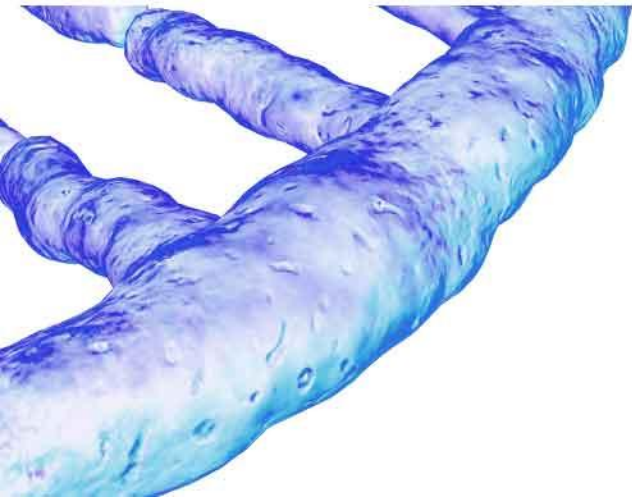


Missing data in clinical trials: developments in practice



*Michael O'Kelly
Quintiles Center for Statistics in Drug
Development*

Acknowledgements



- Bohdana Ratitch, inVentiv Health, co-researcher for many years.
- Sara Hughes, GlaxoSmithKline, work on prevention of missing data.
- Jessica Cooper and Josh Betcher, Quintiles, work on prevention of missing data.
- James Roger, ideas and programming for handling missing data.

Missing data

Missing data

Leave it to the
statisticians?



Missing
data

Leave it to the
statisticians?

Missing data

Leave it to the
statisticians?

Missing data

Clinical experts

Subject recruitment

Missing data

Statisticians

Project managers



Missing data: developments in practice



Ideal development: clinical trial results that are clinically interpretable, despite missing data

- prevent missing data as far as possible
- assumptions about missing data that have a clinical interpretation
- sensitivity analyses with reasonable alternative clinical interpretation

Scope of this talk

- Prevention of missing data
 - > Case studies showing what can be done
- Clinically interpretable assumptions for missing data
 - > Using historic data to identify clinically reasonable assumptions for missing data.

Missing data: developments in practice



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Recommendation 8: All trial protocols should recognize the importance of minimizing the amount of missing data....

Preventing missing data: case study 1, large cardiovascular event trial



- Cardiovascular event trial with tens of thousands of subjects
- Cross-functional approach to preventing missing data
- Include multiple options for withdrawal of consent, e.g.,
 - > withdraw completely from study
 - > stay in study but stop study treatment
 - > withdraw from study but consent to final follow-up visit at end of study
- Result: <1% full withdrawal from study
- Subject recruitment team retained, and became the subject retention team
 - > track subjects who had not returned for planned visit
 - > attempt to re-engage subject
- Statistician input included reports on # study years vs. # years on treatment
 - > target: keep years on treatment close to study years!
- Result: just one subject lost to follow-up (i.e., no contact in last six months)
- Similar experiences have been reported by other companies on other large trials.

Preventing missing data: case study 2, HIV trial



- GSK initiative for prevention of missing data*
- Recent withdrawal rate in HIV trials, 24%, of which 2/3 “avoidable” (i.e., not related to treatment)
- In HIV: all dropouts must be counted as viral suppression failures, regardless of reason for dropout.

*Hughes, S (2014) “The prevention of missing data” in O’Kelly M and Ratitch B, *Clinical trials with missing data: a practitioner’s guide*. Wiley.

Preventing missing data: case study 2, HIV trial



- Statistician uses historic data to estimate differential probability of withdrawal
 - > allows planning to focus adequately on groups most likely to dropout

One-year risk of non-treatment related dropout					
		Not intravenous drug use		Intravenous drug use	
Non-white	Age	Homosexual	Heterosexual	Homosexual	Heterosexual
	≤38	18%	24%	21%	28%
	39-44	12%	16%	15%	20%
	>44	9%	12%	11%	14%
White	≤31	10%	13%	24%	31%
	32-44	8%	10%	19%	25%
	>44	7%	10%	18%	24%

Key:

≤10%

11-15%

16-20%

≥21%

Preventing missing data: case study 2, HIV trial



- Other actions identified by the cross-functional team
 - > Select trial sites with an excellent retention track record
 - > **Pre-trial retention training and workshops for study personnel;**
 - > Education of study subjects as part of consent process
 - > Retention plans tailored for country and site
 - > Minimize of trial burden (e.g., number of assessments, wide visit windows)
 - > Provision of travel/meal re-imbursements, in countries where this is possible
 - > Reminders for appointments, with immediate follow-up after missed appointments
 - including opt-in text message reminders for clinic visits
 - > **Telephone contacts and home visits in case of missed clinic visits**
 - > Study-branded gifts
 - > Payment schedules to investigators that emphasize excellent follow-up (e.g., payments on a per-visit basis)
 - > **Targets for 'acceptable' rates of missing data**
 - > **Use of a specialist retention company**
 - > **Incorporation of trial retention rates** into the measures used to identify the sites that make the most significant contribution to data generation and therefore meet **ICMJE criteria for authorship** (ICMJE, 2010).

Missing data: developments in practice



Ideal development: clinical trial results that are clinically interpretable, despite missing data

- prevent missing data as far as possible
- assumptions about missing data that have a clinical interpretation
- sensitivity analyses with reasonable alternative clinical interpretation

Scope of this talk

- Prevention of missing data
 - > Case studies showing what can be done
- Clinically interpretable assumptions for missing data
 - > Using historic data to identify clinically reasonable assumptions for missing data.

Missing data: developments in practice



Ideal development: clinical trial results that are clinically interpretable, despite missing data

- prevent missing data as far as possible
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Scope of this talk

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 - > Case studies showing what can be done
- **Clinically interpretable assumptions for missing data**
 - > **Using historic data to identify clinically reasonable assumptions for missing data.**

The validity of assumptions concerning the source of missing data can only be assessed jointly by both data analysts and clinicians. Therefore, it is important that the assumptions underlying any selected analysis technique be clearly articulated so that they can be **evaluated by clinicians as well as by statistical analysts.**

Clinically interpretable assumptions for missing data



- Assumptions should be clinically interpretable.
- The tools include
 - > Flexible pattern-mixture-based implementation of a variety of assumptions
 - > (see first presentation).
 - Such assumptions are relatively easy to interpret.
 - » Post-withdrawal outcomes from the experimental arm assumed to be “like” those observed in the control arm.
- Will help interpretation if assumptions are also clinically **reasonable**.
 - > Pattern-mixture approaches have potential to be clinically reasonable.
 - > Can be based on parameters estimated from the study – a relevant population.
- Frequent regulatory requests for scientific justification of assumptions.
- Development: evidence-based choice of assumptions for missing data.
 - > Use historic data if available.
 - > Example.

Using historic data for assumptions, case study: DIA SWG data set



- Similar to data set used in first presentation
- Trial in major depressive disorder (MDD) described by Goldstein (2004)*
 - > includes duloxetine, paroxetine and placebo arms
- Example data were derived as follows
 - > Original placebo arm->placebo data in example
 - > Experimental arm is a random selection from three “active” arms
 - > Data available at www.missingdata.org.uk
 - > Completion rates 76% (64/84) for experimental arm and 74% (65/88) for placebo
- Efficacy score: Hamilton depression 17 item rating scale (HAMDT17)
 - > (lower is better)

*Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA (2004) Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 24: 389-399.

DIA SWG on Missing Data web page



Missing Data - Windows Internet Explorer
http://www.missingdata.org.uk/

www.missingdata.org.uk

search... SEARCH

Home > DIA working group

DIA working group

The following pages contain materials available from the Drug Information Association (DIA) working group.

Please note that these pages are still under construction.

