PCORI FINAL PROGRESS REPORT

Use continuation pages as needed.

Updated: Monday, August 01, 2016

Date (mm/dd/yyyy): 1/31/2017	
Title of Project: Sensitivity Analysis Tools for Clinical Trials with Missing Data	
Period Covered by this Report: Last six months of the project	
Principal Investigator & Institution Updated Contact Information:	
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Key Patient and Other Stakeholder Partner Contact Information (up to three):	
Name:	
Telephone/Email:	
Name:	
Telephone/Email:	
Name:	
Telephone/Email:	

OVERVIEW OF STUDY FINDINGS AND IMPACT

If you have completed analyses for your project, summarize your primary findings *(Limit 100 words). (Your Final Research Report, submitted to PCORI for peer review, will contain a more comprehensive explanation of your project findings.)*

We developed and disseminated methods and open source software (called SAMON and freely available at www.missingdatamatters.org) for conducting sensitivity analysis of randomized trials in which (1) outcomes are scheduled to be assessed at fixed points in times after randomization and (2) some participants prematurely withdraw and/or skip assessments. We also developed sensitivity analysis methods and software for randomized trials in which participants are at high risk of death.

- Summarize any significant change(s) from the funded application, including changes in study protocol, engagement plan, sample size, study outcomes, etc., including the reasons for these change(s), and the effect on internal and external validity of your findings.

Items L1 – L4 of the Deliverables were to be based on the development of new methods and software based on user feedback during Years 1 and 2 of the project. Despite efforts and outreach, we did not receive any substantive feedback.

MILESTONES UPDATE

Record each milestone label, name, description, and projected completion date (columns A-D), as shown in Attachment B (Milestone Schedule) of your Contract. Complete Columns E, F, and G for milestones due or completed during the current reporting period. If any milestones will not be completed, list the reasons why and the implications for your project.

Column E: Check appropriate box indicating milestone completion status during reporting period. Additional information on milestones that were not completed is required and should be provided in the section below this table.

Column F: Select actual date of milestone completion.

Column G: If applicable, select appropriate reason for delay/non-completion of projected milestone during the specified reporting period. Additional information on milestones that were not completed is required and should be provided in the section below this table.

Column A	Column B	Column C	Column D	Column E	Column F	Column G
Milestone Label *(e.g., B-1, etc.)*	**Milestone Name**	**Description**	**Projected Completion Date**	**Completed? (Yes/No)**	**Date Completed**	**If Not Completed, Reason for Delay**
B-1	Website	Expand registration on website to include PCO researchers	7/31/2014	☒Yes☐No	10/31/2014	Choose an item.
B-2	Advisory Board	Convene Meeting	7/31/2014	☒Yes☐No	7/21/2014	Choose an item.
C	Submit Interim Progress Report	Interim Progress Report	7/31/2014	☒Yes☐No	7/31/2014	Choose an item.
D-1	Case studies/training materials	Create PCO-centered case study and training materials	1/31/2015	☒Yes☐No	1/31/2016	Choose an item.
D-2	Short courses	Facilitate two short courses	1/31/2015	☒Yes☐No	1/12/2015	Choose an item.
D-3	Adobe connect session	Adobe connect	1/31/2015	☒Yes☐No	1/12/2015	Choose an item.

Column A	Column B	Column C	Column D	Column E	Column F	Column G
Milestone Label *(e.g., B-1, etc.)*	**Milestone Name**	**Description**	**Projected Completion Date**	**Completed? (Yes/No)**	**Date Completed**	**If Not Completed, Reason for Delay**
		session with users				
D-4	Manuscript for monotone missing data	Submit case study to PCOR focused journal	1/31/2015	☐Yes☒No	10/31/2016	Other (Specify Below) Waiting for main manuscript to be accepted
E	Submit Interim Progress Report	Interim Progress Report	1/31/2015	☒Yes☐No	2/2/2015	Choose an item.
F	Advisory Board	Convene Meeting	7/31/2015	☒Yes☐No	11/31/2015	Choose an item.
G	Submit Interim Progress Report	Interim Progress Report	7/31/2015	☒Yes☐No	8/21/2015	Choose an item.
H1	Case studies/training materials	Create PCO-centered case study and training materials	1/31/2016	☒Yes☐No	9/30/2016	Choose an item.
H2	Short courses	Facilitate two short courses	1/31/2016	☒Yes☐No	7/26/2016	Choose an item.
H3	Adobe connect session	Adobe connect session with users	1/31/2016	☒Yes☐No	5/24/2016	Choose an item.
H4	Manuscript for non-monotone missing data	Submit case study to PCOR focused journal	1/31/2016	☐Yes☒No	5/31/2017	Other (Specify Below) Waiting for main manuscript to be accepted
I	Submit Interim Progress Report	Interim Progress Report	1/31/2016	☒Yes☐No	2/19/2016	Choose an item.
J	Advisory Board	Convene Meeting	7/31/2016	☒Yes☐No		Other (Specify Below) Confer with board members on an as needed basis.
K	Submit Interim Progress Report	Interim Progress Report	7/31/2016	☒Yes☐No	7/31/2016	Choose an item.
L1	Case studies/training	Create PCO-centered	1/31/2017	☐Yes☒No	Click here to enter a date.	Choose an item.

Column A	Column B	Column C	Column D	Column E	Column F	Column G
Milestone Label *(e.g., B-1, etc.)*	**Milestone Name**	**Description**	**Projected Completion Date**	**Completed? (Yes/No)**	**Date Completed**	**If Not Completed, Reason for Delay**
	materials	case study and training materials				
L2	Short courses	Facilitate three short courses	1/31/2017	☐Yes☒No	Click here to enter a date.	Other (Specify Below)
L3	Adobe Connect Session	Adobe connect session with users	1/31/2017	☒Yes☐No	9/20/2016	Choose an item.
L4	Manuscript	Submit case study to PCOR focused journal	1/31/2017	☐Yes☒No	Click here to enter a date.	Other (Specify Below)
L5	Submit Book	Book	1/31/2017	☐Yes☒No	5/31/2017	Other (Specify Below) In Progress
M	Submit Final Progress Report	Final Progress Report	1/31/2017	☒Yes☐No	2/6/2017	Choose an item.

RECRUITMENT, ENROLLMENT, AND RETENTION UPDATE

Instructions for completing recruitment, enrollment, and retention Table 1 and Site Information

Complete tables and site information for the final reporting period. Complete a separate Table 1, requested site information, and Table 2 for each distinct project activity that involves recruitment and enrollment of study participants. Each of the following may be distinct:

- Prospective trials
- Observational studies
- Focus groups
- In-depth interviews
- Surveys
- Recruitment of different participant populations (e.g., patients, providers, caregivers) for any of the above activities

Example:
If your project conducts in-depth interviews with clinicians, then conducts surveys with patients, and then conducts a randomized-controlled trial enrolling patients, then you need to complete three tables and provide the requested Site Information for each project activity.

