may need to be addressed
 - Is MAR consistent with plausible clinical scenarios?
 - see e.g. later case study
 - are the models valid?
 - use less assumptions, e.g. generalised estimating equations (GEEs)

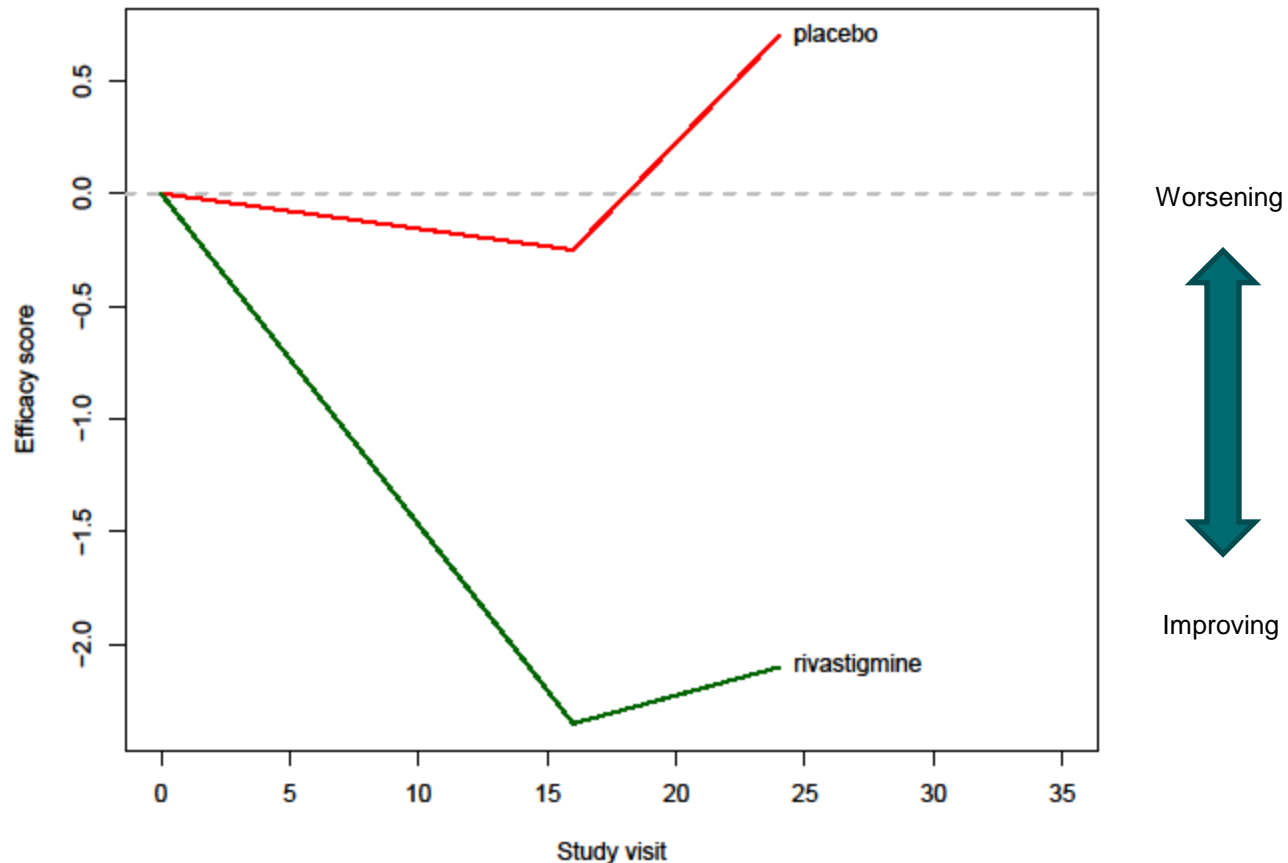
Sensitivity analyses

- EMA: factors that affect the acceptability of individual methods
 - **expected differences between treatment groups in the proportion and timing of patient withdrawals**
 - (e.g. RA: control groups have more withdrawals those treated with biologics)
 - **expected reasons for withdrawal**
 - (e.g. more AEs may be expected in the experimental treatment group)
 - **expected direction of spontaneous changes over time**
 - (e.g. decline in Parkinson's disease; improvement in insomnia, reversion in pain)

- to which we can add
 - **expected post-study treatment after early withdrawal**

Case study: Parkinson's disease (PD) QUINTILES®

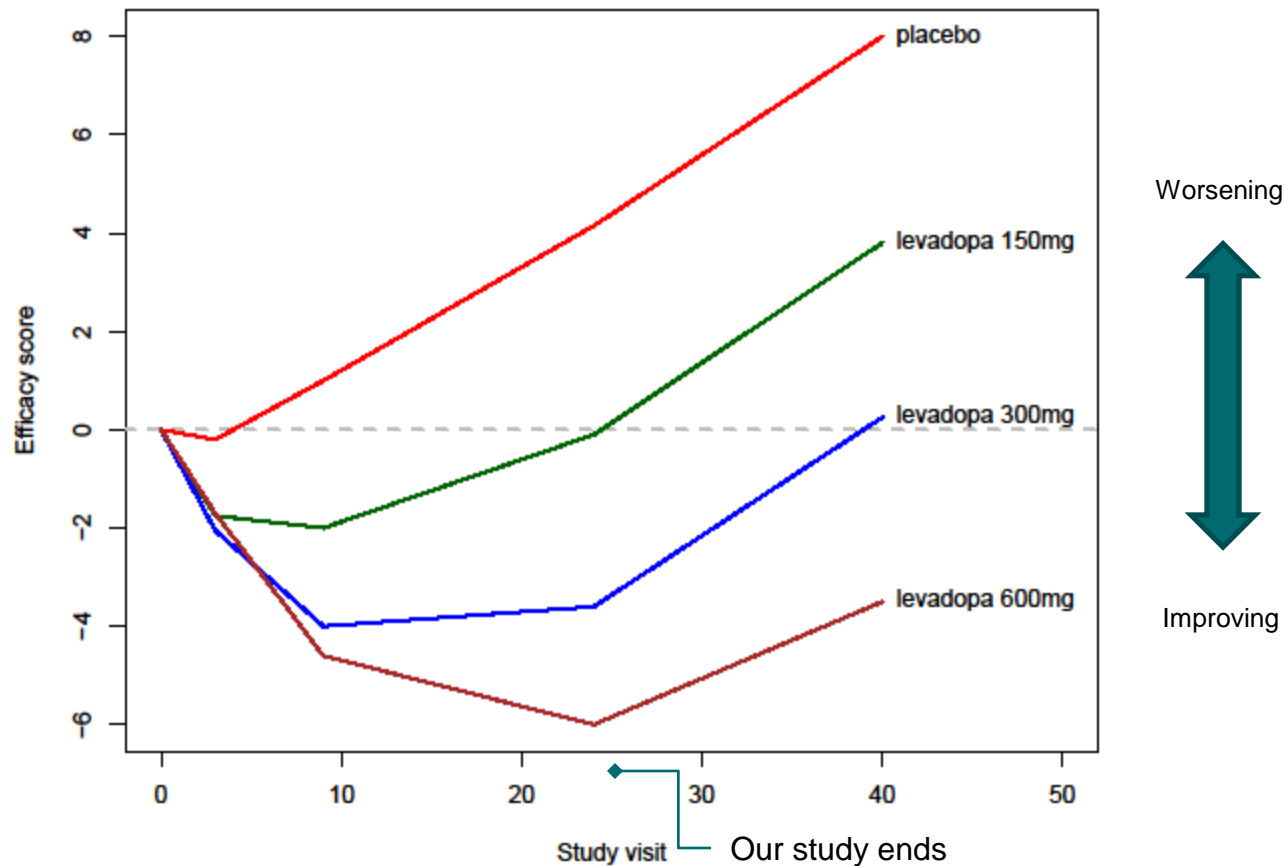
Rivastigmine study, 2 years after diagnosis, 2004



Emre M *et al.*, 2004, Rivastigmine for dementia associated with Parkinson's disease, *NEJM*, 351, 2509-1861-566

PD efficacy over time, what can we expect?

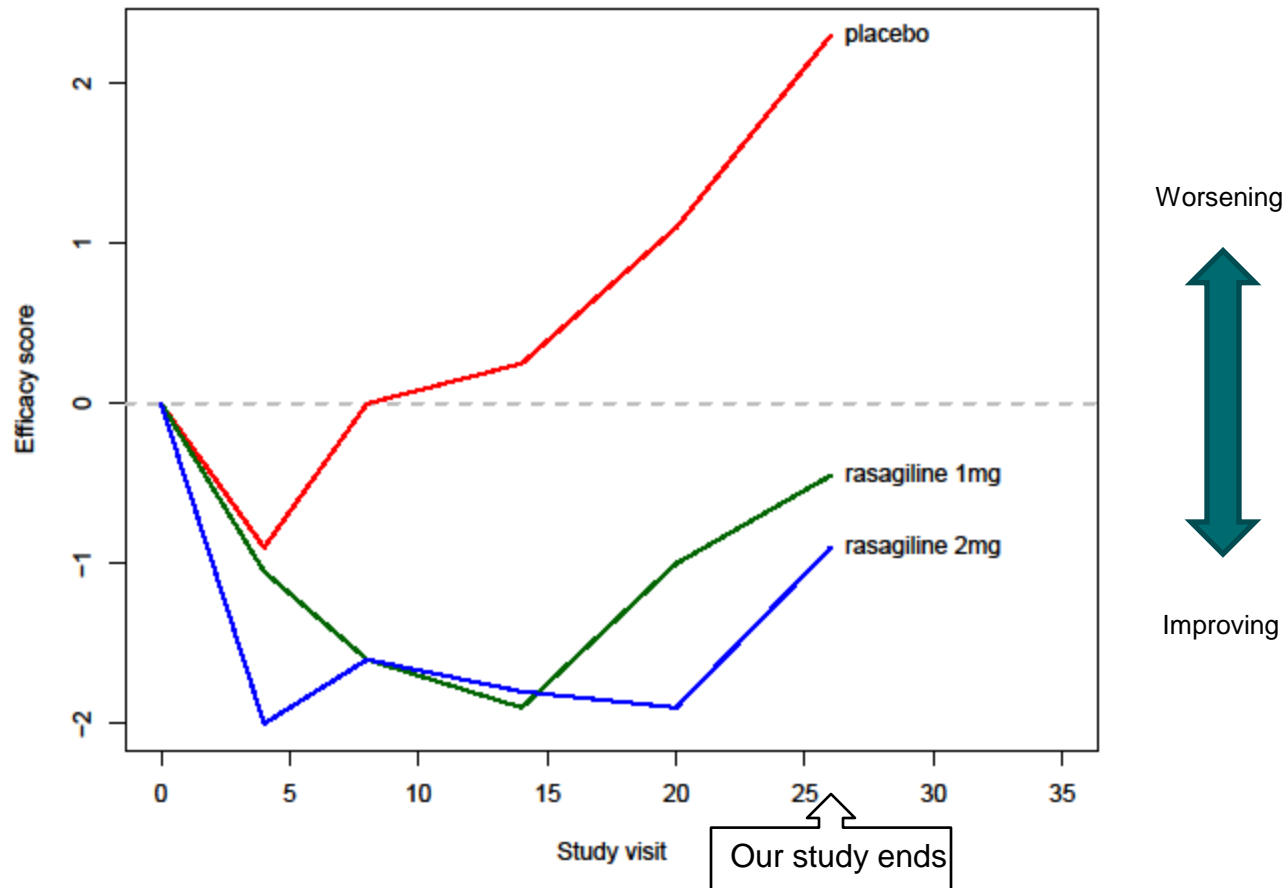
Levodopa study, early Parkinson's, 2004



Parkinson Study Group, 2004, Levodopa and the Progression of Parkinson's Disease, *NEJM*, 351:2498-508

PD efficacy over time, what can we expect?