- [Descriptive Summaries](#) (1 Article)
- [Inclusive Modeling Approaches](#) (4 Articles)
- [Missing Not at Random \(MNAR\) Methods](#) (4 Articles)
- [Control-Based Multiple Imputation](#) (3 Articles)
- [Presentations, Manuscripts and Training Materials](#) (2 Articles)
- [Example Datasets](#) (1 Article)

MAIN MENU

- Home
- Introduction to missing data
- FAQs
- Example analyses
- REALCOM Impute and Stata
- Substantive model compatible FCS
- Talks
- DIA working group
- Bibliography
- Courses / Workshops
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- Contact Us
- Book: MI & its application
- Google Discussion Group

REGISTERED USERS AREA

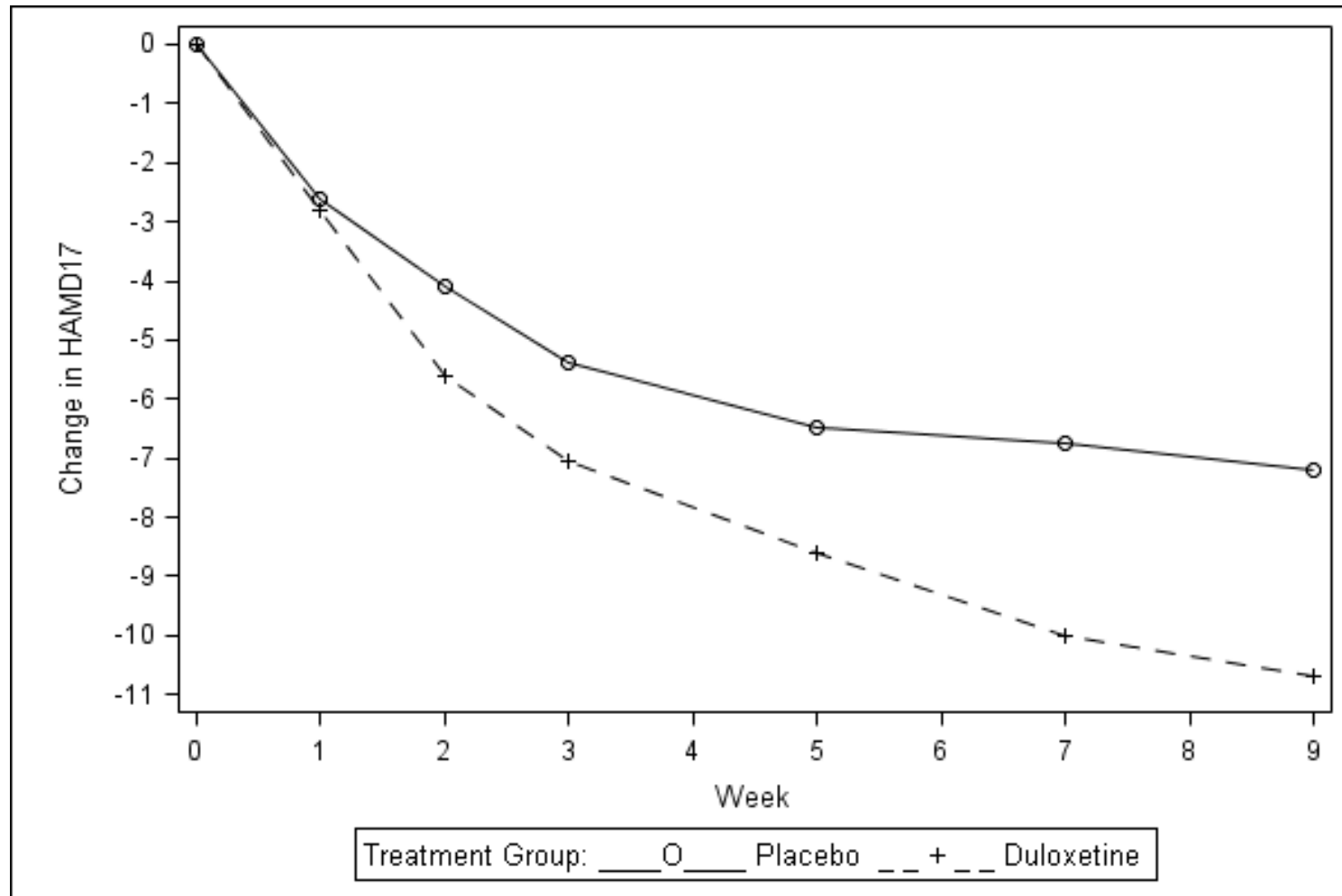
- Course notes
- Monograph: missing data in clinical trials
- MLwiN macros for multiple Imputation
- SAS code for sensitivity analysis using multiple imputation
- LEMMA Missing Data Module

USER MENU

- Login / Logout

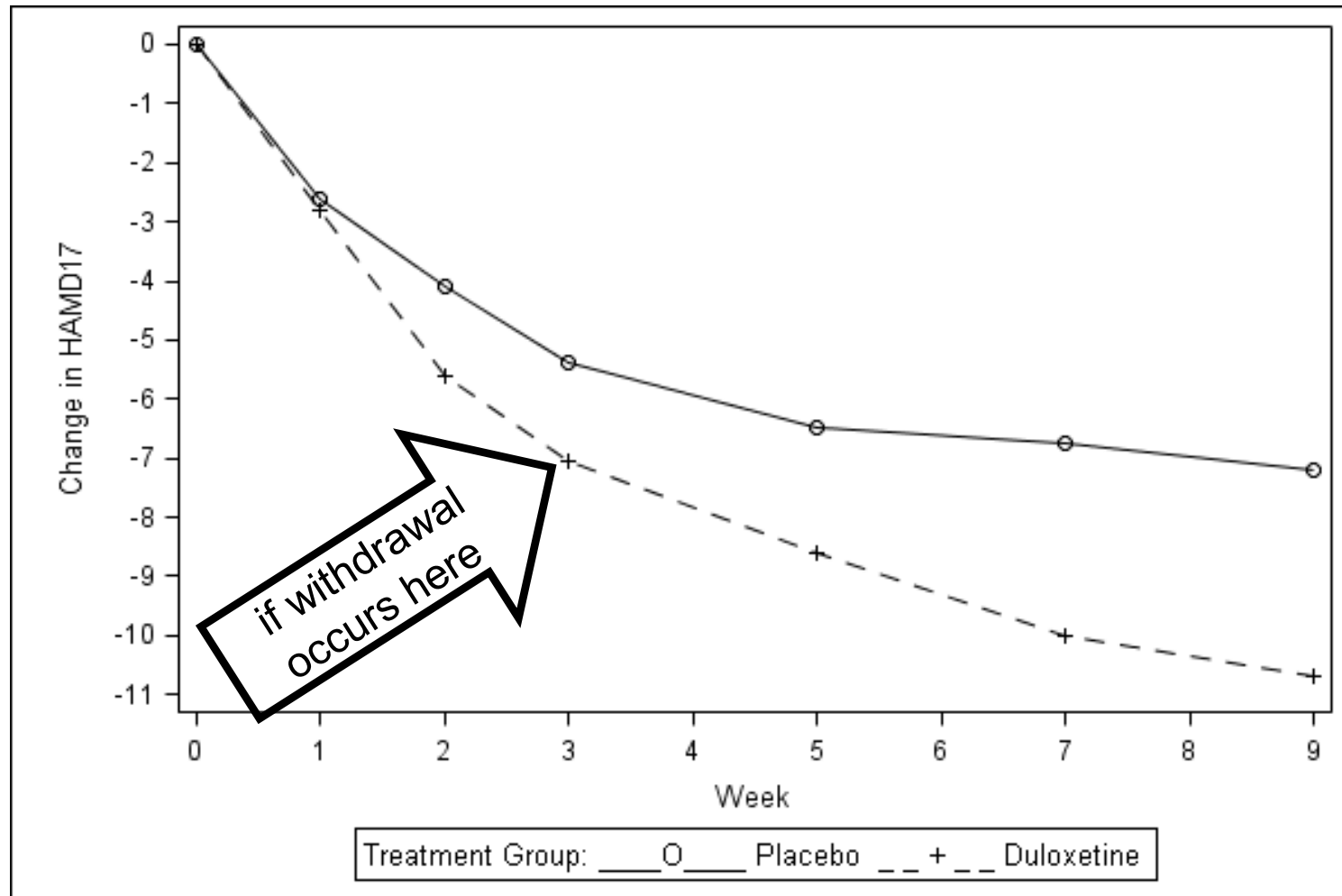
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Historic data, case study: typical trajectories for MDD