Table 1 Recruitment, Enrollment, and Retention of Study Participants
Project Activity (e.g., in-depth interviews, patient focus groups, prospective trial): _____
Participant population (e.g., patients, caregivers, clinicians): _____

Column A	Column B	Column C	Column D	Column E	Column F	Column G
Date of update	**Planned Sample Size**	**Total Screened (N)**	**Total Eligible (N)**	**Total Enrolled (N)**	**Total Lost to Follow-up (N)**	**% Lost to follow-up**

KEY

Column A: Date of update

Column B: Sample size (number of individuals you plan to enroll) in your approved research plan. For group-level data such as a focus group, enter the numbers of groups, not the number of participants for each group.

Column C: Total number of individuals screened for eligibility to date. This is the number approached and tested (e.g., lab tests, review of medical history, survey, etc.) to determine potential eligibility for the project.

Column D: Of the screened individuals, total number of individuals who met the eligibility criteria to date.

Column E: Of the eligible individuals, total number of participants enrolled to date.

Column F: Number of participants that have been lost to follow-up (enter N/A if not applicable to your project).

Column G: Percent of participants lost to follow-up, calculated as Total lost to follow-up/Total enrolled * 100.

Site Information

Number of sites, clinics and/or practices from which you recruited study participants? _____. If you recruited study participants from sources that are not site specific (e.g., websites, newspapers), please provide the number and names of those sources: _____

- **Total** number of sites, clinics, and/or practices that enrolled at least 1 participant: _____
- **Names** of sites, clinics, and/or practices that enrolled at least 1 participant: _____

Please describe the following:

1. Summarize your systematic effort to identify potentially eligible individuals for enrollment in your project over the duration of your project, including a summary of how your efforts may have changed over time (i.e., how did you find potentially eligible individuals for your project?).

2. Summarize your systematic effort to screen individuals who appeared eligible. Refer to Methodology Standard, PC-2, and describe how this standard was met over the course of your project (i.e., of the individuals identified, how did you approach and test them to determine potential eligibility?).
    a. Report reasons for ineligibility and the number of individuals for each reason.

3. Summarize your systematic effort to document information about eligible individuals who declined to enroll in the project.
    a. Report reasons for declining and the number of individuals for each reason.

4. Summarize your systematic effort to reduce attrition of participants enrolled in your project (as applicable).

Complete Table 2 by listing the Racial/Ethnic and Gender breakdown of the participants enrolled in your study to date. Ensure totals are calculated and appropriately recorded. If you have not collected these data, please explain why. Add a separate table for each type of participant recorded in Table 1 above.

Table 2 Racial/Ethnic and Gender Enrollment Table*

Race	Male (N)	Female (N)	Total (N)
American Indian/ Alaska Native			
Asian			
Black/ African			

American			
Hawaiian/ Pacific Islander			
White			
Multi-race			
Other			
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)			
Non-Hispanic			

*If more detailed information is available regarding racial/ethnic subgroups for the participants in your study, please share a separate table with this information in the Additional Documents section.

ACCOMPLISHMENTS AND CHALLENGES

Discuss and document study progress and all significant events **in the final (6-month) reporting period**. In particular, please discuss:

1. Accomplishments achieved during the final reporting period, with reference to planned project activities, milestones, and planned dissemination (include the specific milestone label as relevant).

Revised manuscript for *Biometrics*. Gave 3 hour American Statistical Association (ASA) webinar on 9/20/16, 1 hour ASA webinar (New Jersey chapter) on 10/28/16 and presentation at Novartis on 12/5/16. Posted a new version of software on 10/29/16 that handles non-monotone missing data, includes new case studies and addresses some feedback from an FDA beta tester.

2. Challenges faced during the final reporting period regarding the **project** (e.g., participant retention challenges, data analysis challenges) and how they have been addressed.

This project is co-funded by the FDA. As discussed in our previous progress reports, the manuscripts planned under the PCORI contract are of a more applied nature; they cannot be submitted until the more foundational articles have been accepted. Right now, the foundational article underlying SAMON received an excellent first review at *Biometrics* and a revision attending to the reviewers' comments has been submitted. The more applied PCOR-focused version of a paper describing SAMON has been drafted and will be submitted once the foundational article has been accepted. The same issue applies to the non-monotone missing data manuscript. We fully intend to submit PCOR focused case study manuscripts for monotone and non-monotone missing data and the book.

3. A summary of any reports submitted to the sponsor, a DSMB, an IRB, the FDA, or other regulatory or oversight body about unanticipated problems involving risks to subjects or others relating to the research project (e.g., adverse events, deviation from approved protocol that places subjects at increased risk of harm, data breach, procedural or medication error) that were reported during the reporting period. **N/A**

4. A summary of any significant decisions, findings, recommendations, actions and directions of a DSMB, an IRB, the FDA or any other regulatory or oversight body relating to the research project during the final reporting period. **N/A**

ENGAGEMENT REPORT

1. Descriptive information on engagement of patients and/or other stakeholders **in the past year** should be reported using the link below. This report is intended to capture the perspective of the research team. Patient and stakeholder partners will have additional opportunities to provide input.

   Your Username is your PCORI contract number *(no letters, dashes, or spaces)*.

   https://live.datstathost.com/PCORI-Collector/Survey.ashx?Name=Engagement_Report_Login

When you have completed the questions, record your confirmation code: f9282

2. Now please report on your experience engaging with patients and other stakeholders **across your entire PCORI project:**

   - What were the most notable impacts, both positive and negative, of engaging with patients and/or other stakeholders on the **study operations** (e.g., logistics, budget, efficiency, etc.)? Please provide specific examples.

     N/A

   - What were the most notable impacts, both positive and negative, of engaging with patients and/or other stakeholders on the **study quality** (e.g., scientific rigor, recruitment and retention, credibility of findings, etc.)? Please provide specific examples.

     Collaborating with statisticians was instrumental in improving the rigor of our methods. Interacting with software developers assisted us in developing SAS procedures.

   - What were the most notable impacts, both positive and negative, of engaging with patients and/or other stakeholders on the **usefulness of study findings** to patients and healthcare decision makers and the potential for **uptake of findings**? Please provide specific examples of each.

     Stakeholders could have been more effective in assisting with uptake our methods and software as well as identifying PCOR datasets.