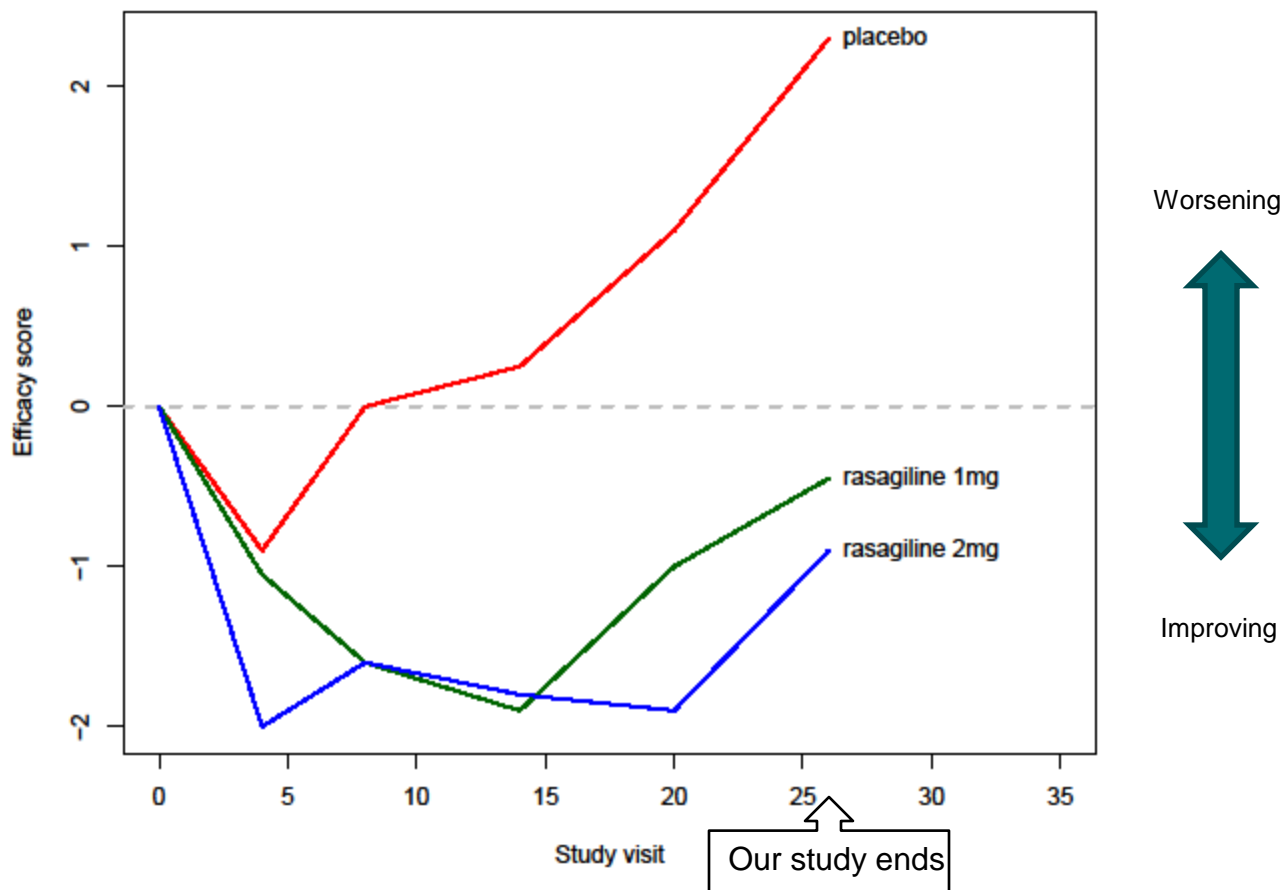
Rasagiline study, early Parkinson's, 2004



Parkinson Study Group, 2004, A controlled, randomized delayed-start study of rasagiline in Early Parkinson Disease, *Arch Neurol.* 2004;61:561-566

Mixed model (MMRM) – assume missings follow study pattern?

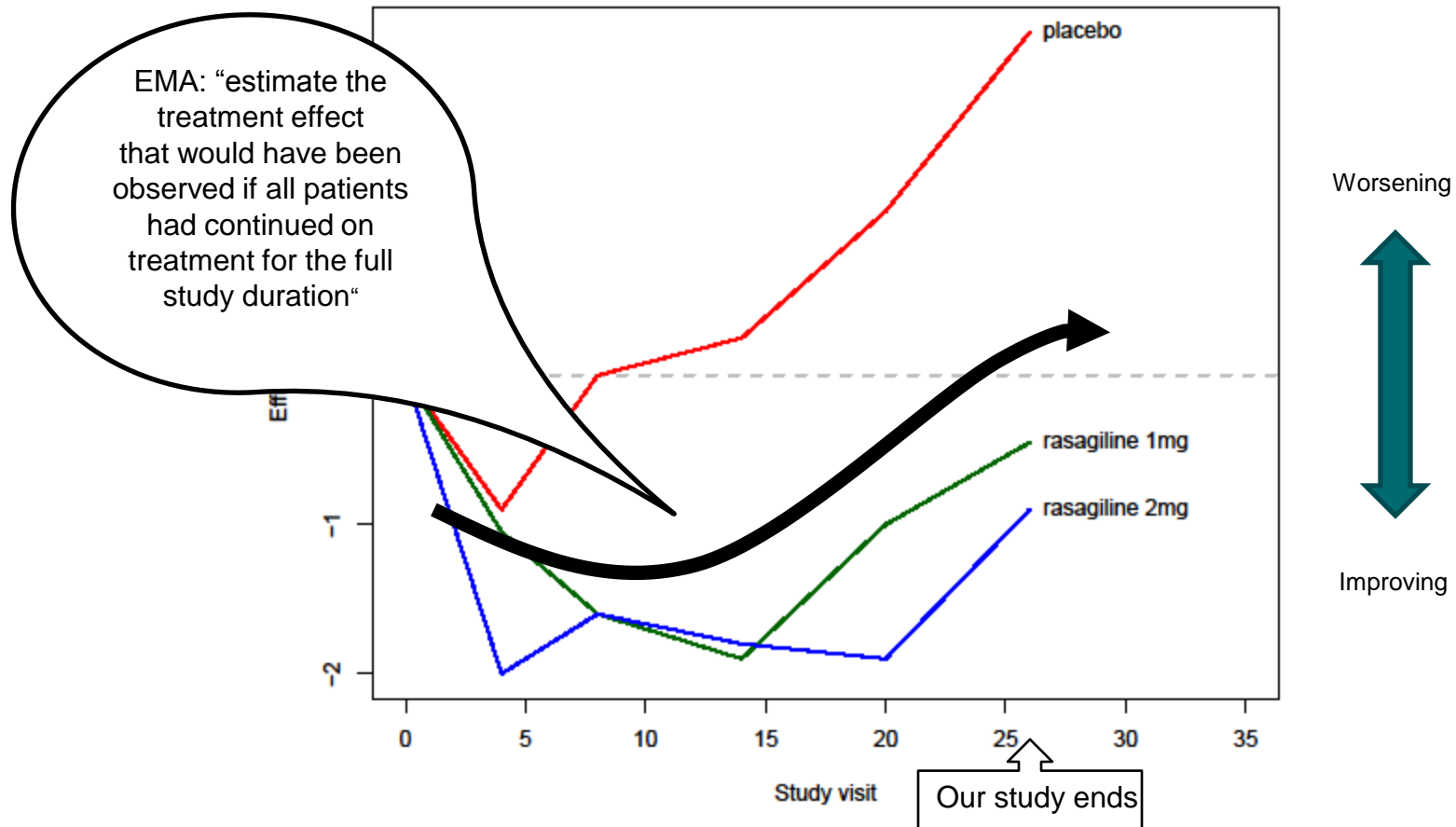
Rasigiline study, early Parkinson's, 2004



Parkinson Study Group, 2004, A controlled, randomized delayed-start study of rasagiline in Early Parkinson Disease, *Arch Neurol.* 2004;61:561-566

Mixed model (MMRM) – assume missings follow study pattern?

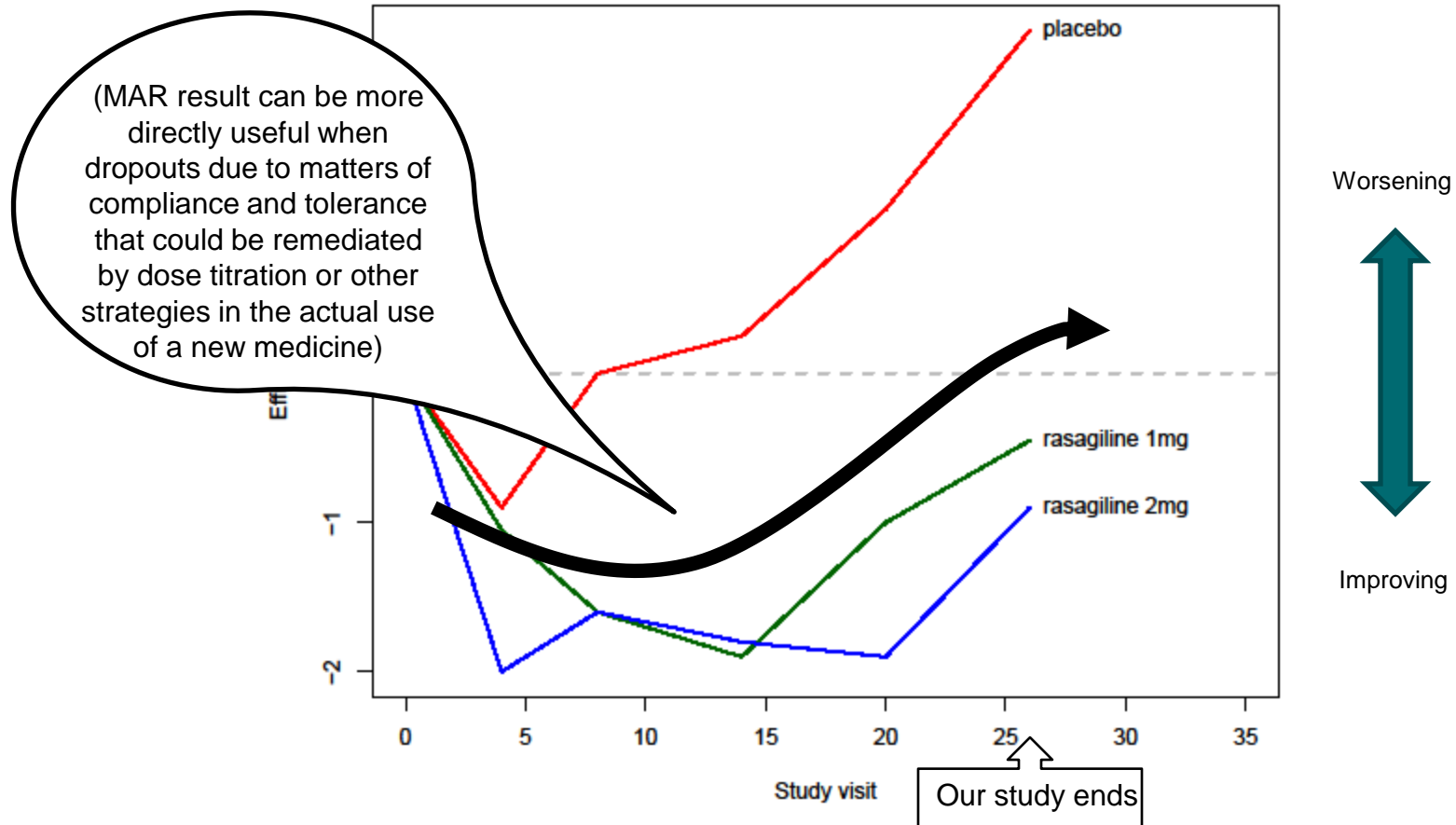
Rasigiline study, early Parkinson's, 2004