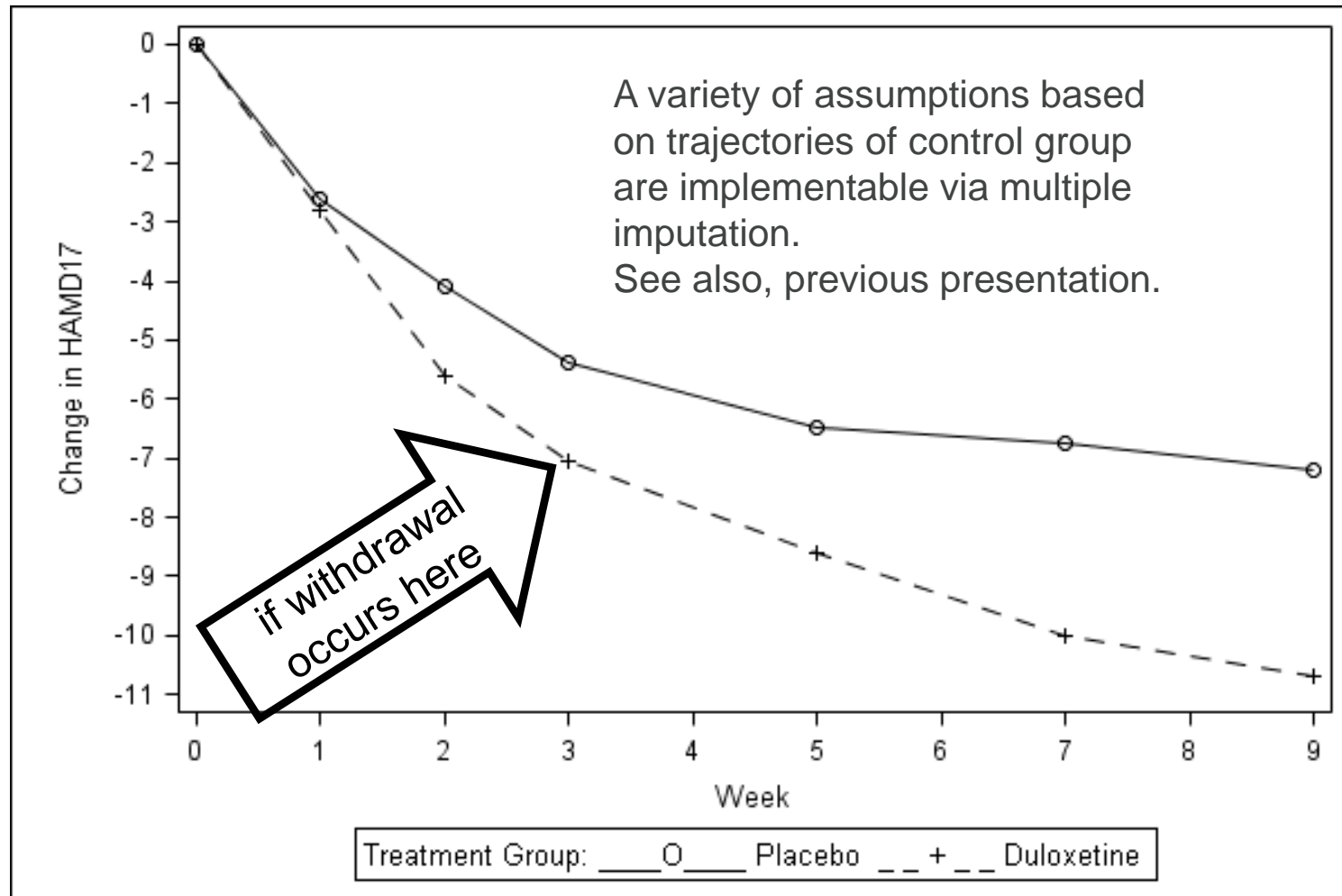
Brannan *et al.* (2005) Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies

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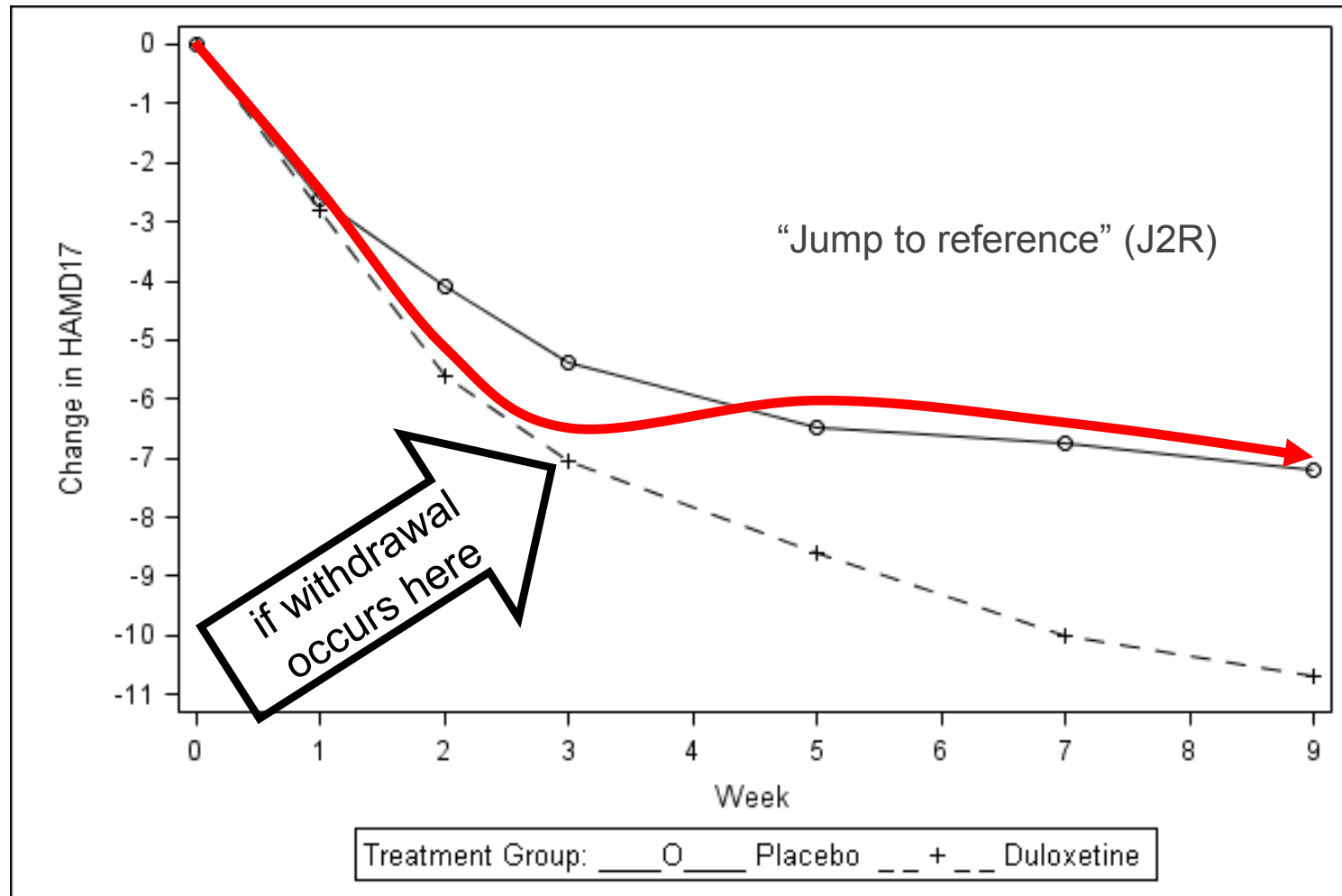
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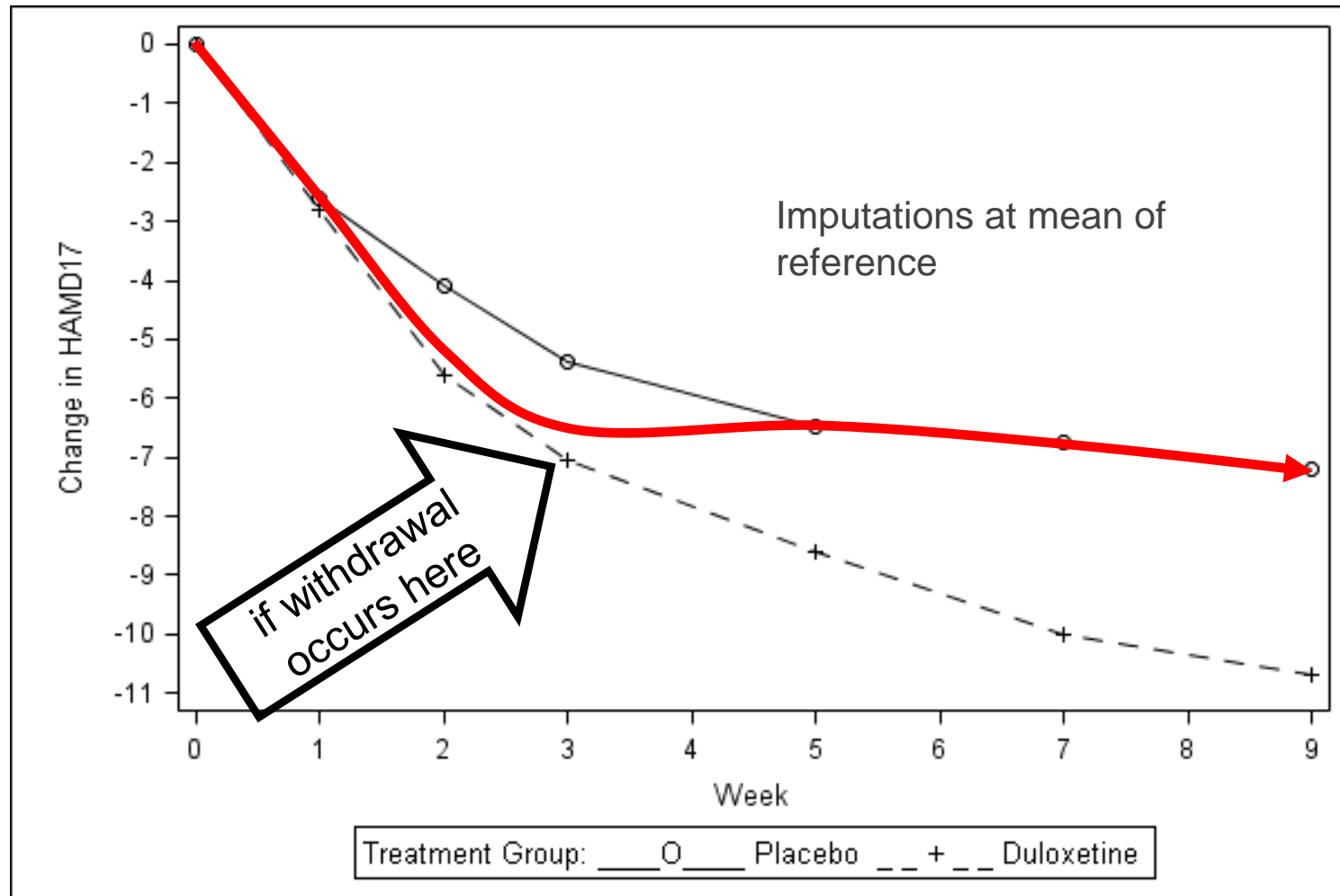
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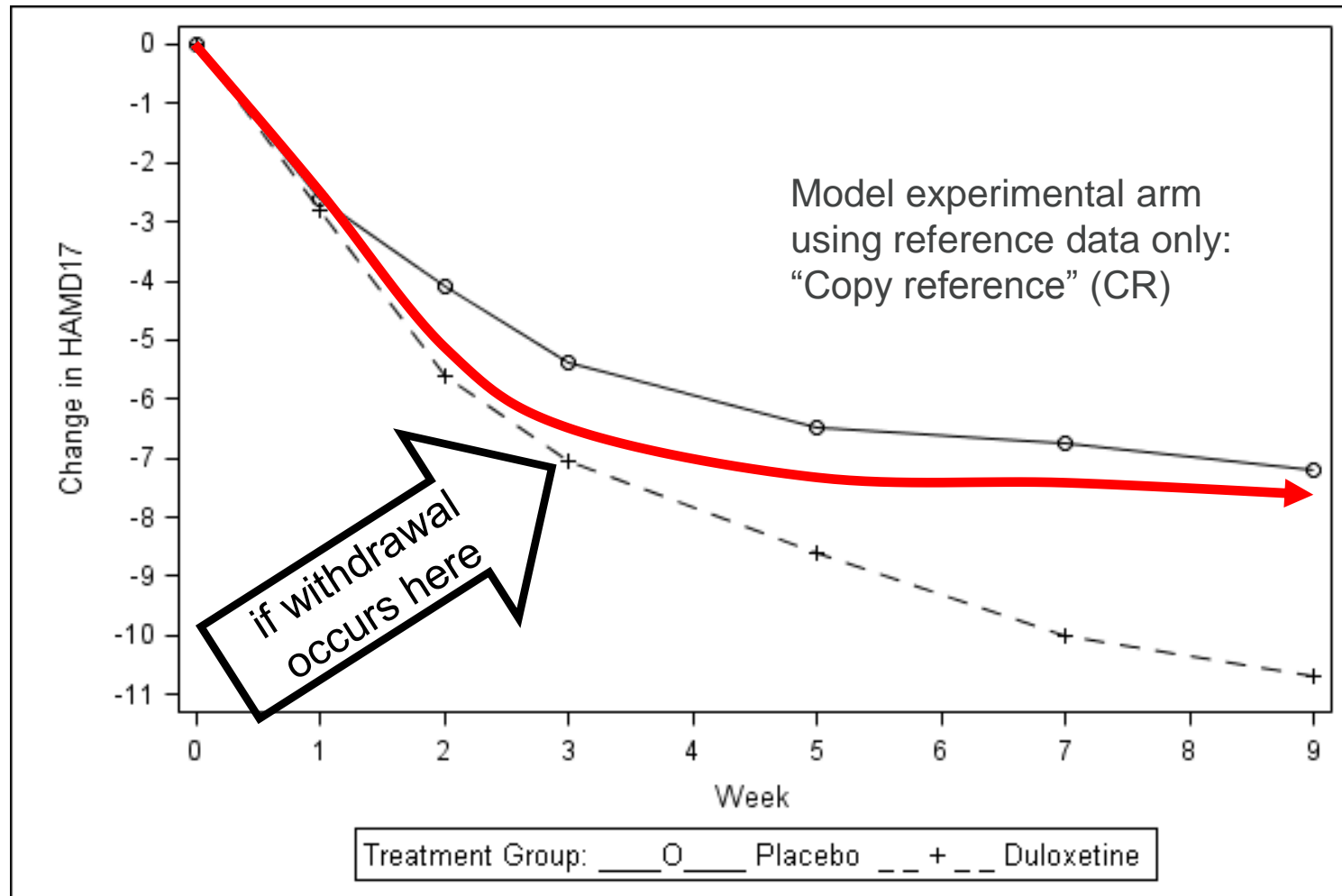
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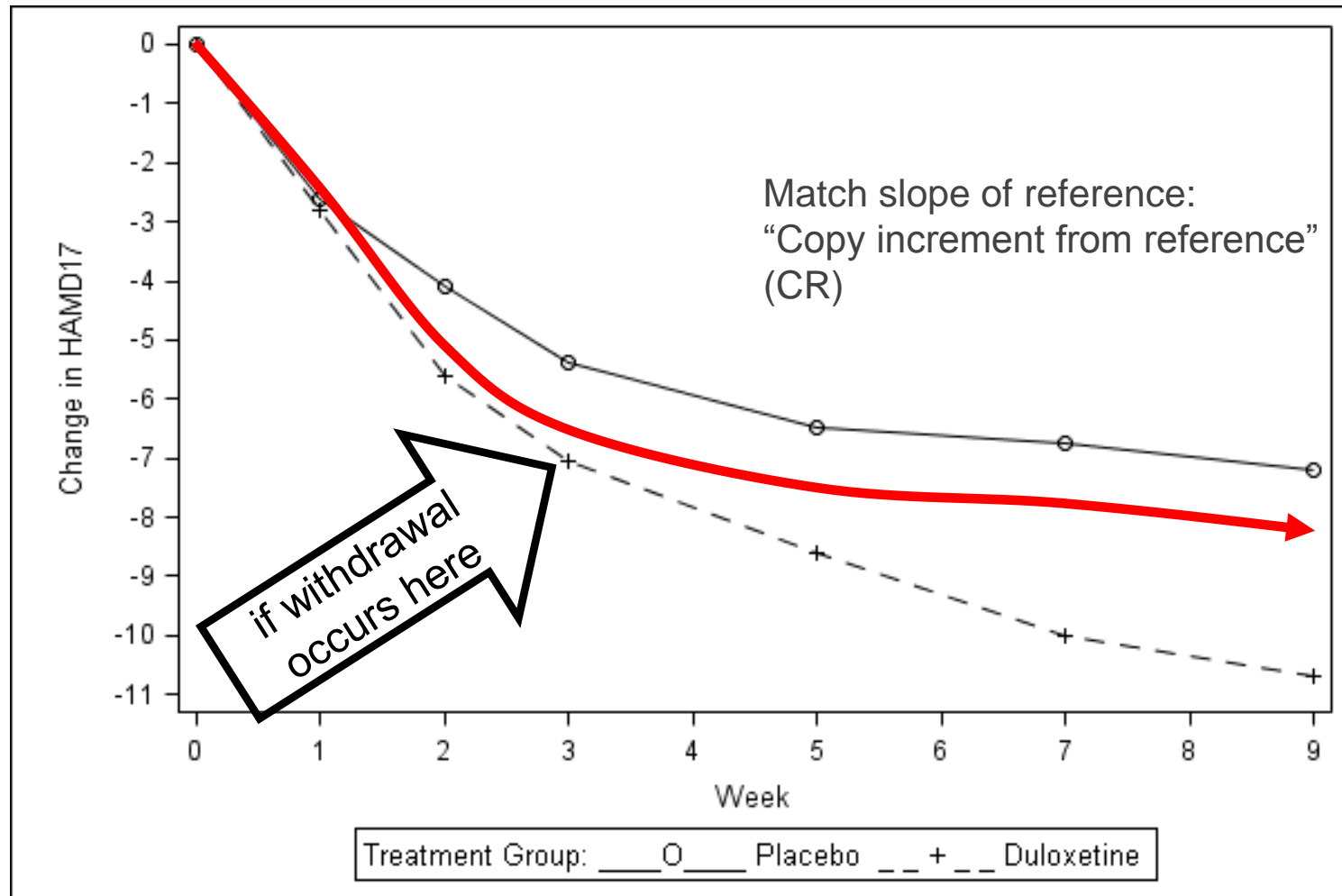
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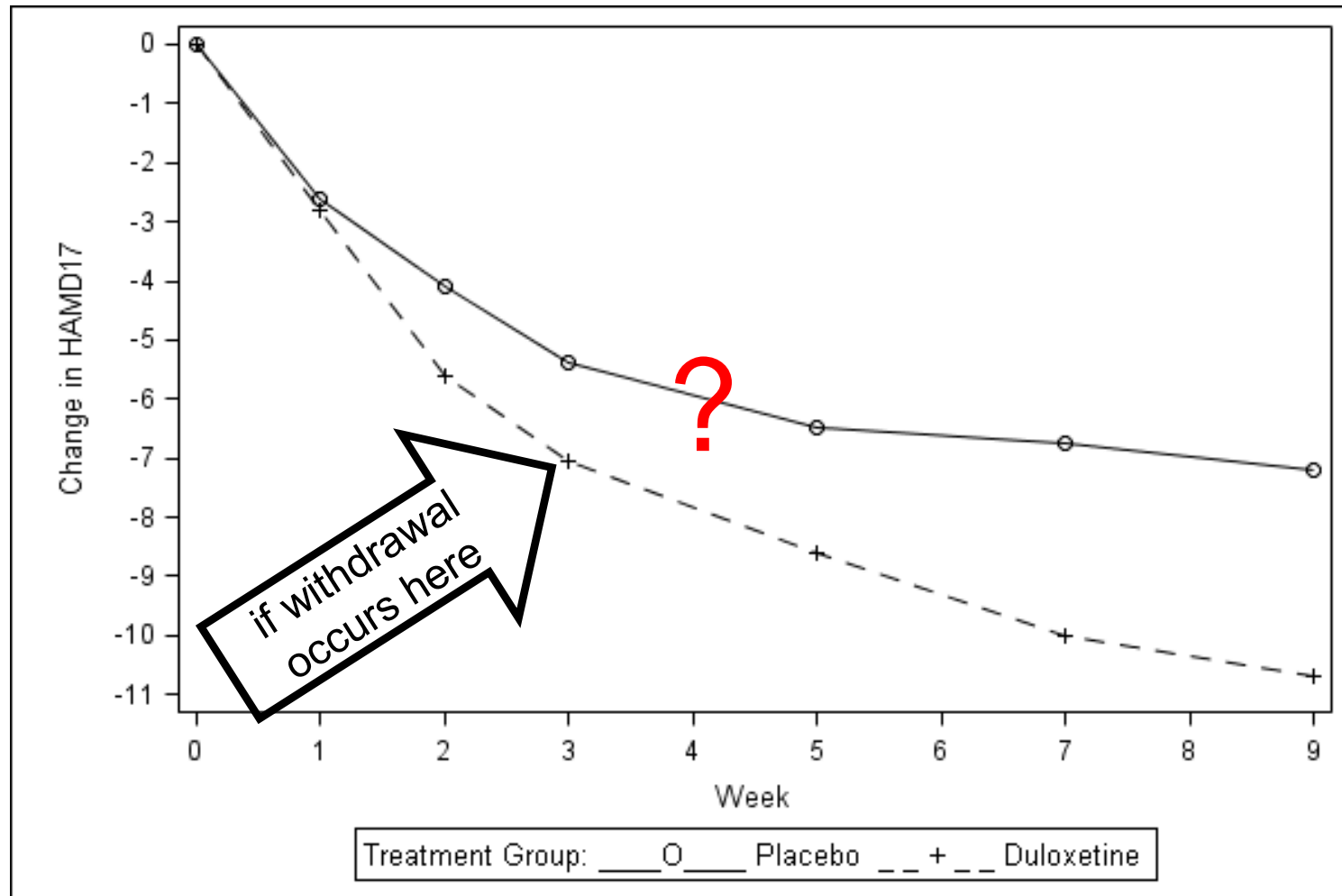
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Historic data, case study: trajectories for MDD