   - Please describe any impacts of engagement on:
     - The investigators,
     - The study participants**, N/A**
     - Your institution **N/A**

     Investigators learned new statistical methods and software development tools.

   - What experiences from this project or other factors affect the likelihood that you will engage with patients and/or other stakeholders on future research projects?

     As a methodology and software development project, it is essential to engage with statisticians and software development experts. We would have liked more successful engagement on dissemination.

- Across your entire project, what strategies worked well for engaging with patients and other stakeholders? Why?

  We reached out to knowledgeable individuals and, when appropriate, offered co-authorship on publication(s).

- What strategies, if any, didn't work as well as intended for engaging with patients and other stakeholders? Why?

  Stakeholders are not enthusiastic in utilizing our methods and software because it requires extra work and there are no incentives to do so. Until the FDA, PCORI and leading journals "require" rigorous sensitivity analysis of randomized trials with missing data, adoption will be slow.

FINANCIAL STATUS UPDATE

Provide a summary/narrative of any changes to your originally approved budget during the entire project period of performance and how those changes have affected the study progress (e.g., staffing and cost estimates).

There have not been any significant deviations in costs and budget.

KEY PERSONNEL EFFORT UPDATE

Key Personnel changes must be reported (see your executed funding contract for changes in key personnel that require prior PCORI approval or advance written notification). Report the individual's role, change in percentage effort, and an explanation for changes. If you have more than five changes to report, please include additional information under "Explanation of Changes."

Name (First, Last)	Title	Contracted Percentage Effort	Actual Percentage Effort
		%	%
		%	%
		%	%
		%	%
		%	%

Explanation of Changes:

PUBLICATIONS UPDATE

REMINDER: Please make sure that all publications/communication/media pieces contain the following acknowledgement of PCORI funding and required disclaimer:

> *"Research reported in this [work, publication, article, report, presentation, etc.] was [partially] funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (##-###-####)."*

> *"The [views, statements, opinions] in this [work, publication, article, report] are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee."*

In the tables below, record information regarding publications and presentations (scientific and non-scientific) related to your PCORI-funded research that occurred as of the reporting date. Retain information submitted in previous reports.

Publications and/or presentations by any member of the research team, including patient and stakeholder partners, should include those:

- In preparation to be submitted
- That have been submitted to a publication
- That have been accepted to a publication
- That are in-press
- That have been published

Please send any submitted or published manuscripts, other publications, and conference abstracts, as described in the Additional Documents section.

Scientific Manuscripts

Title	Type	Status *	Journal **	URL, if applicable
On the Analysis of Tuberculosis Studies with Intermittent Missing Data	Methods	Published	Annals of Applied Statistics	
Inference in Randomized Trials with Death and Missingness	Methods	Published	Biometrics	
Global Sensitivity Analysis for Repeated Measures Studies with Informative Drop-out: A Semi-Parametric Approach	Methods	Revised	Biometrics	
Accounting for Mortality and Missing Data When Comparing Clinical Outcomes Across Treatment Groups in Randomized Trials	Methods	Under Revision	British Medical Journal	
Global Sensitivity Analysis of Clinical Trials with Missing Patient Reported Outcomes	Methods	In Preparation	Clinical Trials	

*** Record manuscript rejections in the table below**
****Target journal for papers in preparation**

Scientific Manuscripts, cont'd:

Please provide this additional information for accepted or published manuscripts only.

	For ACCEPTED or PUBLISHED manuscripts				
Title	**Authors *****	**Publication date**	**Volume (issue)**	**Page #s**	**PMID**
Inference in Randomized Trials with Death and Missingness	Wang, Chenguang; Scharfstein, Daniel; Colantuoni, Elizabeth; Girard, Timothy; Yan, Ying	10/2016			
On the Analysis of Tuberculosis Studies with Intermittent Missing Data	Scharfstein, Daniel; Rotnitzky, Andrea; Abraham, Maria; McDermott, Aidan; Chaisson, Richard; Geiter, Lawrence	12/2015	9	2215-2236	

***** Include all authors, using format: Last name 1, First name 1; Last name 2, first name 2; etc.**

Other Publications (e.g., book chapter, report, organizational journals, newsletters, blogs, other lay press)

Title	Publication Type	Status	Name of publication	Authors **	Publication date	URL, if applicable
Survival Analysis	Book Chapter	Under Review	Handbook of Statistical Methods for Randomized, Controlled Trials	Scharfstein, Daniel; Zhu, Yuxin; Tsiatis, Anastasios		
Prospective EHR-Based Clinical Trials: The Challenge of Missing Data	Editorial	Published	Journal of General Internal Medicine	Kharazzi, Hadi; Wang, Chenguang; Scharfstein, Daniel	4/16/2014	

**** Include all authors, using format: Last name 1, First name 1; Last name 2, first name 2; etc.**

Peer-Reviewed Presentations

Title	Status	Presentation Date	Presenter(s) Name*	Presenter(s) role in the project (Select all that apply)	Conference or Meeting Name	Meeting Location (City, State)	URL, if applicable	Intended Audience (Select all that apply)
	Choose an item.			☐Researcher ☐Patient or Stakeholder partner ☐Other				☐Researchers ☐Patients ☐Caregivers ☐Clinicians ☐Policymakers ☐Students ☐Community organizations ☐Other

***Last, First**

Other presentations (e.g., invited talk, local provider meeting, webinar, YouTube video)

Title	Presentation Type	Presentation Date	Presenter(s) Name*	Presenter(s) role in the project (Select all that apply)	Conference or Meeting Name, if applicable	Presentation Location **	URL, if applicable	Intended Audience (Select all that apply)
Global Sensitivity Analysis of Repeated Measures Studies with Informative Dropout: A Semi-Parametric Approach	Oral	8/3/2014	McDermott, Aidan	Researcher	Joint Statistical Meetings,	Boston, MA		Researchers
Global Sensitivity Analysis of Repeated Measures Studies	Oral	9/18/2014	Scharfstein, Daniel	Researcher	Andrei Yakovlev Colloquium, University	Rochester, NY		Researchers

with Informative Dropout: A Semi-Parametric Approach					of Rochester			
Inference in Randomized Trials with Death and Missingness	Oral	9/24/2014	Wang, Chenguang	Researcher	ASA Biopharmaceutical Section FDA-Industry Workshop	Rockville, MD		Researchers, Practitioners
Global Sensitivity Analysis of Randomized Trials with Missing Data: Recent Advances	Short Course, In-Person	12/8/2014	Scharfstein, Daniel	Researcher	Deming Conference	Atlantic City, NJ		Researchers, Practitioners
Standards in the Prevention and Handling of Missing Data for Patient-Centered Outcomes Research	Oral	12/16/2014	Li, Tianjing	Researcher	Journal Club, Johns Hopkins	Baltimore, MD		Students
Analysis of Randomized Trials with Missing Data	Short Course, In-Person and Adobe Connect	1/12/2015	Scharfstein, Daniel; McDermott, Aidan; Wang, Chenguang	Researchers	Johns Hopkins University	Baltimore, MD		Researchers, Practitioners
Global Sensitivity Analysis of Randomized Trials with Missing Data	Poster	4/27/2015	Scharfstein, Daniel	Researcher	FDA ORSI Symposium	Rockville, MD		Researchers, Practitioners, Policy Makers