Parkinson Study Group, 2004, A controlled, randomized delayed-start study of rasagiline in Early Parkinson Disease, *Arch Neurol.* 2004;61:561-566

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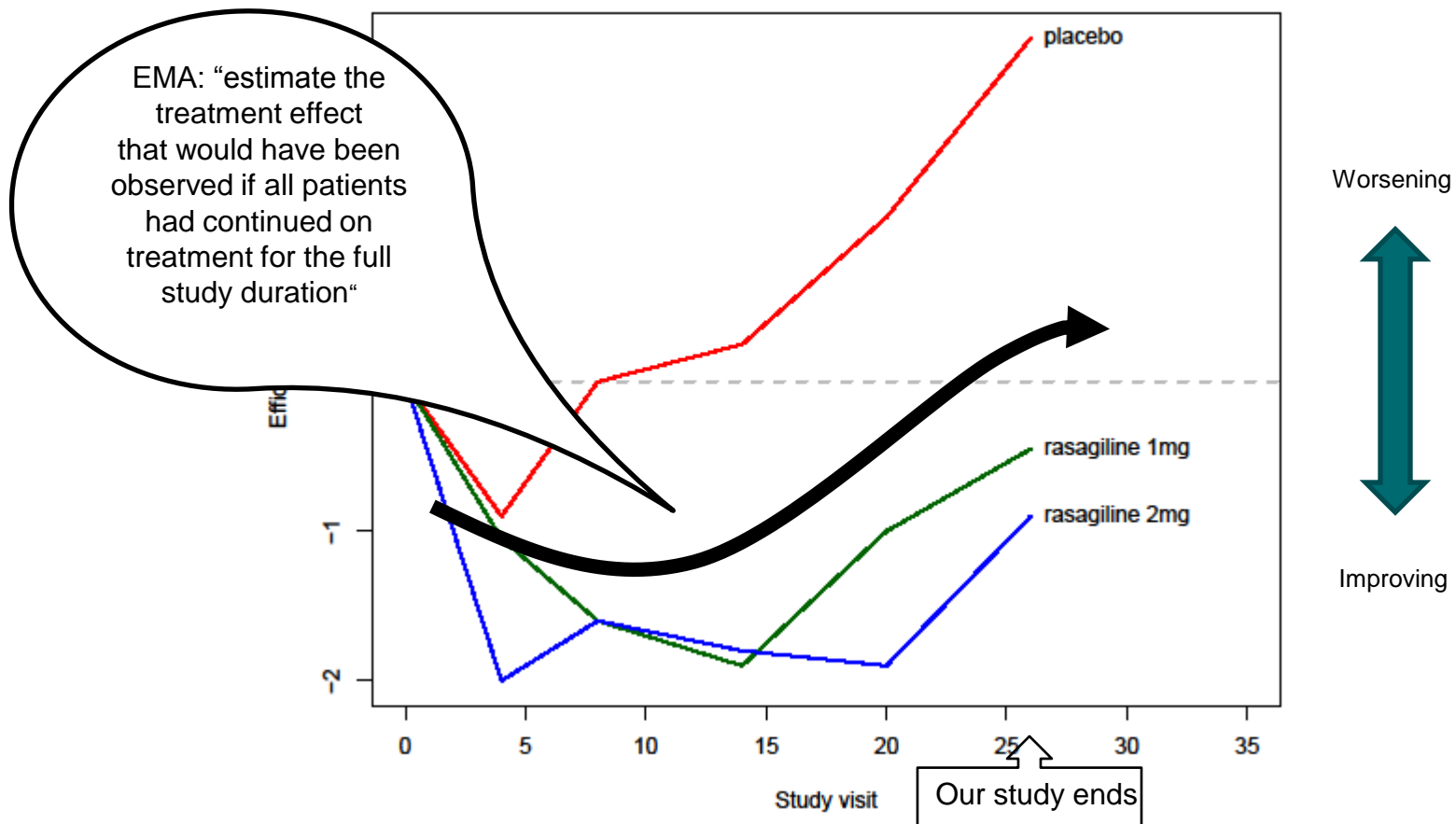
Rasigiline study, early Parkinson's, 2004



Parkinson Study Group, 2004, A controlled, randomized delayed-start study of rasagiline in Early Parkinson Disease, *Arch Neurol.* 2004;61:561-566

Mixed model (MMRM) – assume missings follow study pattern?

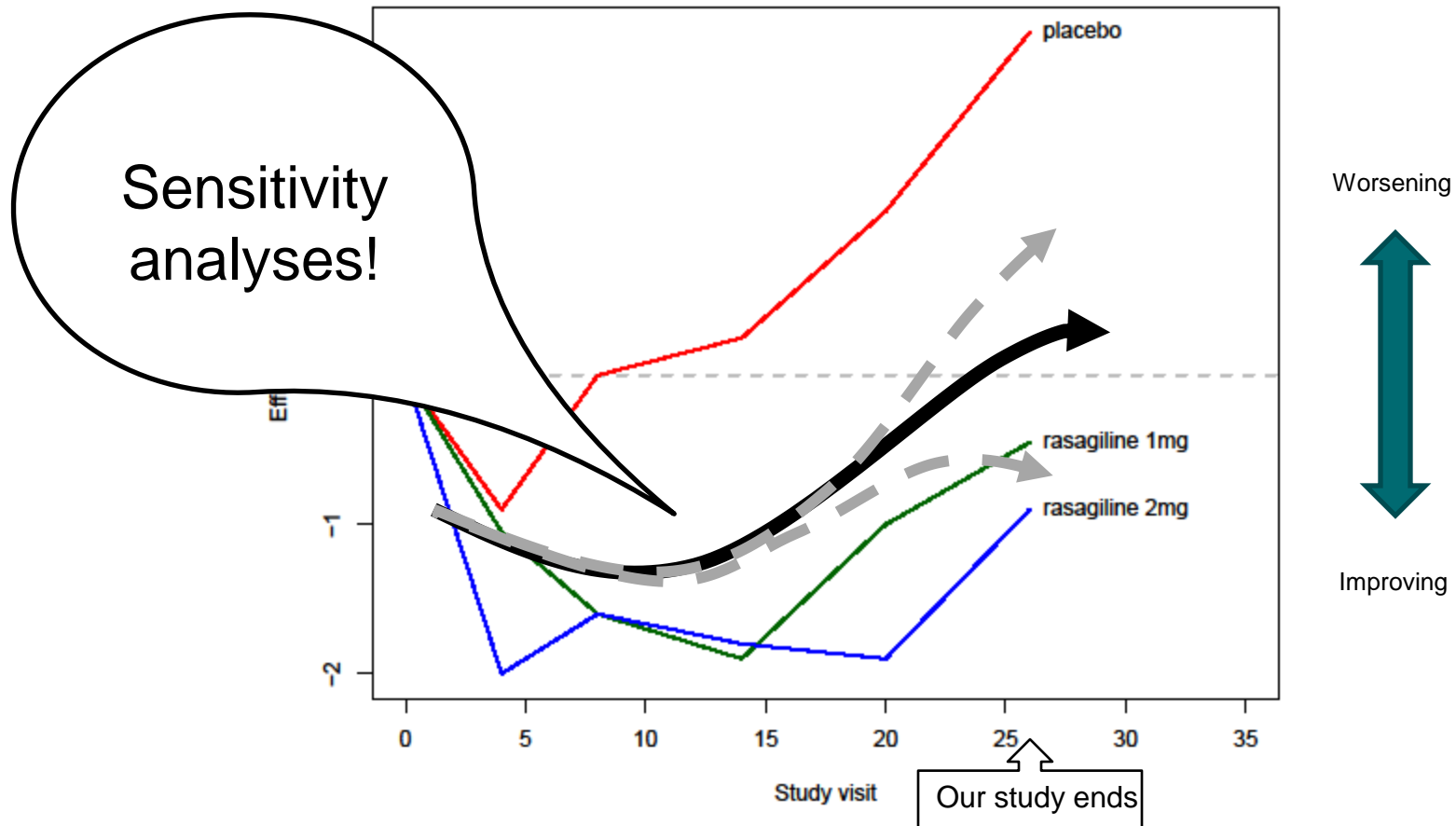
Rasigiline study, early Parkinson's, 2004



Parkinson Study Group, 2004, A controlled, randomized delayed-start study of rasagiline in Early Parkinson Disease, *Arch Neurol.* 2004;61:561-566

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Expected differences in proportions of dropouts

	Percentage dropouts	
	Placebo	Active
Rivastigmine study	18	27
Levodopa study	22	17
Rasigline study	4	6

Expected differences in proportions of dropouts

Our study perhaps more like these two

Percentage dropouts

	Placebo	Active
Rivastigmine study	18	27
Levodopa study	22	17
Rasigline study	4	6

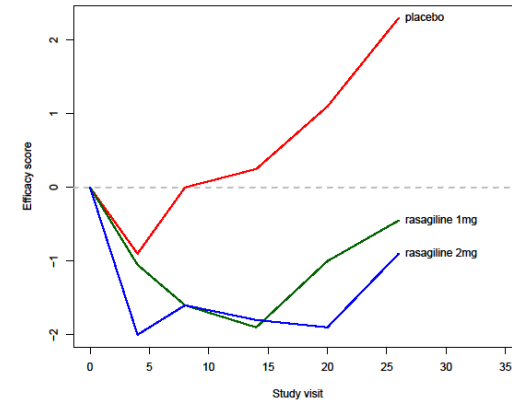
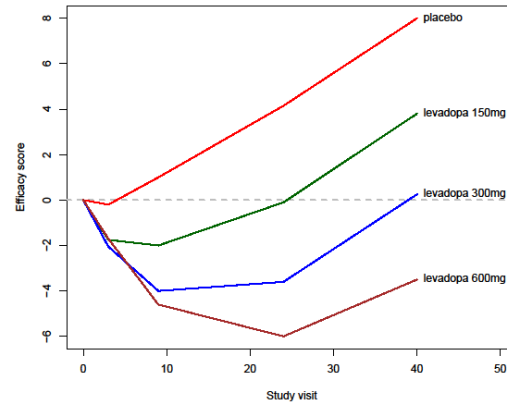
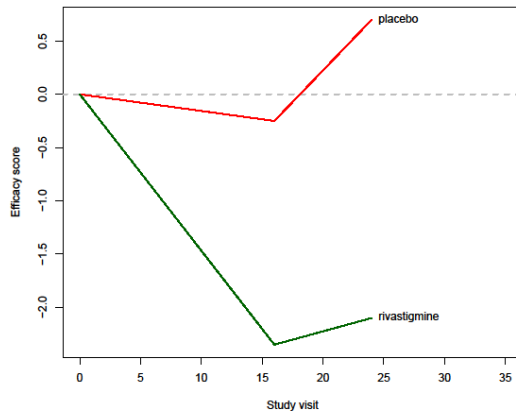
Characteristics of example Parkinson's study

- Objective: superiority to placebo
- 6-month follow-up
- 13 visits, last visit primary

So what do we plan?