Brannan *et al.* (2005) Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies

Best evidence: post-withdrawal data



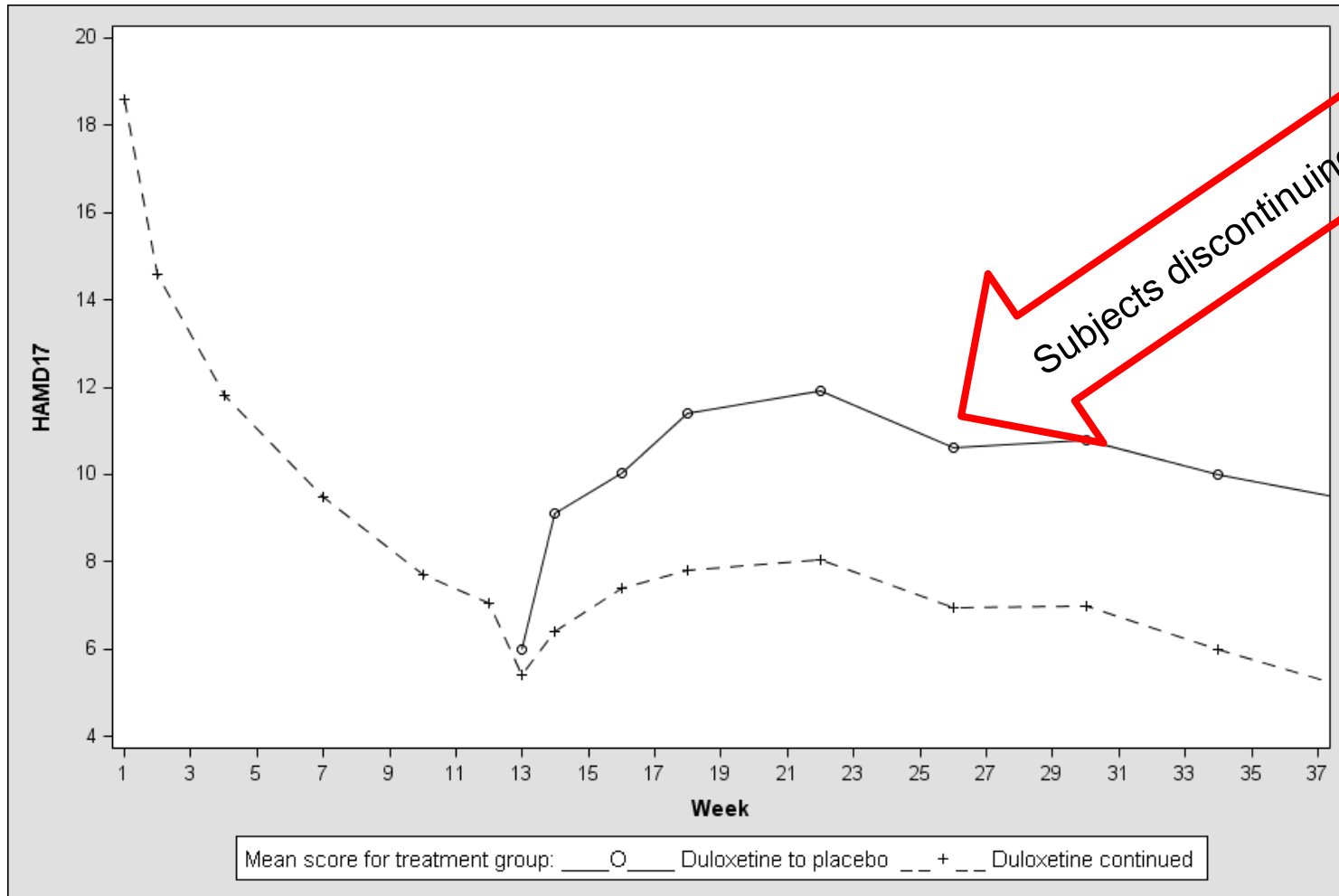
- Motivation to collect post-withdrawal efficacy in early studies
- If post-withdrawal data not available from standard studies, may be available from randomized withdrawal studies