Global Sensitivity Analysis of Randomized Trials with Missing Data	Short Course, In-Person	5/17/2015	Scharfstein, Daniel	Researcher	Society of Clinical Trials	Arlington, VA		Researchers, Practitioners
Analysis of Prospective Studies with Missing Data	On-Line Lecture	7/31/2015	Scharfstein, Daniel; Li, Tianjing	Researchers	Johns Hopkins University	Baltimore, MD		Researchers, Practitioners, Policy Makers
Global Sensitivity Analysis of Randomized Trials with Missing Data: A Frequentist Perspective	Oral	11/6/2015	Scharfstein, Daniel	Researcher	FDA – Center for Tobacco Products	Rockville, MD		Researchers, Practitioners, Policy Makers
Missing Data and Sensitivity Analyses in Randomized Trials	Oral	11/12/2015	Scharfstein, Daniel	Researcher	GlaxoSmith Kline	Valley Forge, PA		Researchers, Practitioners
Global Sensitivity Analysis of Randomized Trials with Missing Data: From the Software Development Trenches	Oral	11/13/2015	Scharfstein, Daniel	Researcher	National Institute of Statistical Sciences	Washington, Dc		Researchers
Analysis of Randomized Trials with Missing Data	Short Course, In-Person and Adobe	11/30/2015	Scharfstein, Daniel; McDermott, Aidan; Wang,	Researchers	FDA	Rockville, MD		Researchers, Practitioners, Policy Makers

	Connect		Chenguang					
Inference in Randomized Trials with Death and Missingness	Oral	4/4/2016	Scharfstein, Daniel	Researcher	Brown University	Providence, RI		Researchers, Practitioners.
Analysis of Randomized Trials with Missing Data	Webinar	5/24/16	Scharfstein, Daniel	Researcher	American Statistical Association			Researchers, Practitioners
Analysis of Randomized Trials with Missing Data	Short Course, In-Person and Adobe Connect	6/22/2016	Scharfstein, Daniel; McDermott, Aidan; Wang, Chenguang	Researchers	Johns Hopkins University	Baltimore, MD		Researchers, Practitioners
Analysis of Randomized Trials with Missing Data	Short Course, In-Person	7/26/2015	Scharfstein, Daniel	Researcher	University of Washington	Seattle, WA		Researchers, Practitioners,
Analysis of Randomized Trials with Missing Data	Webinar	9/20/16	Scharfstein, Daniel	Researcher	American Statistical Association			Researchers, Practitioners
Inference in Randomized Trials with Death and Missingness with Software Demonstration	Webinar	10/28/16	Wang, Chenguang	Researcher	American Statistical Association – New Jersey Chapter			Researchers, Practitioners
Analysis of Randomized Trials with Missing Data	Oral	12/5/16	Scharfstein, Daniel	Researcher	Novartis	East Hanover, NJ		Practitioners

*** Last, First**

****City, State or online (e.g., webinar)**

Additional Dissemination Updates

1. How will your study findings and other lessons learned be shared with:
   - Your study participants
   - Research partners (i.e., researchers, patients and other stakeholders engaged in the planning and conduct of your study)
   - Other investigators

Through publications, project website, short courses and webinars.

2. Who are the key end-users of your findings? How will these individuals or organizations use the information?

FDA, Pharma, Clinical trial statisticians. They should use our methods and software to evaluate the robustness of their trial results to missing data assumptions.

3. How will your study findings and other lessons learned be shared with these end-users?

Through publications, project website, short courses and webinars.

DATA SHARING

Please describe the data management and sharing plan that you have implemented to enable sharing of Research Project data (e.g., full analyzable data set, full protocol, full statistical analysis plan and analytic code) in a manner that is consistent with applicable privacy, confidentiality and other legal requirements.

We posted R and SAS versions of the software SAMON on the www.missingdatamatters.org website. An R version of a software package (called idem) for conducting sensitivity analysis of randomized trials with death and missingness is posted on CRAN. Example datasets are posted as part of our software distribution.

FUTURE DIRECTIONS

1. What, if anything, will you do differently in future research as a result of your experience with this PCORI project?

Be more realistic about the timeline for deliverable of manuscripts. The time scale for publication of statistical methods papers is very long and application papers cannot be submitted until the methods papers have been accepted.

Set up deliverables that are not contingent on feedback from the user community. Our last set of deliverables were based on the development of methods and software based on feedback from beta testers. With the exception of a beta tester hired by the FDA, we received no meaningful feedback.

PROGRESS STATEMENT FOR PUBLIC USE

Summarize project findings and impact, as well as engagement/stakeholder experiences using nontechnical language that is ready for public use. (Note: This information may be publicly disseminated by PCORI.) *Limit 250 words.*

Missing outcome data are a widespread problem in clinical trials, including those with patient centered outcomes. In the presence of missing data, inference about treatment effects relies on unverifiable assumptions. It is widely recognized that the way to address this problem is to posit varying assumptions about the missing data mechanism and evaluate how inference about treatment effects is affected by these assumptions. In this project, we created and disseminated novel statistical methods and software for evaluating the robustness of trial results to missing data assumptions. The software is posted on the project website http://www.missingdatamatters.org/. To illustrate the methods and software, six case studies were developed. During the project, six in-person short courses were delivered, along with three webinars, one videotaped lecture, nine oral presentations and one poster. In addition, two manuscripts were accepted for publication, one has been revised and one is under revision; additional manuscripts and a book are in preparation. Throughout the project, we were engaged with statistical methodologists and software developers as well as the FDA, a key stakeholder and co-funder. Despite wide dissemination efforts, uptake of our methods and software has been slower than expected. Until investigators are incentivized by FDA, PCORI, NIH and journals to rigorously evaluate the robustness of trial results to missing data assumptions, adoption of our technology is likely to be slow. Once the incentives are in place, our tools will be ready for use.

ADDITIONAL DOCUMENTS

All attachments should be combined with this document and submitted to PCORI as one PDF to fundedpfa@pcori.org.