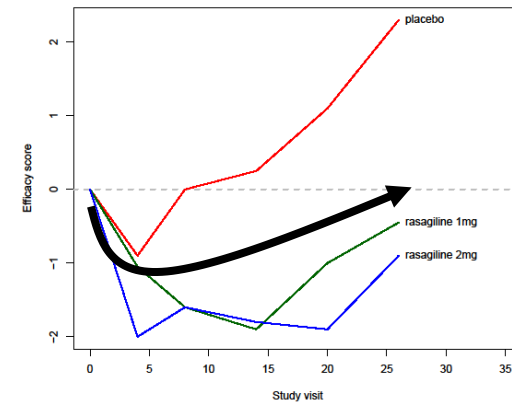
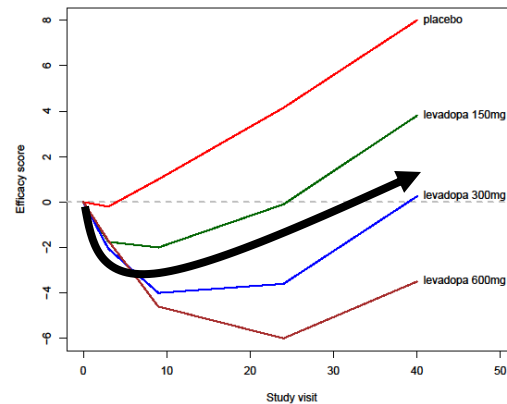
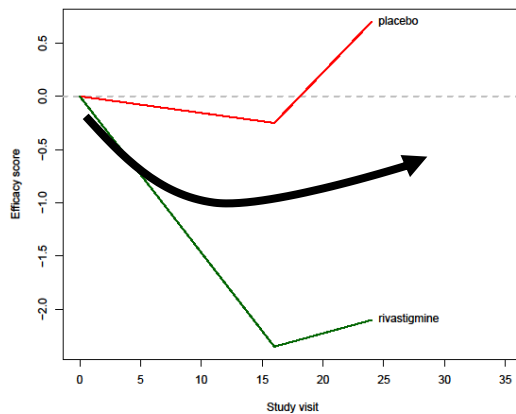
- complete cases/available cases?
- last observation carried forward (LOCF)?
- MAR approach (MMRM – mixed models repeated measures - or multiple imputation)?
- (weighted GEEs - doubly robust methods?)

MAR for primary analysis?



MAR for primary analysis?

“unlikely to be biased in favour of experimental treatment to an important degree (under reasonable assumptions)”?

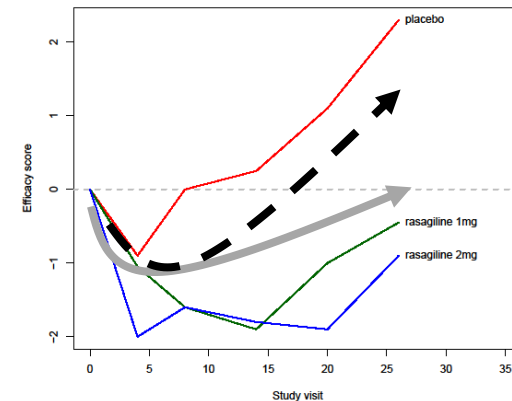
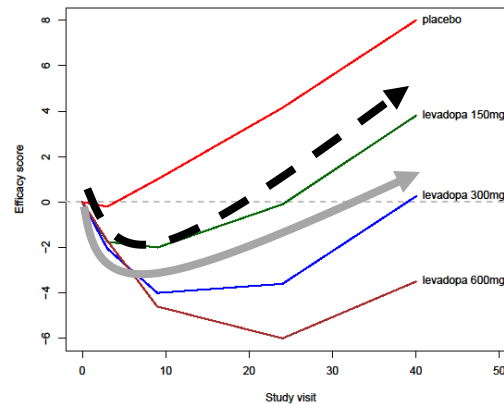
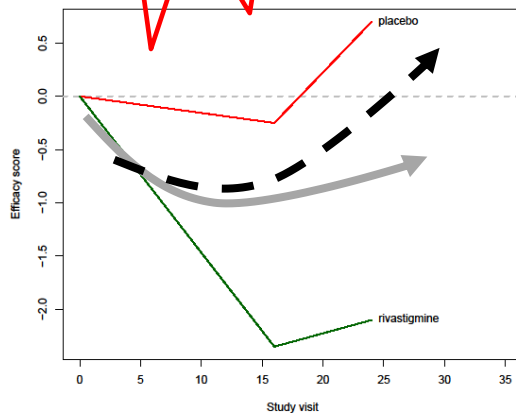


MAR for primary analysis?

“unlikely to be biased in favour of experimental treatment to an important degree (under reasonable assumptions)”?

But supposing dropouts do worse than most in the study?

sensitivity analysis needed!

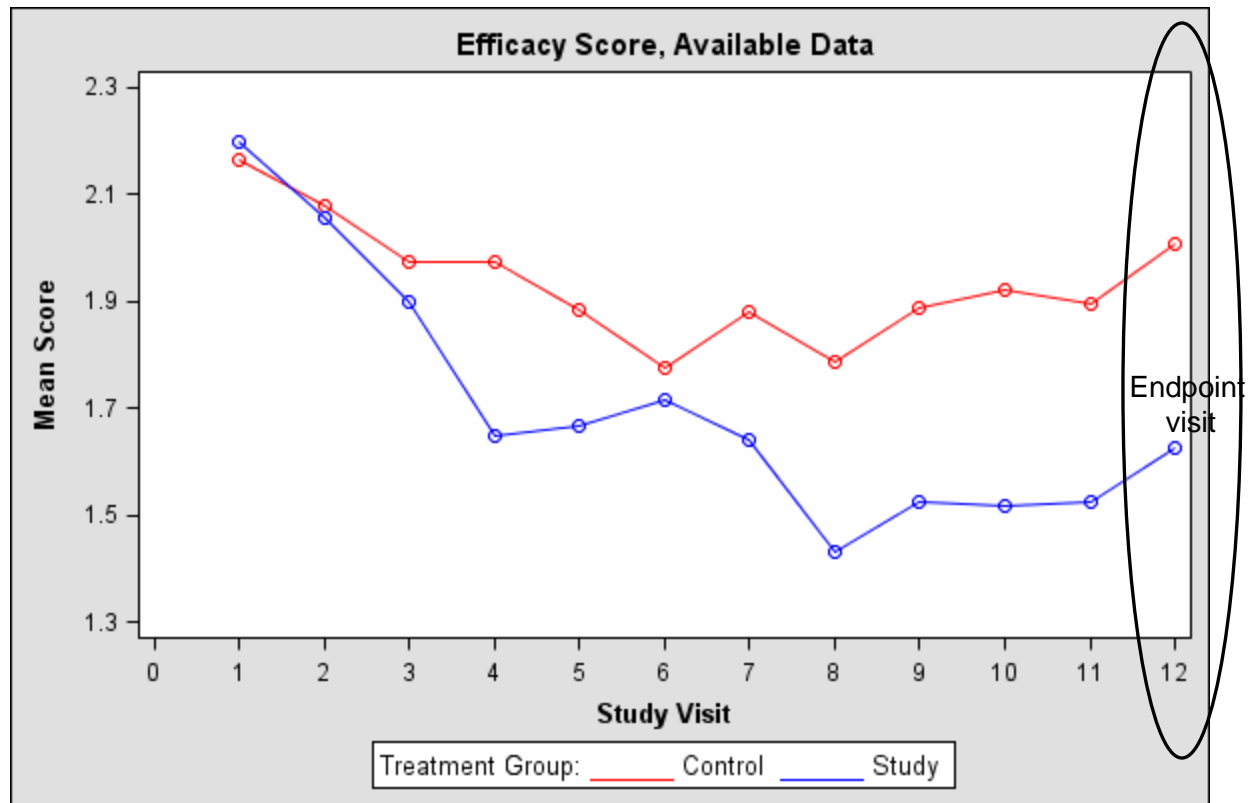


A plan for this PD example

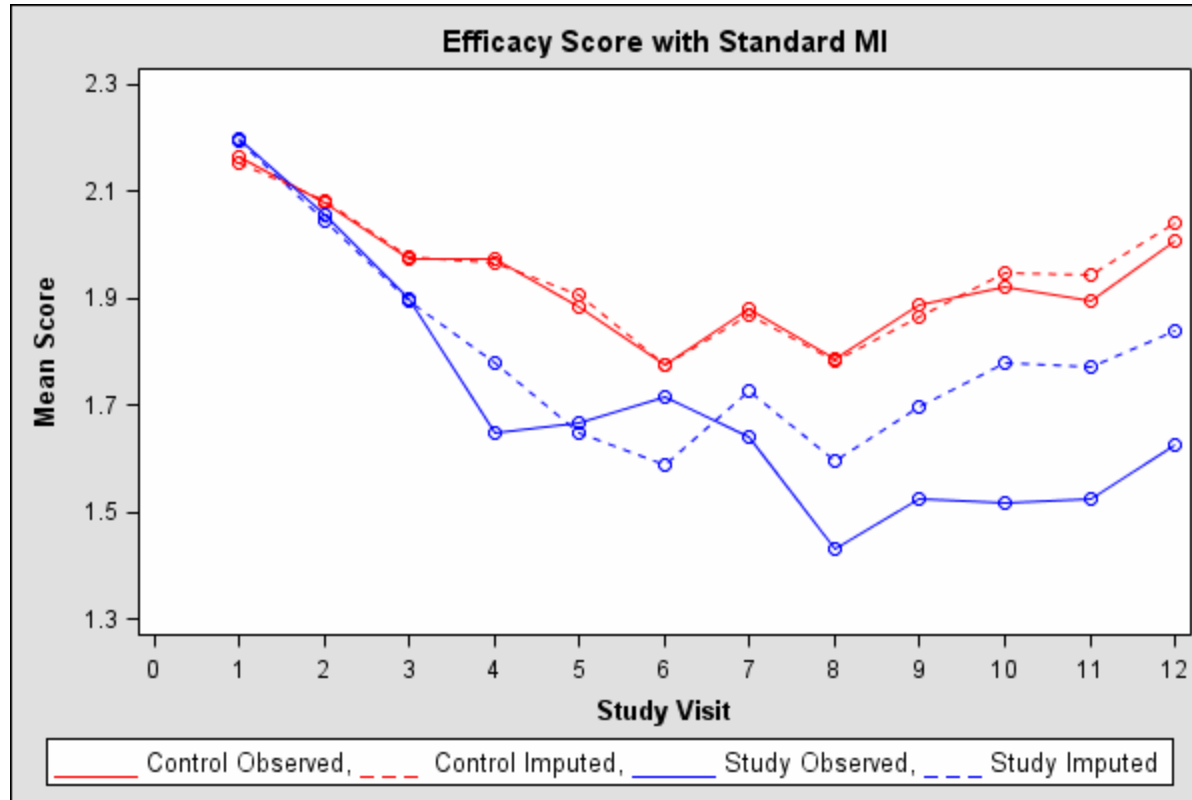
- Primary analysis:
 - “likelihood approach” ~ “mixed models repeated measures” (MMRM) or
 - multiple imputation (MI)
 - – missing data follows general study trend
- THEN sensitivity analysis
 - **1) What if** discontinuations (no longer treated) have trajectory of placebo group?
 - “Copy difference from control (CDC)” - Roger
 - No longer a PP estimate – more like an ITT estimate
 - Reasonable estimate of actual result when treatment no longer taken?
 - Dropouts in active will give lower efficacy estimate
 - idea of Roger, Carpenter and Kenward (2009), see also Little and Yau (1996)
 - **2) What if** value of missings depends on reason for discontinuation?
 - AE/Lack of efficacy/Withdrew consent: values have distribution of placebo group
 - Lost to follow-up/Protocol violation: values have trajectory of placebo group
 - Implemented via MI, using methods of Ratitch and O’Kelly (2011)