Best evidence: post-withdrawal data



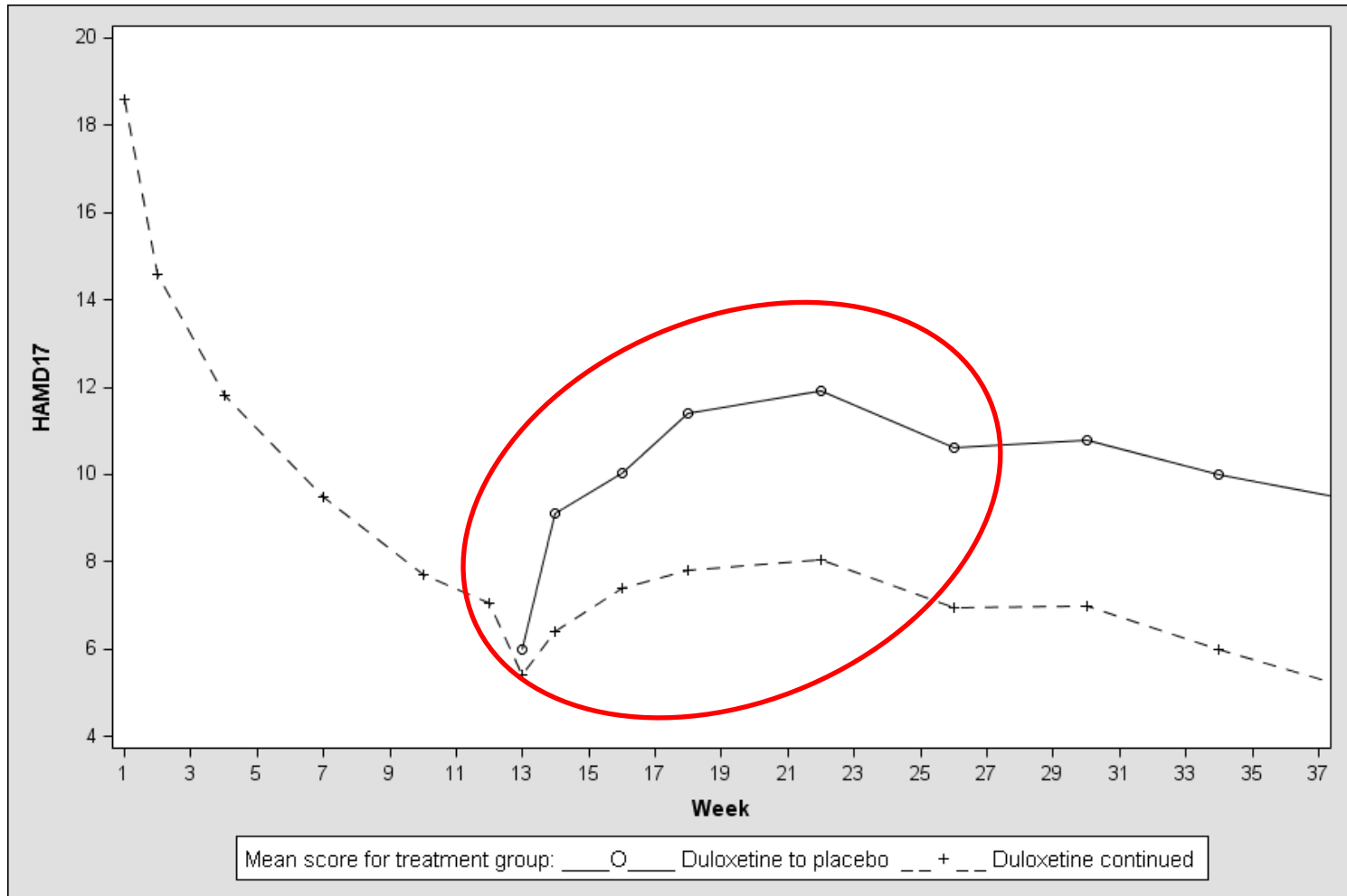
- Motivation to collect post-withdrawal efficacy in early studies
- If post-withdrawal data not available from standard studies, may be available from randomized withdrawal studies
- Perahia *et al.* (2006) *Duloxetine in the prevention of relapse of major depressive disorder: Double-blind placebo-controlled study*