Any relevant document, not already delivered, such as:

- Copies of drafts of instruments, data dictionaries, educational materials, manuals, or other project materials
- Minutes or summaries from patient and/or stakeholder meetings
- Bibliographies
- Summaries from DSMB meetings
- Final study protocol
- Other communications efforts
- Copies of reports from any consultants or advisors, where applicable
- Other documents or materials, as appropriate
- Websites, blogs, or other Internet-based links
- Public affairs or popular press coverage of the study online, on television, radio, etc.
- Abstracts from presentations made to professional groups or associations
- Submitted and published manuscripts

CERTIFICATION

This document must be certified by the Principal Investigator (PI) and the designated Administrative Official (AO).

Principal Investigator:

☒ I certify that I, as the Principal Investigator, have reviewed and approved this document (and any associated attachments, if applicable) and the information provided in this document is correct.

PI First Name: Daniel
Last Name: Scharfstein
Date: 2/6/17

Administrative Official:

☐ certify that I, as the designated Administrative Official, have reviewed and approved this document (and any associated attachments, if applicable) and the information provided in this document is correct.

AO First Name:
AO Last Name:
Date:

Biometrics 000, 000–000 DOI: 000
000 0000

Global Sensitivity Analysis for Repeated Measures Studies with Informative Drop-out: A Semi-Parametric Approach

Daniel Scharfstein[1,*], Aidan McDermott[1], Ivan Diaz[2], Marco Carone[3], Nicola Lunardon[4] and Ibrahim Turkoz[5]

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[3]University of Washington School of Public Health, Seattle, WA, U.S.A.

[4]Ca' Foscari University of Venice, Venice, Italy

[5]Janssen Research and Development, LLC, Titusville, NJ, U.S.A.

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Summary: In practice, both testable and untestable assumptions are generally required to draw inference about the mean outcome measured at the final scheduled visit in a repeated measures study with drop-out. Scharfstein *et al.* (2014) proposed a sensitivity analysis methodology to determine the robustness of conclusions within a class of untestable assumptions. In their approach, the untestable and testable assumptions were guaranteed to be compatible; their testable assumptions were based on a fully parametric model for the distribution of the observable data. While convenient, these parametric assumptions have proven especially restrictive in empirical research. Here, we relax their distributional assumptions and provide a more flexible, semi-parametric approach. We illustrate our proposal in the context of a randomized trial for evaluating a treatment of schizoaffective disorder.

Key words: Bootstrap; Cross-Validation; Exponential Tilting; Generalized Newton-Raphson Estimator; Jackknife; Identifiability; Selection Bias; Substitution Estimator

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1. Introduction

We consider a prospective cohort study design in which outcomes are scheduled to be collected after enrollment at fixed time-points and the parameter of interest is the mean outcome at the last scheduled study visit. We are concerned with drawing inference about this target parameter in the setting where some study participants prematurely stop providing outcome data.

Identifiability of the target parameter requires untestable assumptions about the nature of the process that leads to premature withdrawal. A common benchmark assumption, introduced by Rubin (1976), is that a patient's decision to withdraw between visits k and $k+1$ depends on outcomes through visit k (i.e., past), but not outcomes after visit k (i.e., future). This assumption has been referred to as *missing at random* (MAR). A weaker version of this assumption, termed *sequential ignorability* (SI), posits that the withdrawal decision depends on outcomes through visit k, but not the outcome at the last scheduled study visit (Birmingham et al., 2003). The former assumption yields identification of the entire joint distribution of the outcomes, while the latter assumption only admits identification of the distribution of the outcome at the last scheduled visit. Both parametric (see, for example, Schafer, 1997; Little and Rubin, 2014) and semi-parametric (see, for example, van der Laan and Robins, 2003; Tsiatis, 2006) approaches have been proposed for drawing inference about the target parameter under these assumptions.

For such untestable assumptions, it is important to conduct a sensitivity analysis to evaluate the robustness of the resulting inferences (see, for example, Little et al., 2010; ICH, 1998; CHMP, 2009). As reviewed by Scharfstein *et al.* (2014), sensitivity analyses can generally be classified as ad-hoc, local and global. Ad-hoc sensitivity analysis involves analyzing the data using a variety of methods and evaluating whether the inferences they yield are consistent with one another (CHMP, 2009). Local sensitivity analysis evaluates

how inferences vary in a small neighborhood of the benchmark assumption (see, for example, Copas and Eguchi, 2001; Verbeke et al., 2001; Troxel et al., 2004; Ma et al., 2005). In contrast, global sensitivity analysis considers how inferences vary over a much larger neighborhood of the benchmark assumption (see, for example, Nordheim, 1984; Baker et al., 1992; Little, 1994; Rotnitzky et al., 1998; Scharfstein et al., 1999; Robins et al., 2000; Rotnitzky et al., 2001; Birmingham et al., 2003; Vansteelandt et al., 2006; Daniels and Hogan, 2008; Little et al., 2010; Scharfstein et al., 2014).

In addition to untestable assumptions, testable restrictions are needed to combat the so-called "curse of dimensionality" (Robins et al., 1997). Scharfstein *et al.* (2014) developed a global sensitivity analysis approach whereby the untestable and testable assumptions were guaranteed to be compatible. Their testable assumptions were based on a fully parametric model for the distribution of the observable data. In our own practice, we have found it particularly challenging to posit parametric models that correspond well with the observed data, as we illustrate in Section 4 below. This has motivated the current paper, in which we relax distributional assumptions and develop a more flexible, semi-parametric extension of the Scharfstein et al. (2014) approach. The techniques of Daniels and Hogan (2008) and Linero and Daniels (2015) provide Bayesian solutions to the same problem and also ensure the compatibility of the untestable and testable assumptions. However, in contrast to our proposal, the scalability of their approach to settings including a large number of post-baseline assessments has yet to be demonstrated.

The paper is organized as follows. In Section 2, we introduce the data structure and the define the target parameter of interest. We also review the identification assumptions of Scharfstein *et al.* (2014). In Section 3, we present our inferential approach. In Section 4, we present results from the re-analysis of a clinical trial in which there was substantial premature

withdrawal. In Section 5, we describe the results of a simulation study. We provide concluding remarks in Section 6.