Results from disguised study in Parkinson's disease

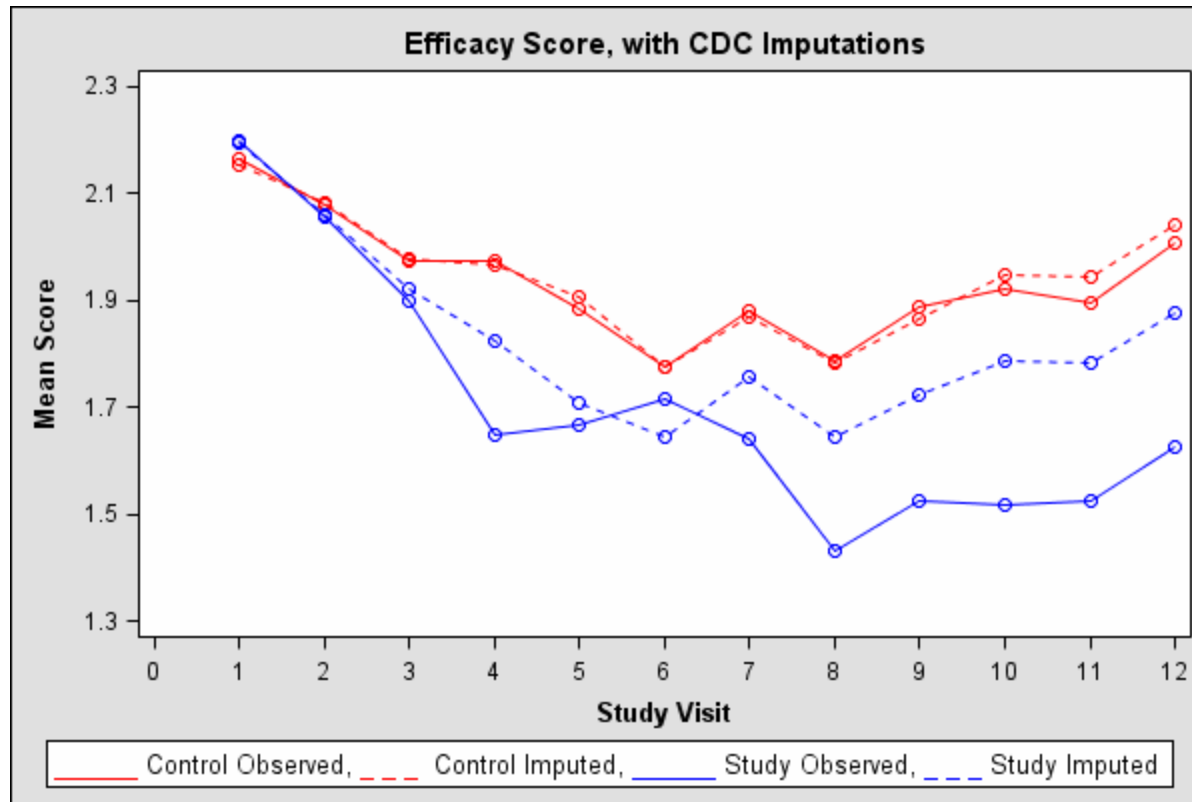
OLS ANCOVA, available data only (ignore missings)



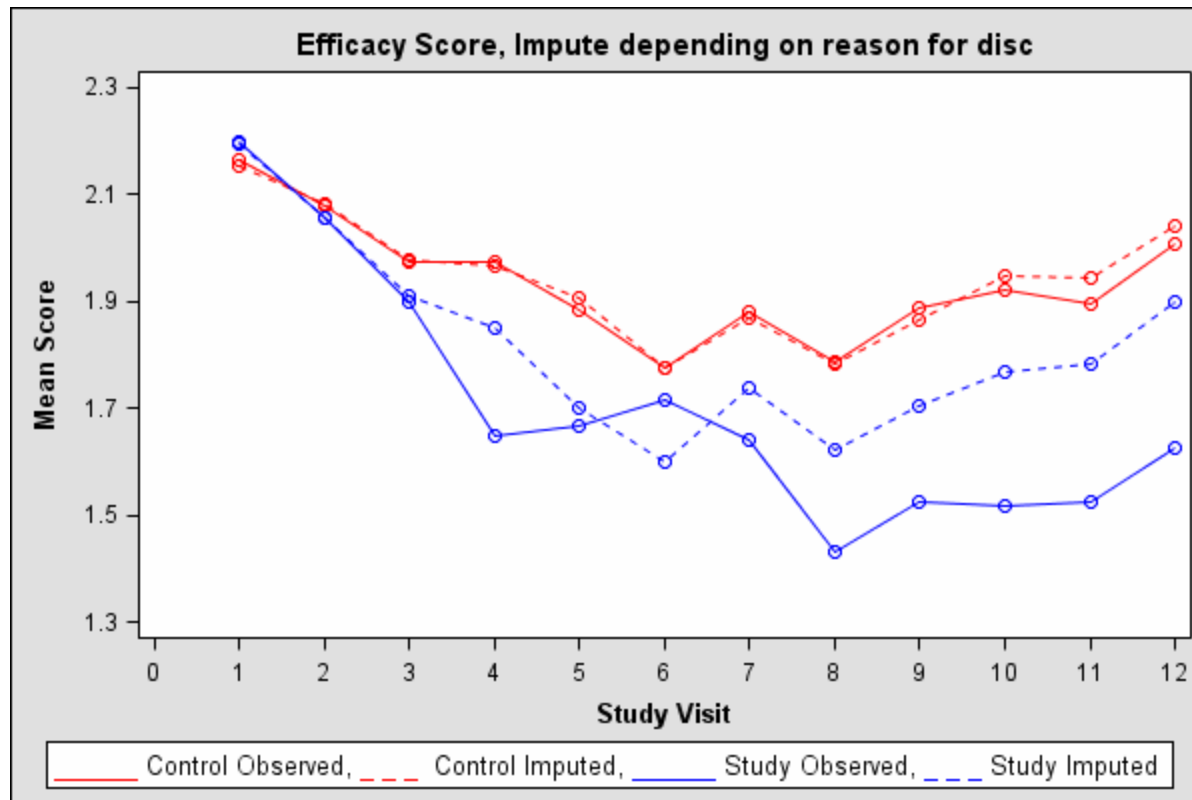
Available data and MAR



Add sensitivity analysis: what if study treatment had trajectory of control?



Add sensitivity analysis: what if assumption depends on reason for discontinuation?



PD case study conclusions

- LOCF unsuitable
- Available cases analysis misses substantial evidence from early dropout
- MAR: gives lower estimate of treatment effect vs. available cases
 - captures worsening of subjects who remain in study: dropouts assumed to worsen also
 - study treatment: more dropouts, estimate of its mean “worsened” more by MAR
 - needs stress test: assume efficacy for dropouts has slope like placebo

Case study: control-based sensitivity approved by FDA

- CNS indication: use of control-based sensitivity analysis approved
 - likely withdrawals regarded as significant in interpreting efficacy
 - control-based sensitivity analysis proposed
 - assume withdrawals have trajectory of control
 - FDA approved description in statistical analysis plan
 - sensitivity analyses used multiple imputation
 - simple method uses SAS/STAT and base SAS
 - can accomplish a variety of sensitivity
 - see Ratitch and O’Kelly, *Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures*

Case study:

Missing not at random (MNAR) primary analysis

- Superiority study
- Dropouts expected to switch to effective alternative medication
- MNAR planned as primary
- Assume missing values for efficacy are
 - like baseline OR
 - representative in-study value
- ...depending on reason for discontinuation and record of post-withdrawal treatment

Case study: rheumatoid arthritis, non-inferiority

- Objective: non-inferiority vs. biologic
- Patients improve up to a point under all treatments
- Cochrane review*: compared to control
 - biologics tend to have fewer dropouts overall
 - biologics tend to have more dropouts due to AEs
- Any strategy that imputes missings similarly in both treatment arms may bias towards non-inferiority
 - rule out LOCF!
- Plan for this example study
 - Primary analysis: MAR with separate imputation for each treatment group
 - Sensitivity analyses:
 - Different imputations depending on reason for withdrawal