Historic data, case study: trajectories for MDD



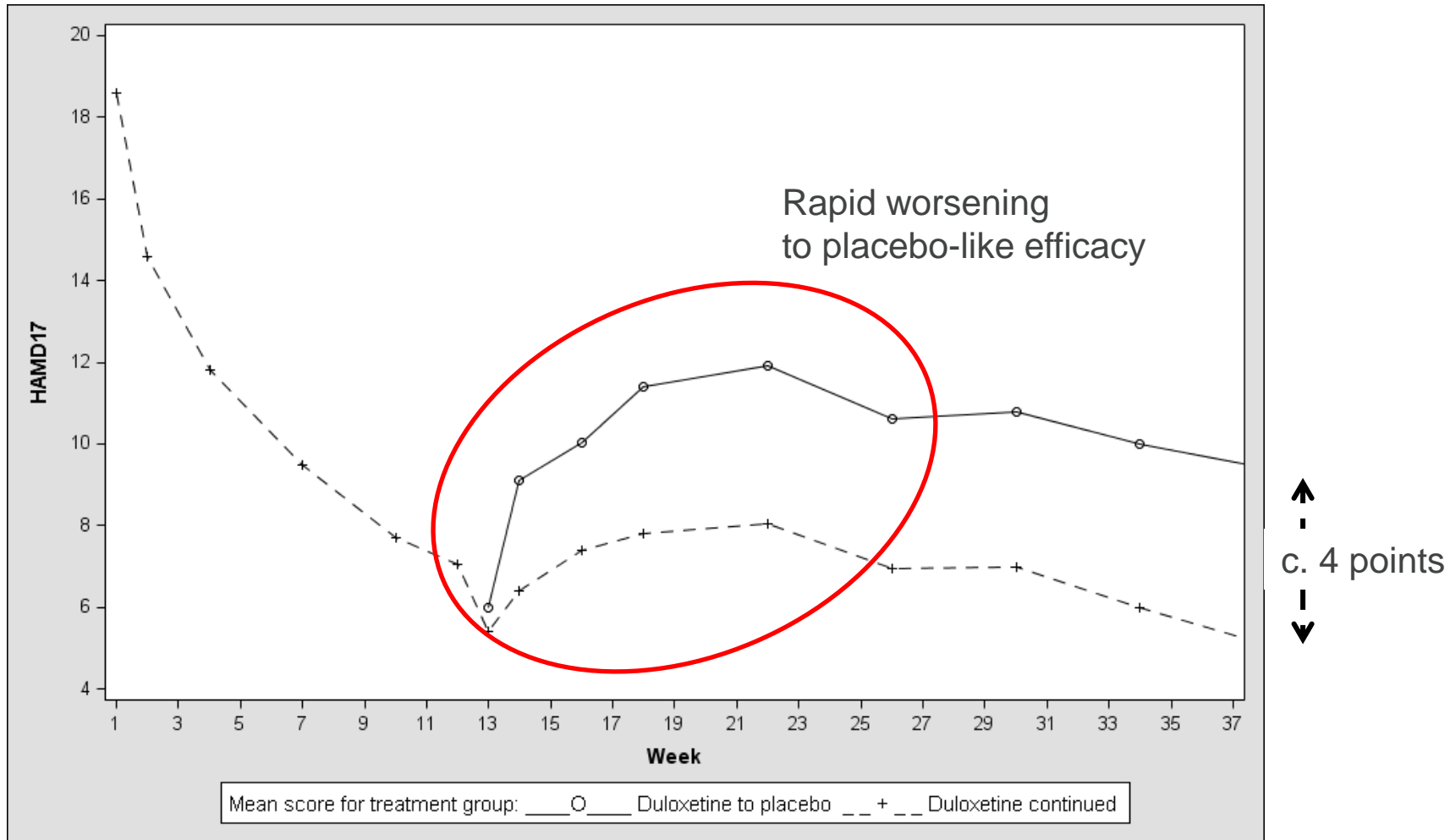
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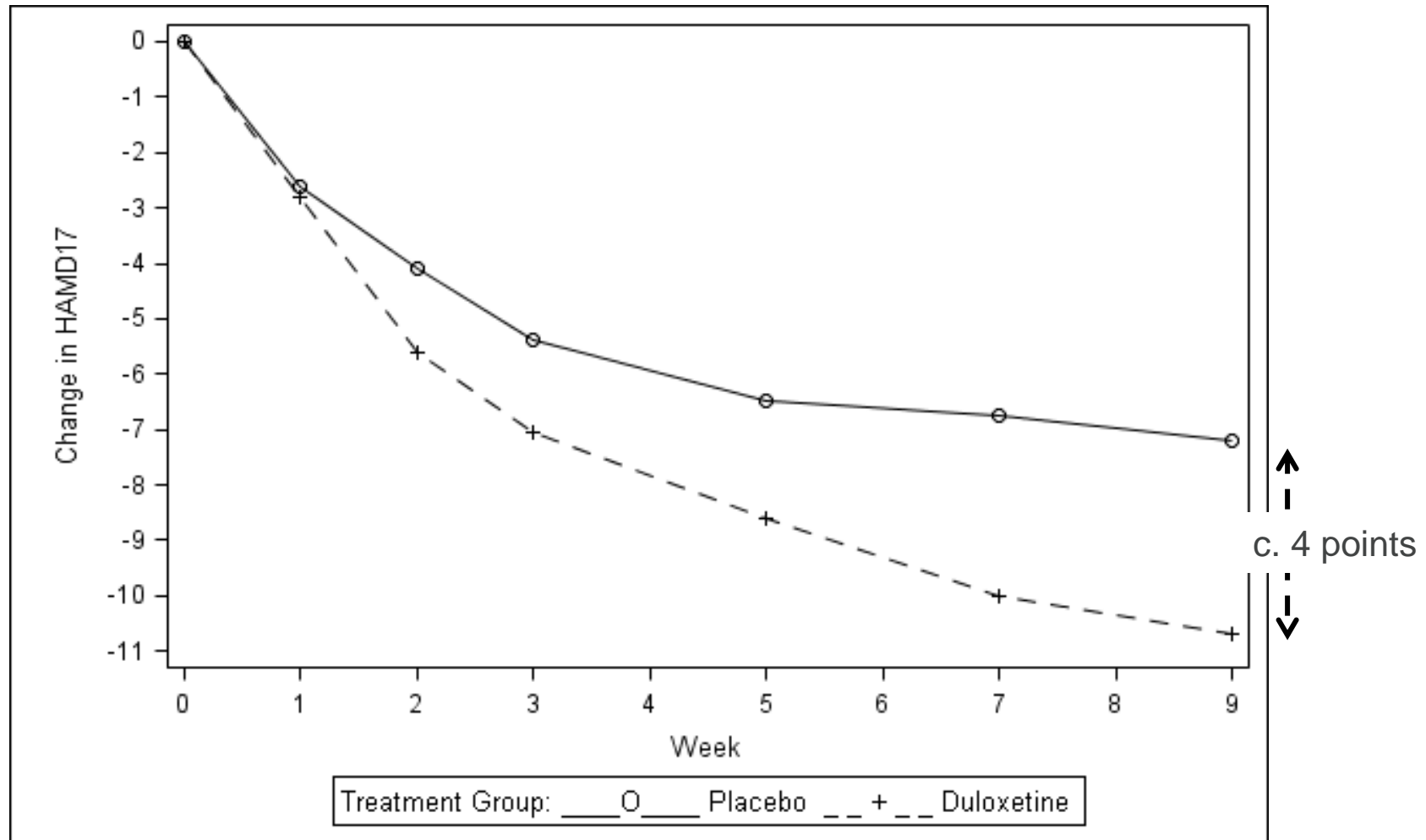
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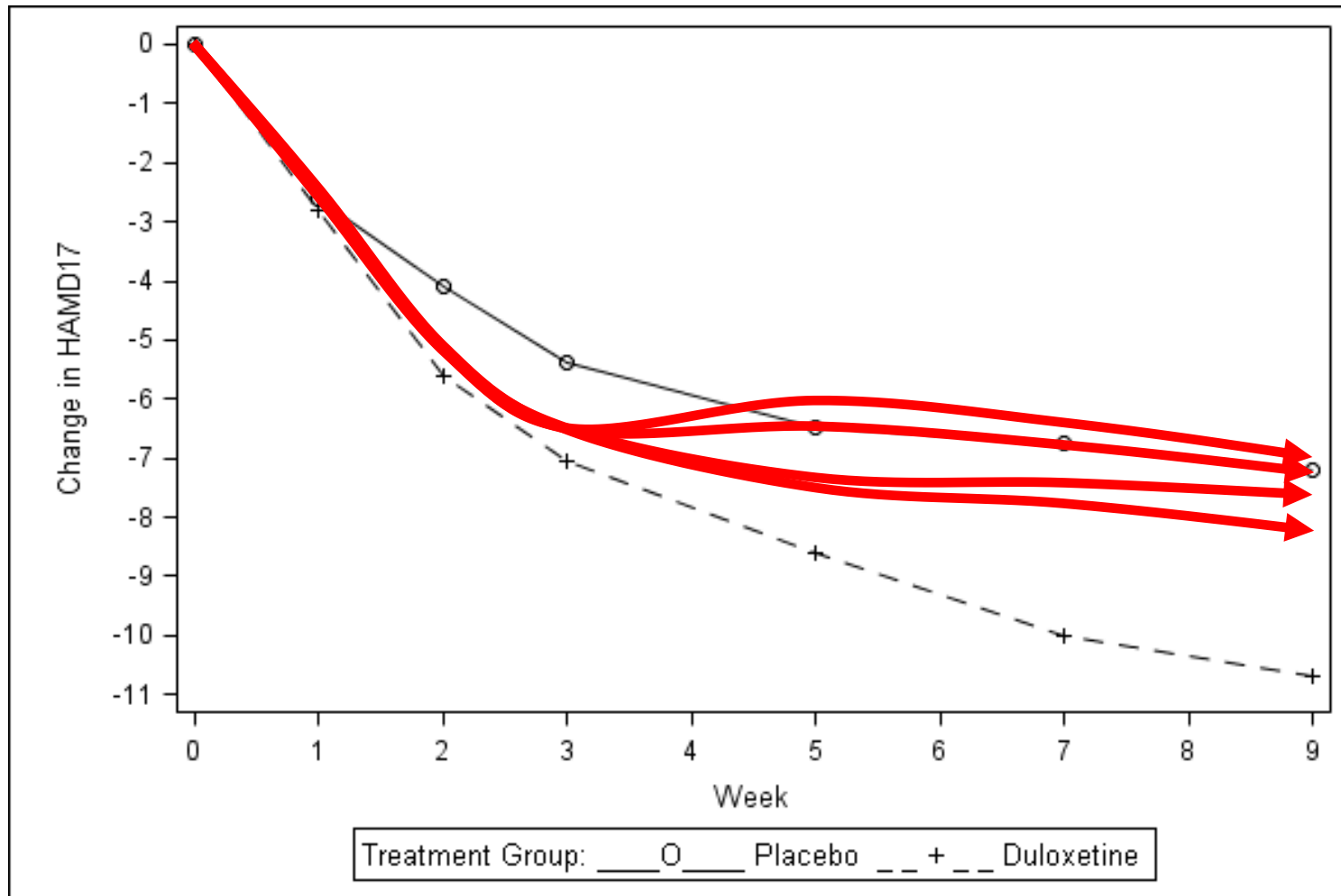
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Historic data, case study: typical trajectories for MDD



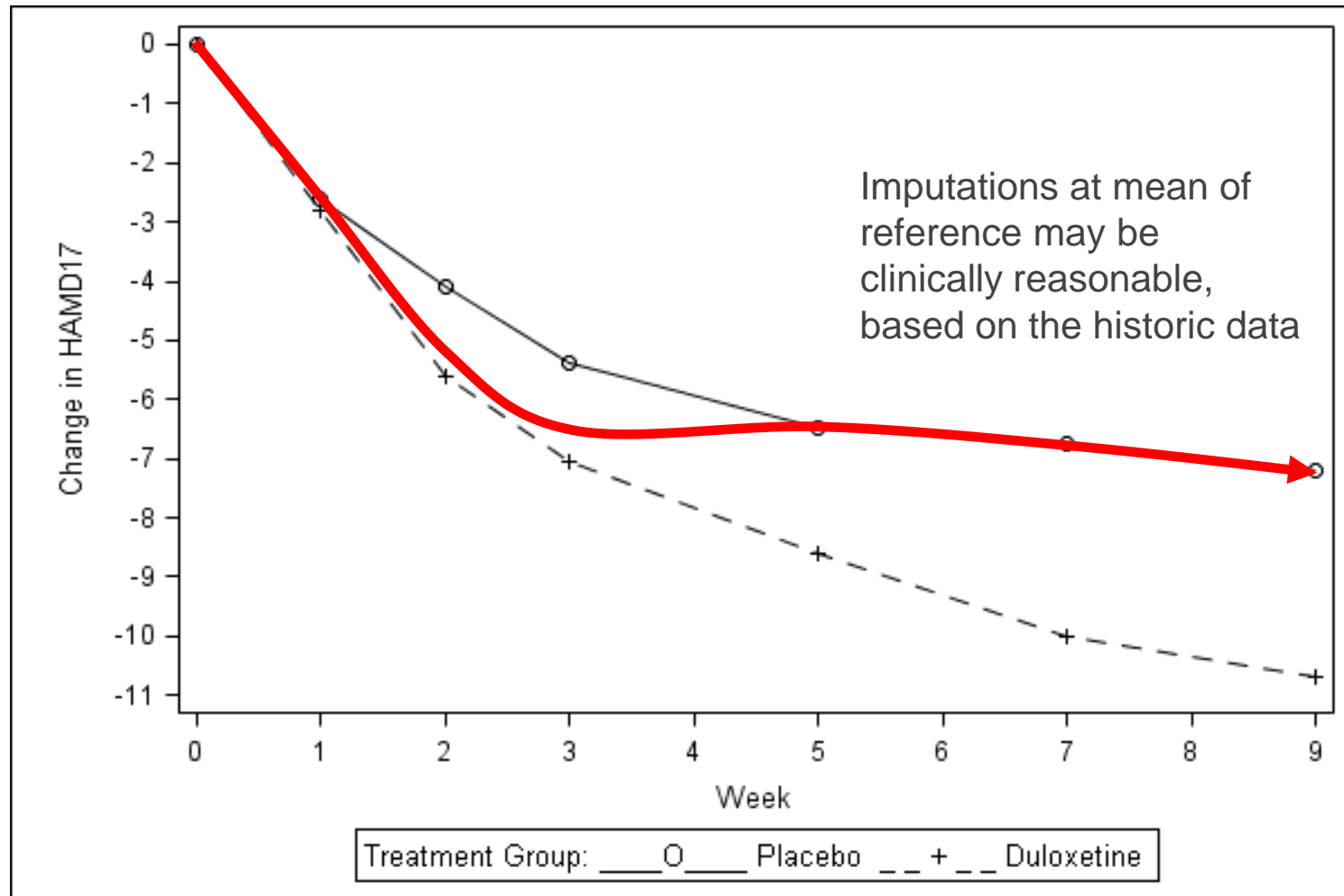
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Select suitable control-based trajectory?