2. Data structure, target parameter, assumptions and identifiability

2.1 *Data structure and target parameter*

Let $k = 0, 1, \ldots, K$ refer in chronological order to the scheduled assessment times, with $k = 0$ corresponding to baseline. Let Y_k denote the outcome scheduled to be measured at assessment k. Define R_k to be the indicator that an individual is on-study at assessment k. We assume that all individuals are present at baseline, that is, $P(R_0 = 1) = 1$. Furthermore, we assume that individuals do not contribute any further data once they have missed a visit, so that $P(R_{k+1} = 0 \mid R_k = 0) = 1$ for each k. This pattern is often referred to as monotone drop-out. Let $C = \max\{k : R_k = 1\}$ and note that $C = K$ implies that the individual must have completed the study. For any given vector $z = (z_1, z_2, \ldots, z_K)$, we use the notational convention $\overline{z}_k = (z_0, z_1, \ldots, z_k)$ and $\underline{z}_k = (z_{k+1}, z_{k+2}, \ldots, z_K)$. For each individual, the data unit $O = (C, \overline{Y}_C)$ is drawn from some distribution P^* contained in the non-parametric model $\mathscr{M}$ of distributions. The observed data consist of n independent draws $O_1, O_2, \ldots, O_n$ from P^*. Throughout, the superscript $*$ will be used to denote the true value of the quantity to which it is appended.

By factorizing the distribution of O in terms of chronologically ordered conditional distributions, any distribution $P \in \mathscr{M}$ can be represented by

- $F_0(y_0) := P\left(Y_0 \leqslant y_0\right)$;
- $F_{k+1}(y_{k+1} \mid \overline{y}_k) := P\left(Y_{k+1} \leqslant y_{k+1} \mid R_{k+1} = 1, \overline{Y}_k = \overline{y}_k\right)$, $k = 0, 1, \ldots, K-1$;
- $H_{k+1}(\overline{y}_k) := P\left(R_{k+1} = 0 \mid R_k = 1, \overline{Y}_k = \overline{y}_k\right)$, $k = 0, 1, \ldots, K-1$.

Our main objective is to draw inference about $\mu^* := E^*(Y_K)$, the true mean outcome at visit K in a hypothetical world in which all patients are followed to that visit.

2.2 *Assumptions*

Assumptions are required to draw inference about μ^* based on the available data. We consider a class of assumptions whereby an individual's decision to drop out in the interval between visits k and $k+1$ is not only influenced by past observable outcomes but by the outcome at visit $k+1$. Towards this end, we adopt the following two assumptions introduced in Scharfstein *et al.* (2014):

ASSUMPTION 1: For $k = 0, 1, \ldots, K-2$,

$$P^*\left(Y_K \leqslant y \mid R_{k+1} = 0, R_k = 1, \overline{Y}_{k+1} = \overline{y}_{k+1}\right) \;=\; P^*\left(Y_K \leqslant y \mid R_{k+1} = 1, \overline{Y}_{k+1} = \overline{y}_{k+1}\right).$$

This says that in the cohort of patients who (1) are on-study at assessment k, (2) share the same outcome history through that visit and (3) have the same outcome at assessment $k+1$, the distribution of Y_K is the same for those last seen at assessment k and those still on-study at $k+1$.

ASSUMPTION 2: For $k = 0, 1, \ldots, K-1$,

$$dG^*_{k+1}(y_{k+1} \mid \overline{y}_k) \;\propto\; \exp\{\rho_{k+1}(\overline{y}_k, y_{k+1})\} dF^*_{k+1}(y_{k+1} \mid \overline{y}_k)\ ,$$

where $G^*_{k+1}(y_{k+1} \mid \overline{y}_k) := P^*\left(Y_{k+1} \leqslant y_{k+1} \mid R_{k+1} = 0, R_k = 1, \overline{Y}_k = \overline{y}_k\right)$ and $\rho_{k+1}(\overline{y}_k, y_{k+1})$ is a known, pre-specified function of $\overline{y}_k$ and y_{k+1}.

Conditional on any given history $\overline{y}_k$, this assumption relates the distribution of Y_{k+1} for those patients who drop out between assessments k and $k+1$ to those patients who are on study at $k+1$. The special case whereby ρ_{k+1} is constant in y_{k+1} for all k implies that, conditional on the history $\overline{y}_k$, individuals who drop out between assessments k and $k+1$ have the same distribution of Y_{k+1} as those on-study at $k+1$. If instead ρ_{k+1} is an increasing (decreasing) function of y_{k+1} for some k, then individuals who drop-out between assessments k and $k+1$ tend to have higher (lower) values of Y_{k+1} than those who are on-study at $k+1$.

Setting

$$\ell^*_{k+1}(\overline{y}_k) := \text{logit}\left\{H^*_{k+1}(\overline{y}_k)\right\} - \log\left\{\int \exp\{\rho_{k+1}(\overline{y}_k, u)\} dF^*_{k+1}(u \mid \overline{y}_k)\right\} \ ,$$

it can be shown that Assumptions 1 and 2 jointly imply that

$$\text{logit}\left\{P^*\left(R_{k+1} = 0 \,\middle|\, R_k = 1, \overline{Y}_{k+1} = \overline{y}_{k+1}, Y_K = y_K\right)\right\} = \ell^*_{k+1}(\overline{y}_k) + \rho_{k+1}(\overline{y}_k, y_{k+1}) \ .$$

We note that since H^*_{k+1} and F^*_{k+1} are identified from the distribution of the observed data, so is $\ell^*_{k+1}(\overline{y}_k)$. Furthermore, we observe that ρ_{k+1} quantifies the influence of Y_{k+1} on the risk of dropping out between assessments k and $k+1$, after controlling for the past history $\overline{y}_k$. In particular, Y_K is seen to not additionally influence this risk. When ρ_{k+1} does not depend on y_{k+1}, we obtain an assumption weaker than missing at random but stronger than sequential ignorability – we refer to it as SI-1. Under SI-1, the decision to withdraw between visits k and $k+1$ depends on outcomes through visit k but not on the outcomes at visits $k+1$ and K. For specified ρ_{k+1}, Assumptions 1 and 2 place no restriction on the distribution of the observed data. As such, ρ_{k+1} is not an empirically verifiable function.