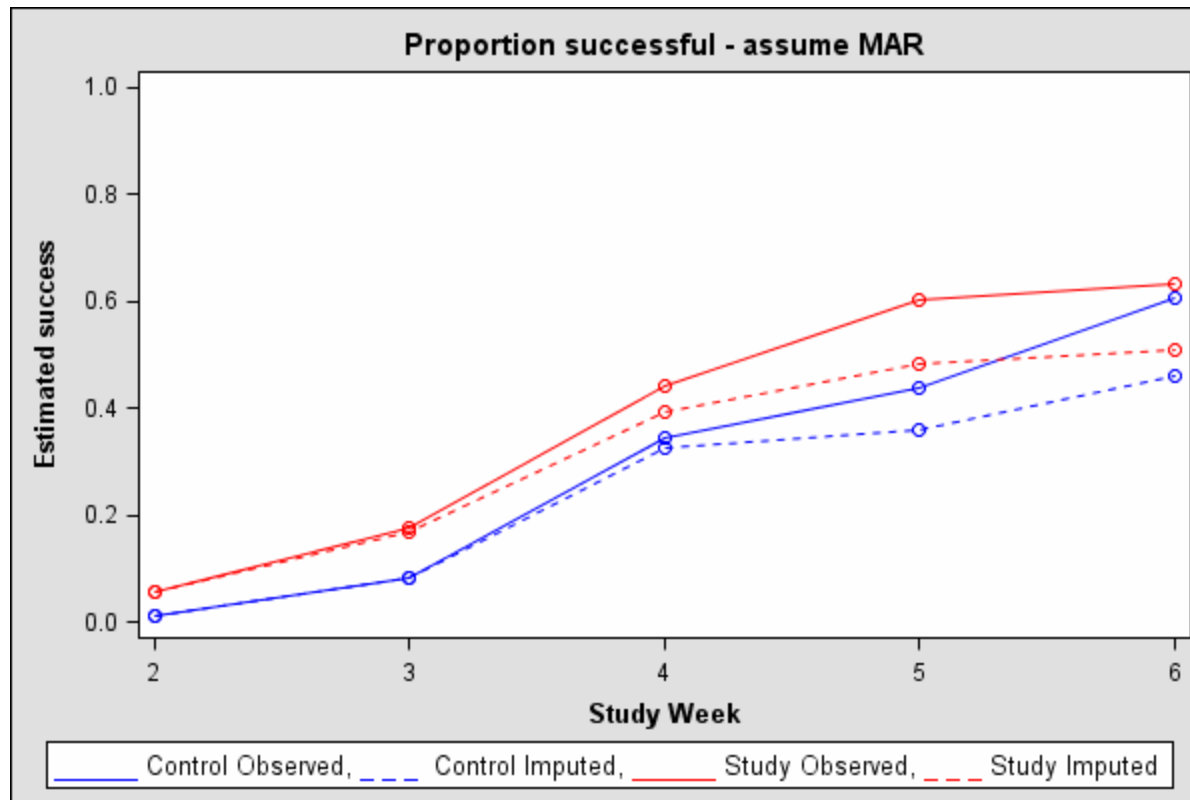
*Singh JA, Christensen R, et al., Biologics for rheumatoid arthritis, an overview... *Cochrane database of systematic reviews*, 2009

Using evidence on withdrawals in manic depression

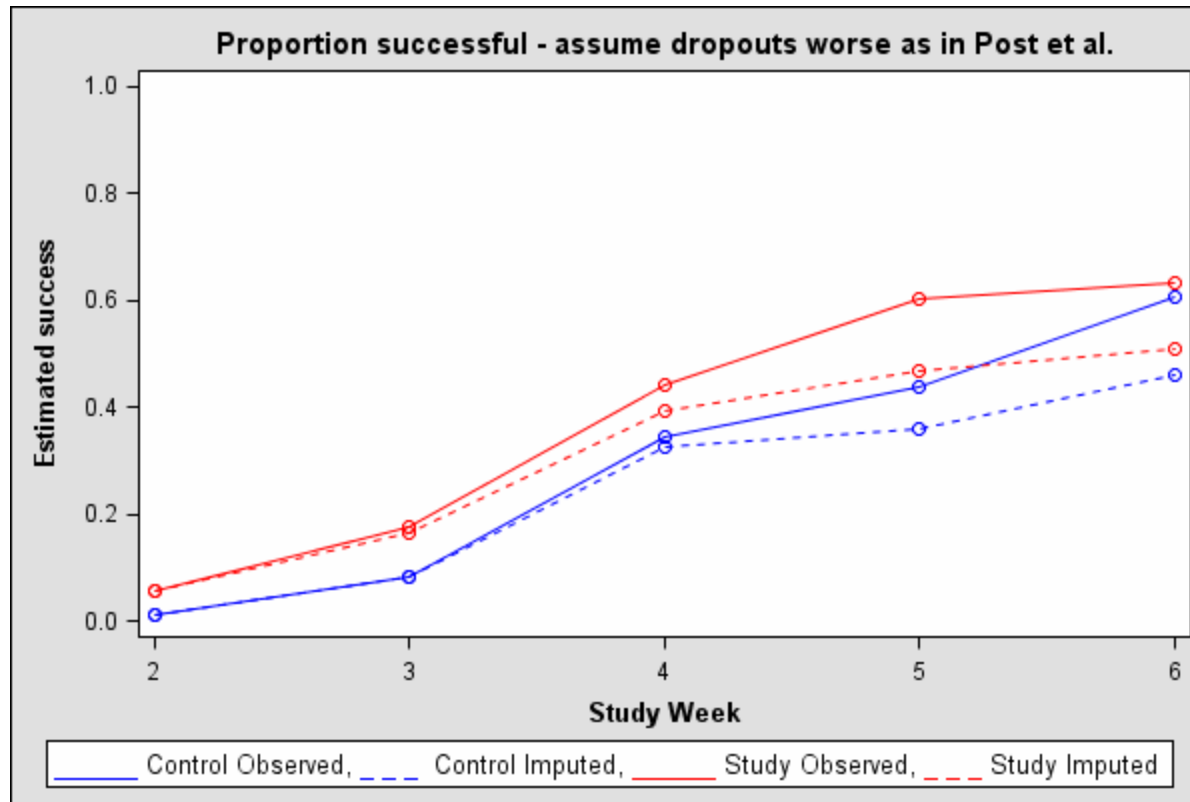
- Objective: superiority to placebo
- Many patients (on control and “active”) tend to improve over time
- Evidence from Post et al. (2005, nine patients)
 - some patients may worsen rapidly after dropout
- Evidence about proportion of withdrawals (“active” vs. placebo) is mixed
 - Bowden (2005), switch study
 - higher rates of withdrawal in placebo group
 - Bowden (2000)
 - more patients in placebo group withdraw due to mania/depression/other
 - more patients in “active” group withdraw due to intolerance/noncompliance
- Plan for this example study, binary endpoint, using MI
 - primary analysis MAR
 - sensitivity analyses
 - by reason for discontinuation
 - tipping point analysis, imputing progressively worse scores over time for dropouts
- If binary endpoint is dichotomisation, try imputing the source(s) of the endpoint, rather than the binary endpoint itself?

Results from disguised study in mania

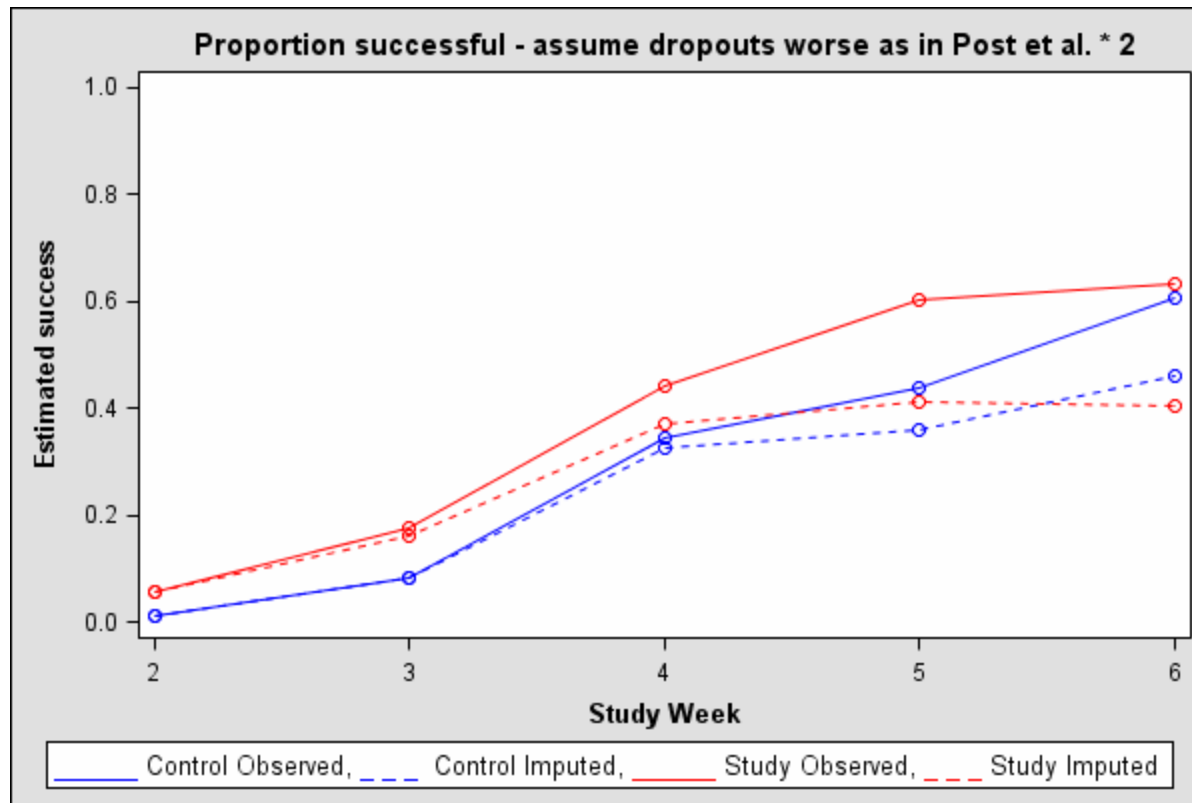
MAR



Dampen mean as per examples in Post et al.



Dampen mean: Post et al. * 2



Case study: auxiliary data

- CNS study
 - use logistic regression to identify factors associated with withdrawal
 - use those factors in MI to model likely MAR values
 - e.g.
 - total CNS score was primary efficacy
 - one key item in questionnaire was significant predictor of withdrawal

Selected references

Carpenter J and Kenward M, 2008, *Missing data in randomised controlled trials – a practical guide*, Birmingham: National Health Service Co-ordinating Center for Research Methodology, www.missingdata.org.uk, accessed 07May2010

European Medicines Agency, Committee for medicinal products for human use, 2010, *Guideline on missing data in confirmatory clinical trials*, Doc. Ref. CPMP/EWP/1776/99 Rev. 1, July 2010

Panel on Handling Missing Data in Clinical Trials, 2010, *The Prevention and Treatment of Missing Data in Clinical Trials*, pre-publication copy, <http://www.nap.edu/catalog/12955.html>, accessed 02Sep2010, National Academies Press

Molenberghs G and Kenward M, 2007, *Missing data in clinical studies*, Wiley

Roger J and Kenward M, *Repeated measures approach to What if questions for longitudinal data studies with withdrawal*, presentation at PSI conference 2009

Siddiqui O, Hung HMJ and O'Neill, R, MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 datasets, *Journal of Biopharmaceutical Statistics*, 19, 227-246

Carpenter J, Roger, J and Kenward M, 2009, *Relevant, accessible sensitivity analyses using multiple imputation*, revision in preparation.