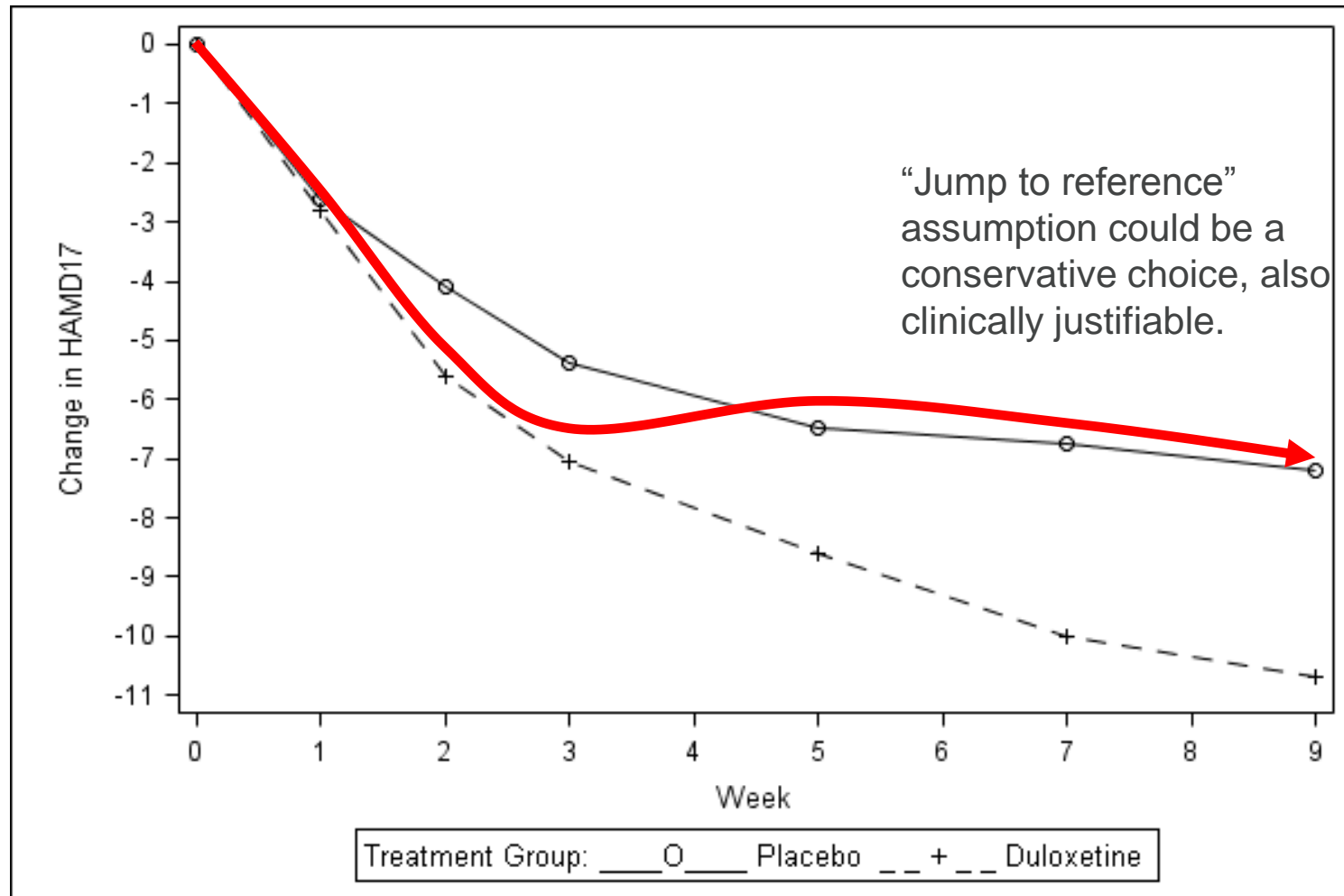


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Select suitable control-based trajectory?



Select suitable control-based trajectory?



Using historic data for assumptions, case study: DIA SWG data set



- Based on historic data, clinically interpretable (and clinical reasonable) assumptions for missing data could be
 - > Imputations for experimental arm have the mean of the placebo group at each visit,
or
 - > Imputations for experimental arm follow the “jump to control” assumption: withdrawal from experimental arm, usually with poor HAMDT17, will be imputed to perform similarly poorly in the control arm.

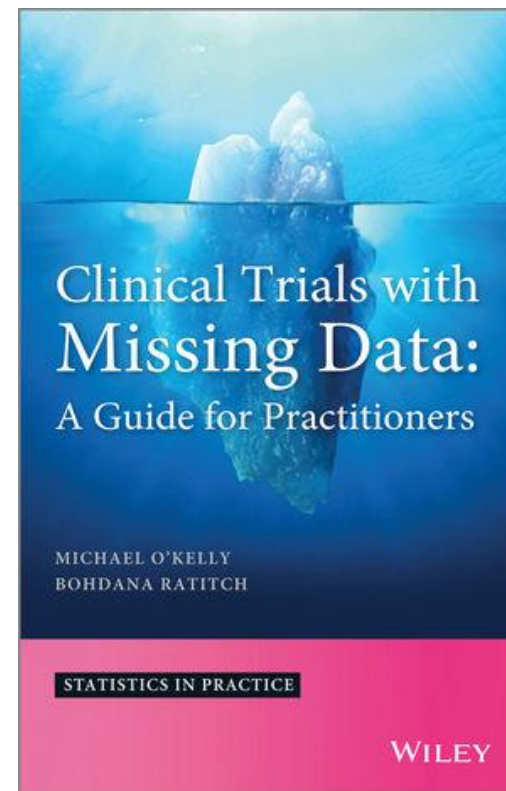
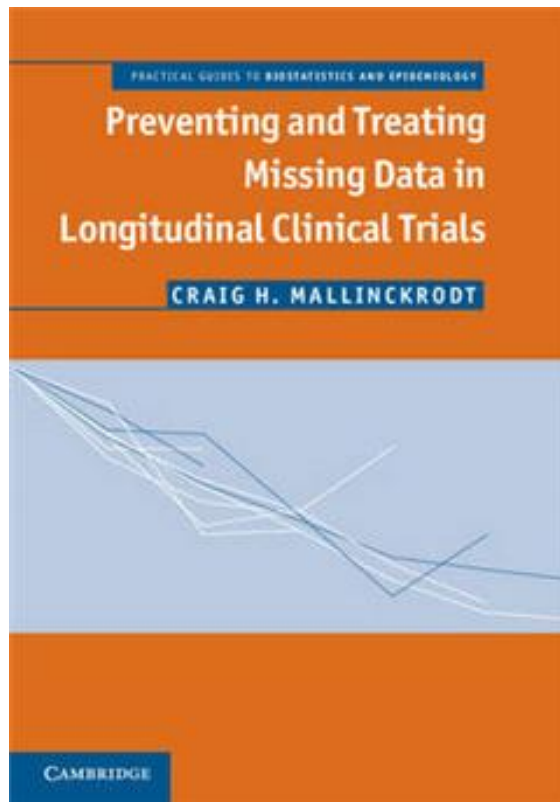
- Missing data are too important to be left to the statisticians alone.
- The statistician can be an important catalyst in alerting the study team and study participants to the importance of missing data.
 - > Recent case studies show that the resulting cross-functional initiatives can greatly improve patient retention.
- Assumptions about missing data will be most useful if they reflect reasonable clinical scenarios: statisticians and clinicians can work together to identify these.
 - > Regulators often now request scientific justification for missing data strategy.
 - > Historic data are often available to help clinicians and statisticians identify likely clinical outcomes for withdrawals and thus provide justification for the chosen strategy for missing data in the protocol or statistical analysis plan.

References



- Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions and inference via multiple imputation. *Journal of Biopharmaceutical Statistics*, 23(6):1352–1371.
- See also references in previous presentation

References



Questions?