Assumptions 1 and 2 allow the existence of unmeasured common causes of $Y_0, Y_1, \ldots, Y_K$, but does not allow these causes to directly impact, for patients on study at visit k, the decision to drop out before visit $k+1$. This is no different than under missing at random or sequential ignorability. To allow for a direct impact, one could utilize the sensitivity analysis model of Scharfstein, Rotnitzky and Robins (1998), which specifies

$$\text{logit}\left\{P^*\left(R_{k+1} = 0 \,\middle|\, R_k = 1, \overline{Y}_k = \overline{y}_k, Y_K = y_K\right)\right\} = h^*_{k+1}(\overline{y}_k) + q_{k+1}(\overline{y}_k, y_K) \ ,$$

where

$$h^*_{k+1}(\overline{y}_k) := \text{logit}\left\{H^*_{k+1}(\overline{y}_k)\right\} - \log\left\{\int \exp\{\rho_{k+1}(\overline{y}_k, u)\} dF^*_{K,k}(u \mid R_k = 1, \overline{y}_k)\right\}$$

and $F^*_{K,k}(u \mid R_k = 1, \overline{y}_k) := P^*(Y_K \leqslant u | R_k = 1, \overline{Y}_k = \overline{y}_k)$. Here, $q_{k+1}(\overline{y}_k, y_K)$ quantifies the influence of the outcome scheduled to be measured at the end of the study on the conditional hazard of last being seen at visit k given the observable past $\overline{y}_k$. The key disadvantage of

this model is that we have found that it is challenging for scientific experts to articulate how a distal endpoint affects a more proximal event (i.e., drop-out).

2.3 *Identifiability of target parameter*

Under Assumptions 1 and 2 with given ρ_{k+1}, the parameter μ^* is identifiable. To establish identifiability, it suffices to demonstrate that μ^* can be expressed as a functional of the distribution of the observed data. In the current setting, this follows immediately by noting, through repeated applications of the law of iterated expectations, that

$$\mu^* = \mu(P^*) = E^* \left[\frac{R_K Y_K}{\prod_{k=0}^{K-1} [1 + \exp\{\ell^*_{k+1}(\overline{Y}_k) + \rho_{k+1}(\overline{Y}_k, Y_{k+1})\}]^{-1}} \right]$$

The functional $\mu(P^*)$ can be equivalently expressed as

$$\int_{y_0} \cdots \int_{y_K} y_K \prod_{k=0}^{K-1} \left[dF^*_{k+1}(y_{k+1} \mid \overline{y}_k) \left\{ 1 - H^*_{k+1}(\overline{y}_k) \right\} + \frac{\exp\{\rho_{k+1}(\overline{y}_k, y_{k+1})\} dF^*_{k+1}(y_{k+1} \mid \overline{y}_k)}{\int \exp\{\rho_{k+1}(\overline{y}_k, u)\} dF^*_{k+1}(u \mid \overline{y}_k)} H^*_{k+1}(\overline{y}_k) \right] dF^*_0(y_0) \ . \quad (1)$$

3. Statistical inference

3.1 *Naive substitution estimator*

Given a fixed function ρ_{k+1}, Scharfstein *et al.* (2014) proposed to estimate μ^* via the substitution principle. Specifically, they consider specifying parametric models for both F^*_{k+1} and H^*_{k+1}, estimating parameters in these models by maximizing the likelihood function, estimating F^*_0 nonparametrically using the empirical distribution function, and finally, estimating (1) by Monte Carlo integration using repeated draws from the resulting estimates of F^*_{k+1}, H^*_{k+1} and F^*_0. Since the expression in (1) represents a smooth functional of F^*_0 and of the finite-dimensional parameters of the models for F^*_{k+1} and H^*_{k+1}, the resulting estimator of μ^* is $n^{1/2}$-consistent and, suitably normalized, tends in distribution to a mean-zero Gaussian random variable.

While simple to describe and easy to implement, this approach has a major drawback: the

inferences it generates will be sensitive to correct specification of the parametric models imposed on F^*_{k+1} and H^*_{k+1}. Since the fit of these models is empirically verifiable, the plausibility of the models imposed can be scrutinized in any given application. In several instances, we have found it difficult to find models providing an adequate fit to the observed data. This is a serious problem since model misspecification will generally lead to inconsistent inference, which can translate into inappropriate and misleading scientific conclusions. To provide greater robustness, we instead adopt a more flexible modeling approach.

As noted above, the distribution P^* can be represented in terms of $\{(F^*_{k+1}, H^*_{k+1}) : k = 0, 1, \ldots, K-1\}$. Suppose that P^* is contained in the submodel $\mathscr{M}_0 \subset \mathscr{M}$ of distributions that exhibit a first-order Markovian structure in the sense that $F_{k+1}(y_{k+1} \mid \overline{y}_k) = F_{k+1}(y_{k+1} \mid y_k)$ and $H_{k+1}(\overline{y}_k) = H_{k+1}(y_k)$. We can then estimate F^*_0 by the empirical distribution based on the sample of observed Y_0 values, while F^*_{k+1} and H^*_{k+1} can be estimated using the Nadaraya-Watson kernel estimators

$$\widehat{F}_{k+1,\lambda_F}(y_{k+1} \mid y_k) := \frac{\sum_{i=1}^n R_{k+1,i} I(Y_{k+1,i} \leqslant y_{k+1}) \phi_{\lambda_F}(Y_{k,i} - y_k)}{\sum_{i=1}^n R_{k+1,i} \phi_{\lambda_F}(Y_{k,i} - y_k)} \text{ and} \tag{2}$$

$$\widehat{H}_{k+1,\lambda_H}(y_k) := \frac{\sum_{i=1}^n R_{k,i}(1 - R_{k+1,i}) \phi_{\lambda_F}(Y_{k,i} - y_k)}{\sum_{i=1}^n R_{k,i} \phi_{\lambda_F}(Y_{k,i} - y_k)} , \tag{3}$$

where ϕ is a symmetric probability density function, ϕ_λ refers to the rescaled density $y \mapsto \phi(y/\lambda)/\lambda$, and (λ_F, λ_H) is a vector of tuning parameters. In practice, the values of these tuning parameters need to be carefully chosen to ensure the resulting estimators of F^*_{k+1} and H^*_{k+1} perform well. As discussed next, we select the tuning parameters via J-fold cross validation.

Writing $F := (F_1, F_2, \ldots, F_K)$ and $H := (H_1, H_2, \ldots, H_K)$, and denoting a typical realization of the prototypical data unit as $o = (c, \overline{y}_c)$, we may define the loss functions

$$L_F(F; F^\circ)(o) := \sum_{k=0}^{K-1} r_{k+1} \int \{I(y_{k+1} \leqslant u) - F_{k+1}(u \mid y_k)\}^2 \, dF^\circ_{k+1}(u) ,$$

$$L_H(H; H^\circ)(o) := \sum_{k=0}^{K-1} r_k \left[r_{k+1} - \{1 - H_{k+1}(y_k)\}\right]^2 H^\circ_{k+1}$$