Little R and Yau L, 1996, Intention-to-treat analysis for longitudinal studies with drop-outs, *Biometrics*, 1324-1333

Ratitch B and O'Kelly M, 2011, Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, PharmaSUG <http://www.quintiles.com/elements/media/inthenews/implementation-pattern-mixture-models-using-standard-sasstat-procedures.pdf>

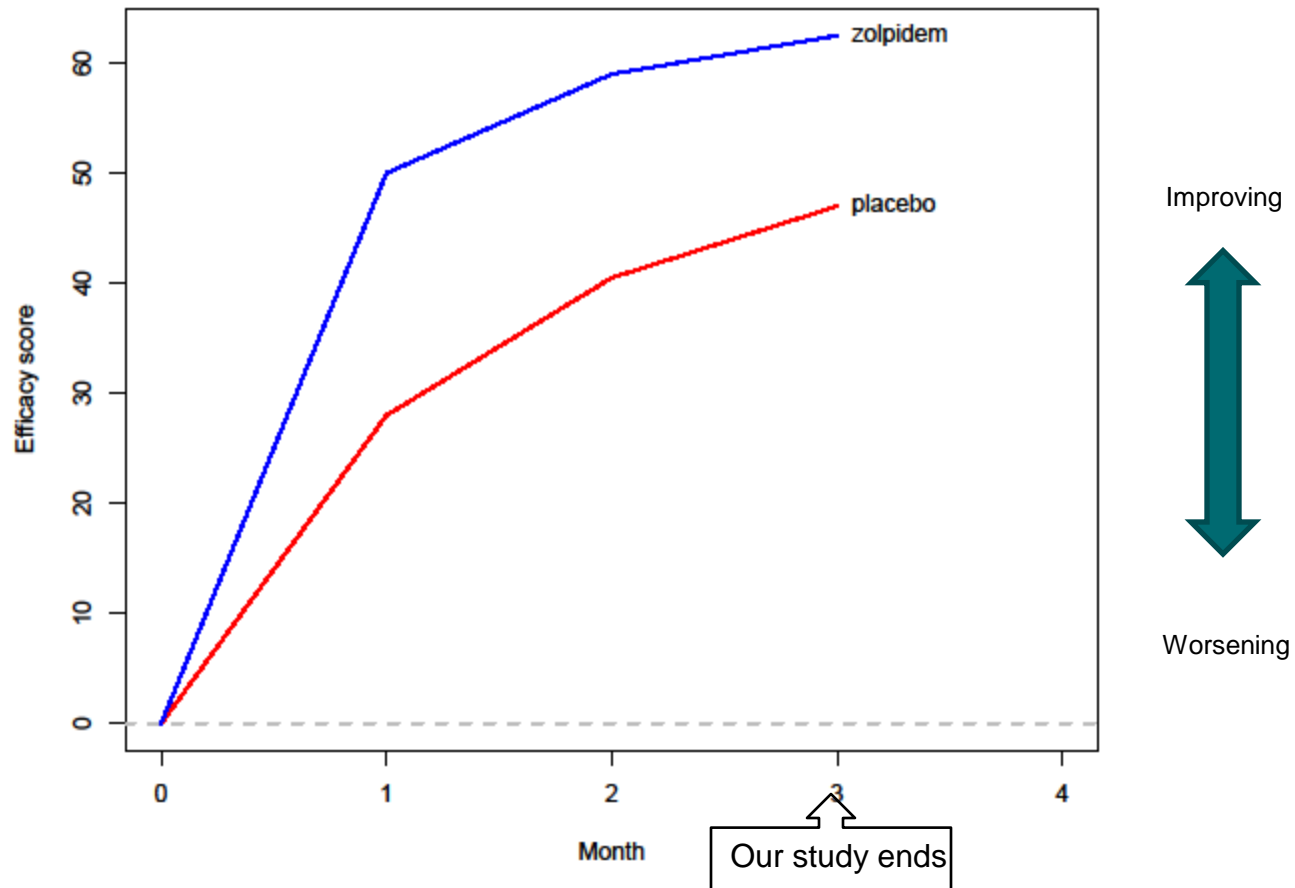
Extra case study

Case study: insomnia

- “Little data...regarding clinical course of insomnia” (Szuba M et al., 2003)

Insomnia, historical data, #1

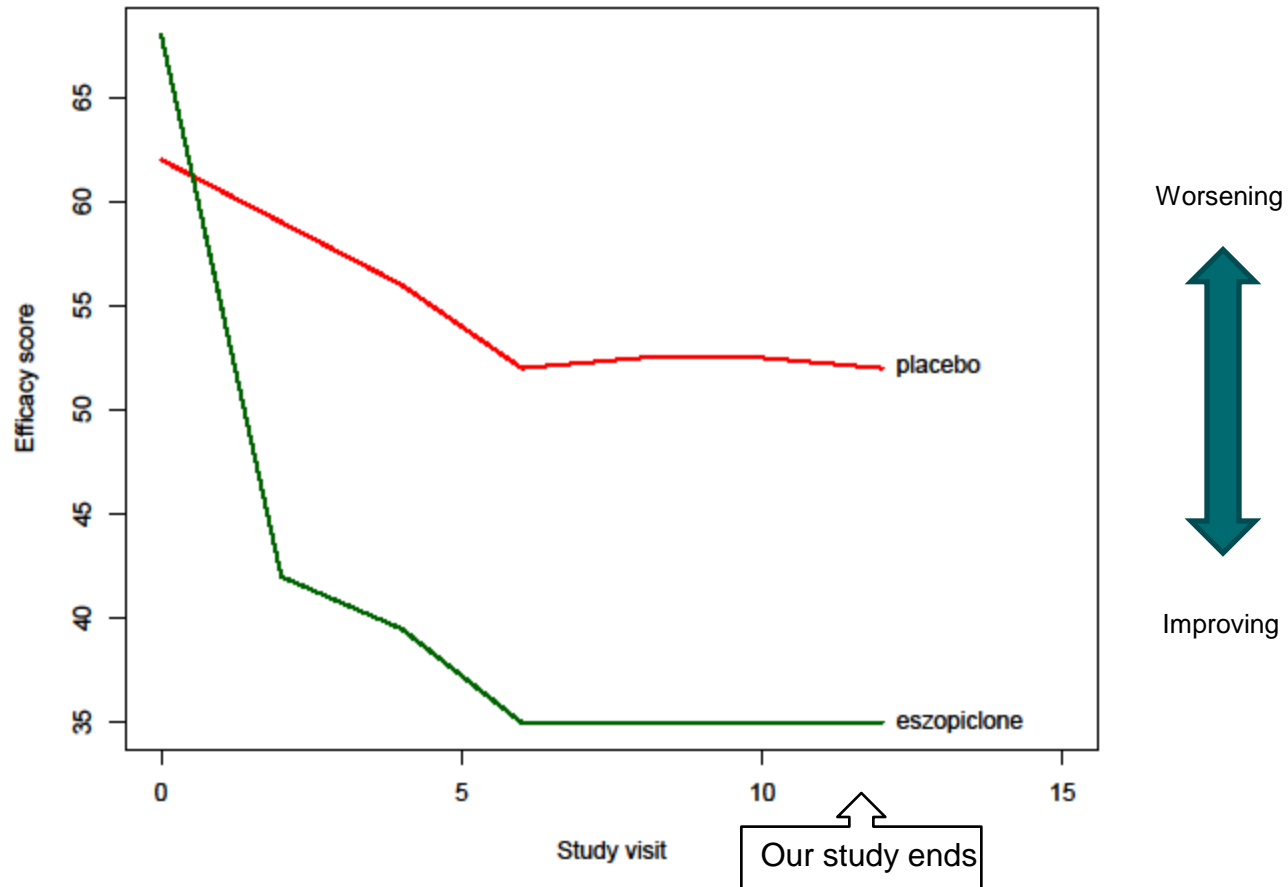
Zolpidem study, 2006



ZOLONG study group, 2006, Long-Term Efficacy and Safety of Zolpidem ..., *Sleep*, 31

Insomnia, historical data, #2

Eszopiclone study, 2005



Roth T, Walsh J, Krystal A, et al. An evaluation of the efficacy and safety of eszopiclone... *Sleep Med.* 2005;6: 487–495

Insomnia: expected dropout patterns

	Percentage dropouts	
	Placebo	Active
Zolpidem study	53	65
Eszopiclone study	43	40

Insomnia: expected dropout patterns

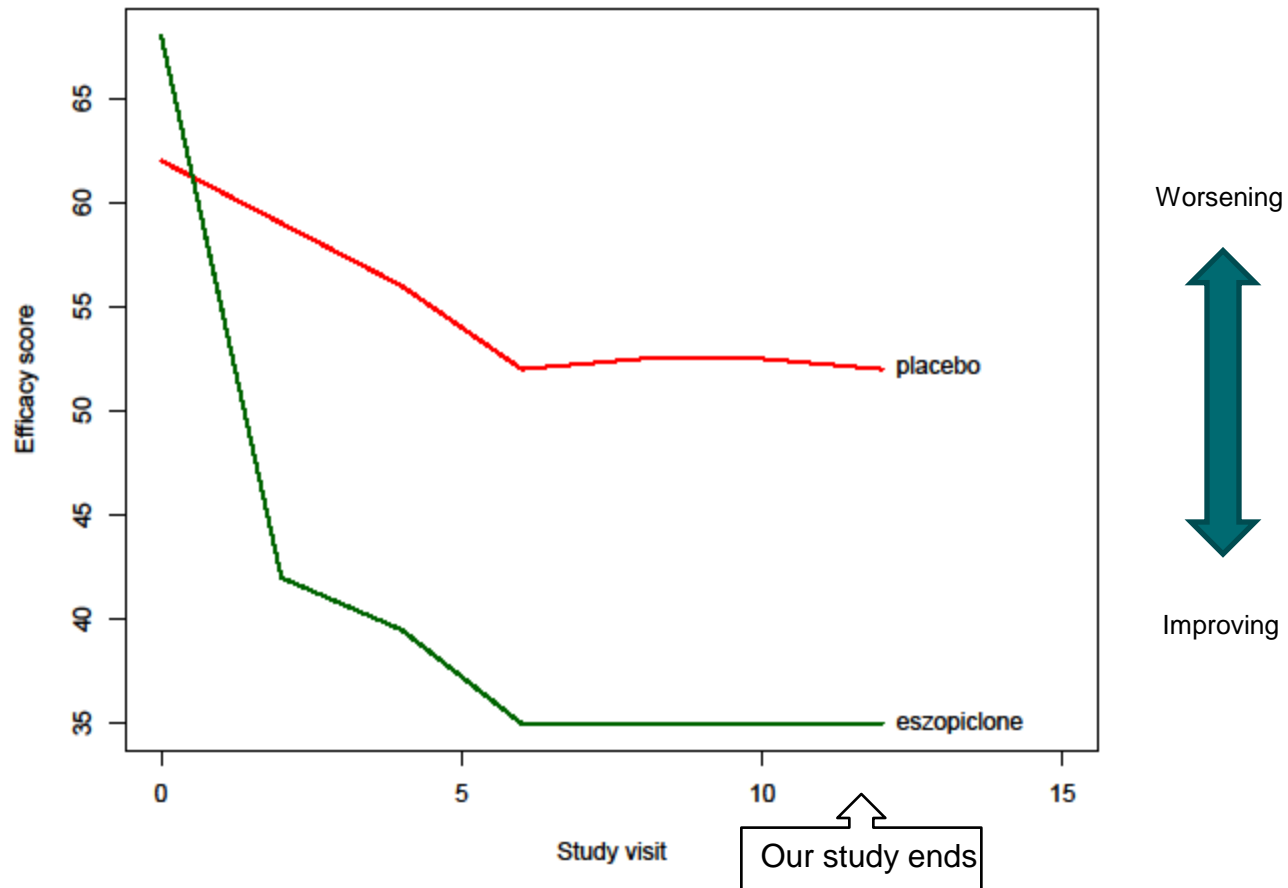
	Percentage dropouts	
	Placebo	Active
Zolpidem study	53	65
Eszopiclone study	43	40

Characteristics of example insomnia study

- Objective: superiority over placebo control
- 8 weeks follow-up
- 6 visits, last visit primary

Recall historical data

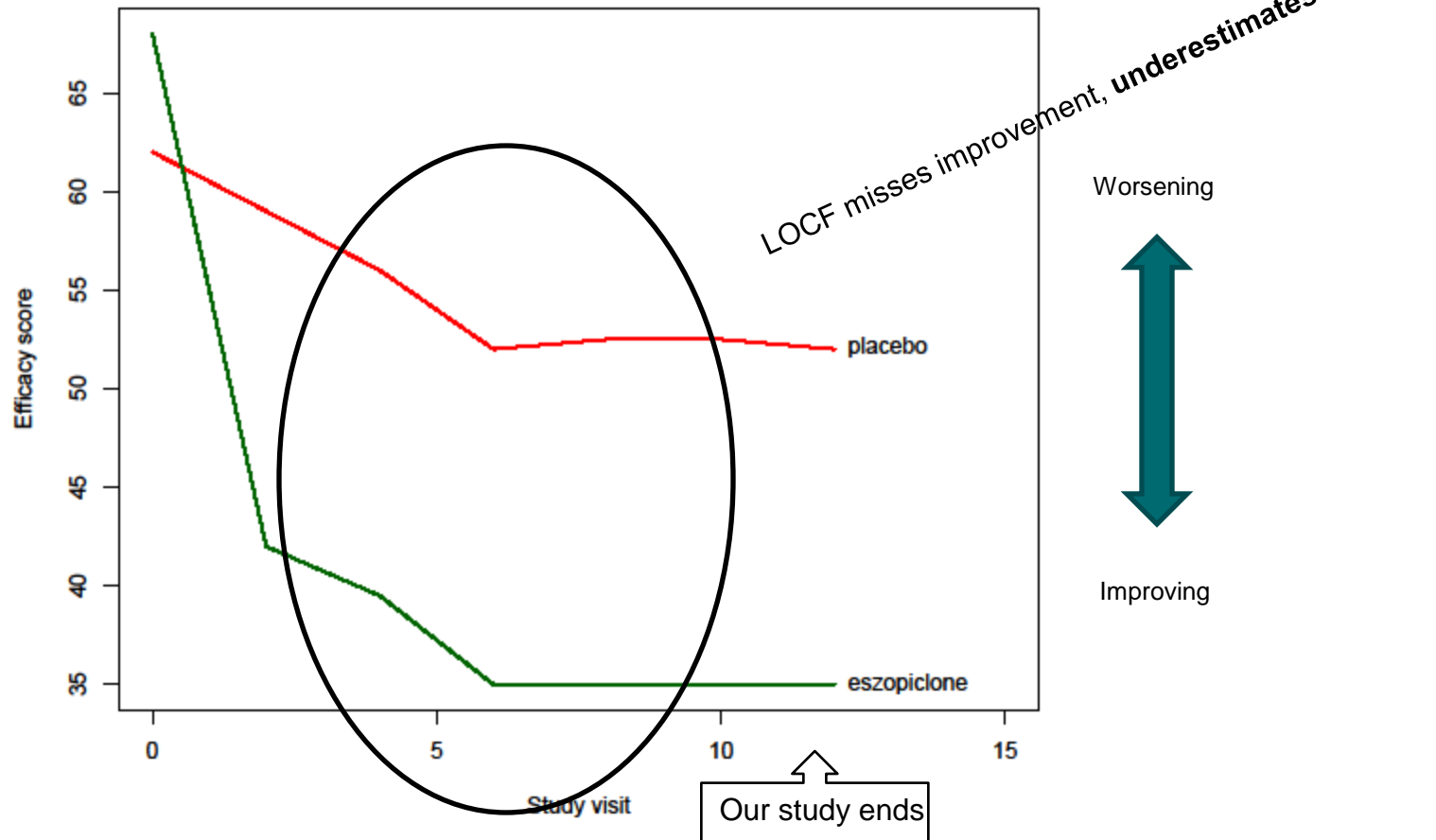
Eszopiclone study, 2005



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Recall historical data

Eszopiclone study, 2005



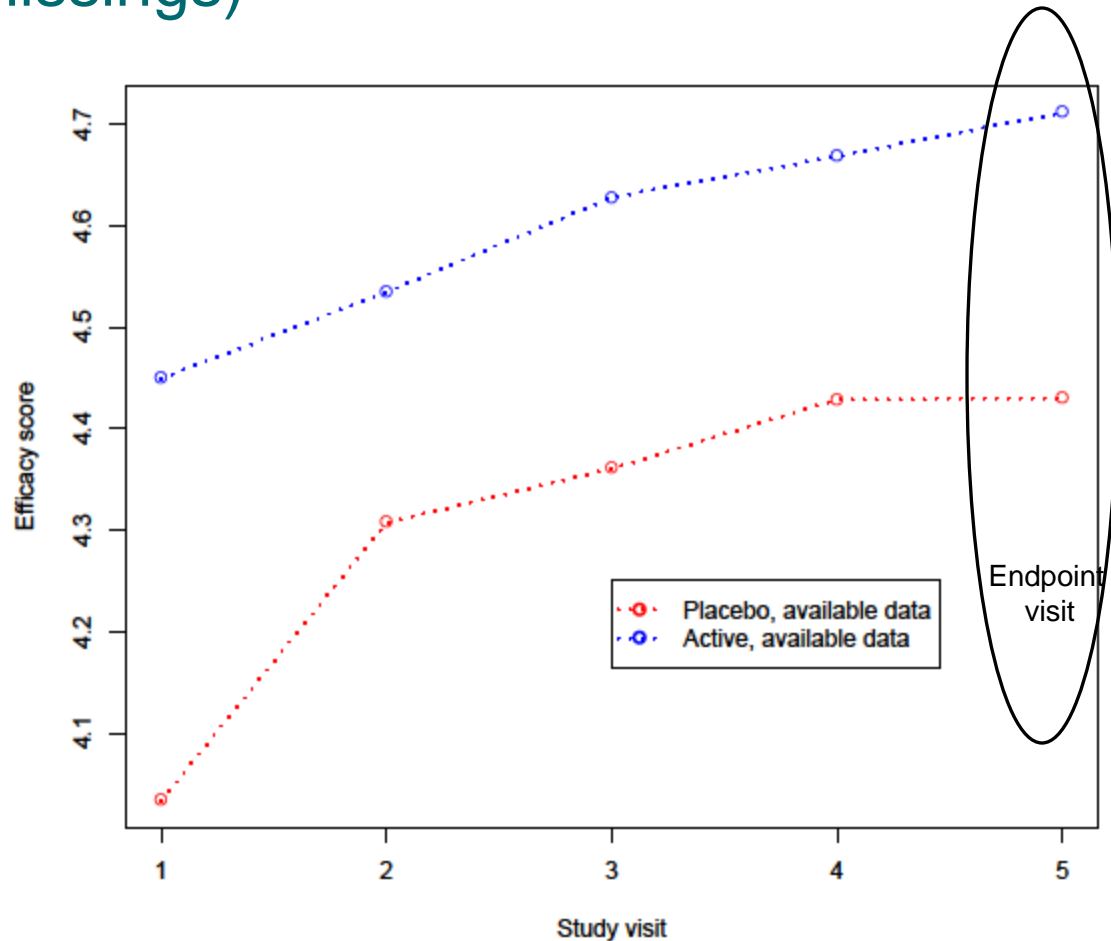
Roth T, Walsh J, Krystal A, et al. An evaluation of the efficacy and safety of eszopiclone... *Sleep Med.* 2005;6: 487–495

A plan for this insomnia example

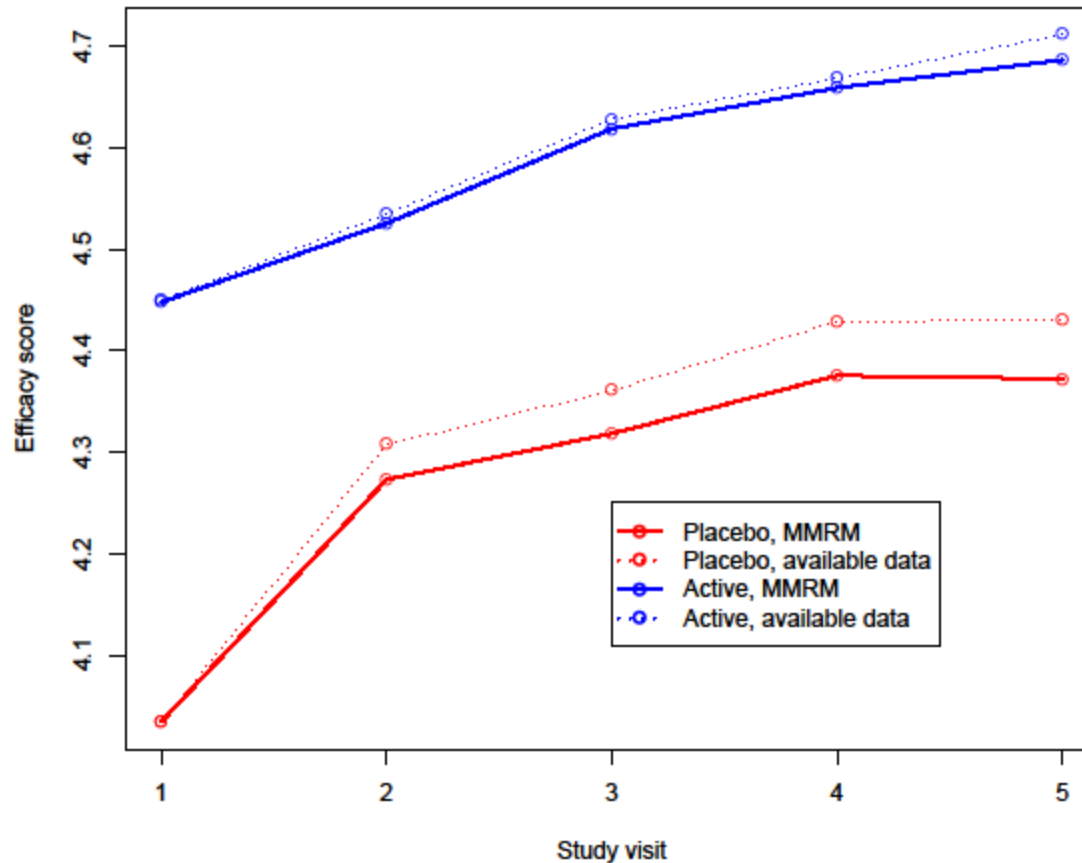
- Primary analysis: MMRM
- THEN sensitivity analysis
 - **what if** no improvement after dropout?
 - “LOCF” - carry forward last available value
 - insomnia: subjects tend to improve in medium term
 - group with more/earlier dropouts will have worse treatment mean
 - EMA: “suboptimal statistical properties”
 - LOCF estimates have artificially low variance
 - remedy: implement via Roger’s method: use **distribution** of data last time point for the group
 - » last mean carried forward (LMCF)

Results from disguised study in insomnia

OLS ANCOVA, available data only (ignore missings)



Available data and MMRM



Add sensitivity analysis: what if no improvement after dropout (last mean carried forward)?