with $F^\circ := (F_1^\circ, F_2^\circ, \ldots, F_K^\circ)$ and $H^\circ := (H_1^\circ, H_2^\circ, \ldots, H_K^\circ)$ defined by $F_{k+1}^\circ(u) := P(Y_{k+1} \leqslant u \mid R_{k+1} = 1)$ and $H_{k+1}^\circ := P(R_{k+1} = 0 \mid R_k = 1)$. Here, F° and H° represent collections of distributions and probabilities that can be estimated nonparametrically without the need for smoothing. It can be shown that the true risk mappings $F \mapsto E^*[L_F(F; F^{\circ *})(O)]$ and $H \mapsto E^*[L_H(H; H^{\circ *})(O)]$ are minimized at $F = F^*$ and $H = H^*$, where $F^{\circ *}$ and $H^{\circ *}$ denote the true value of F° and H°, respectively. Given a random partition of the dataset into J validation samples $\{V_1, V_2, \ldots, V_J\}$ with sample sizes $n_1, n_2 \ldots, n_J$, taken to be approximately equal, the oracle selectors for λ_F and λ_H are (van der Vaart et al., 2006)

$$\widetilde{\lambda}_F := \underset{\lambda_F}{\operatorname{argmin}} \frac{1}{J} \sum_{j=1}^{J} E^*[L_F(\widehat{F}_{\lambda_F}^{(j)}; \widehat{F}^\circ)(O)] \quad \text{and} \quad \widetilde{\lambda}_H := \underset{\lambda_H}{\operatorname{argmin}} \frac{1}{J} \sum_{j=1}^{J} E^*[L_H(\widehat{H}_{\lambda_H}^{(j)}; \widehat{H}^\circ)(O)].$$

Here, $\widehat{F}_{k+1,\lambda_F}^{(j)}$ and $\widehat{H}_{k+1,\lambda_H}^{(j)}$ are obtained by computing (2) and (3), respectively, on the dataset obtained by excluding individuals in V_j. The estimates of nuisance parameter estimators $\widehat{F}_{k+1}^\circ$ and $\widehat{H}_{k+1}^\circ$ are given by the empirical distribution of the observed values of Y_{k+1} within the subset of individuals with $R_{k+1} = 1$ and by the empirical proportion of individuals with $R_{k+1} = 0$ among those with $R_k = 1$, respectively. The quantities $\widetilde{\lambda}_F$ and $\widetilde{\lambda}_H$ cannot be computed in practice since P^* is unknown. Empirical tuning parameter selectors are given by

$$\widehat{\lambda}_F := \underset{\lambda_F}{\operatorname{argmin}} \widehat{\mathcal{R}}_F(\lambda_F) \quad \text{and} \quad \widehat{\lambda}_H := \underset{\lambda_H}{\operatorname{argmin}} \widehat{\mathcal{R}}_H(\lambda_H),$$

where

$$\begin{aligned} \widehat{\mathcal{R}}_F(\lambda_F) &:= \frac{1}{J} \sum_{j=1}^{J} \frac{1}{n_j} \sum_{i \in V_j} L_F(\widehat{F}_{\lambda_F}^{(j)}; \widehat{F}^\circ)(O_i) \\ &= \frac{1}{J} \sum_{j=1}^{J} \frac{1}{n_j} \sum_{i \in V_j} \sum_{k=0}^{K-1} R_{k+1,i} \left[\frac{\sum_\ell R_{k+1,\ell} \{ I(Y_{k+1,i} \leqslant Y_{k+1,l}) - \widehat{F}_{k+1,\lambda_F}^{(j)}(Y_{k+1,l} \mid Y_{k,i}) \}^2}{\sum_\ell R_{k+1,\ell}} \right] \end{aligned}$$

and

$$\widehat{\mathcal{R}}_H(\lambda_H) := \frac{1}{J} \sum_{j=1}^{J} \frac{1}{n_j} \sum_{i \in V_j} L_H(\widehat{H}_{\lambda_H}^{(j)}; \widehat{H}^\circ)(O_i)$$

$$= \frac{1}{J}\sum_{j=1}^{J}\frac{1}{n_j}\sum_{i\in V_j}\sum_{k=0}^{K-1}\frac{R_{k,i}[R_{k+1,i}-\{1-\widehat{H}^{(j)}_{k+1,\lambda_H}(Y_{k,i})\}]^2\sum_\ell R_{k,\ell}(1-R_{k+1,\ell})}{\sum_\ell R_{k,\ell}}\,.$$

The naive substitution estimator of μ^* is $\mu(\widehat{P})$, where $\widehat{P}$ is determined by (2) and (3) computed with tuning parameters $(\widehat{\lambda}_F, \widehat{\lambda}_H)$.

3.2 *Generalized Newton-Raphson estimator*

3.2.1 *Preliminaries.* In order to estimate F^*_{k+1} and H^*_{k+1}, smoothing techniques, as used in (2) and (3), must be utilized in order to borrow strength across subgroups of individuals with differing observed outcome histories. The implementation of smoothing techniques requires the selection of tuning parameters governing the extent of smoothing. As in the above procedure, tuning parameters are generally chosen to achieve an optimal finite-sample bias-variance trade-off for the quantity requiring smoothing - here, conditional distribution and probability mass functions. However, this trade-off may be problematic, since the resulting plug-in estimator $\mu(\widehat{P})$ defined in Section 3.1 may suffer from excessive and asymptotically nonnegligible bias due to inadequate tuning. This may prevent the naive estimator from having regular asymptotic behavior, upon which statistical inference is generally based. In particular, the resulting estimator may have a slow rate of convergence, and common methods for constructing confidence intervals, such as the Wald and bootstrap intervals, can have poor coverage properties. Such naive plug-in estimators must therefore be regularized in order to serve as an appropriate basis for drawing statistical inference, as is discussed in greater detail below.

If the parameter of interest is a sufficiently smooth functional on the space of possible data-generating distributions, it is sensible to expect a first-order expansion of the form

$$\mu(P) - \mu(P^*) = \int D(P)(o)d(P-P^*)(o) + Rem(P, P^*) \tag{4}$$

to hold, where $D(P)(o)$ is the evaluation at an observation value o of a so-called gradient of μ at P, and $Rem(P, P^*)$ is a second-order remainder term tending to zero as P tends to P^*.

This is established formally in the context of the current problem in Lemma 1. Here, much in parallel to its counterpart in multivariate calculus, the gradient D is an analytic object used to compute, at any given data-generating distribution P, the change in $\mu(P)$ following a slight perturbation of P. In general, the gradient is not uniquely defined, although it must be the case that any gradient D is such that $D(P)(O)$ has mean zero and finite variance under sampling from P. A discussion on gradients of statistical parameters can be found, for example, in Pfanzagl (1982) and in Appendix A.4 of van der Laan and Rose (2011).

Provided (4) holds and for a given estimator $\widehat{P}$ of P^*, algebraic manipulations leads to

$$\begin{aligned}\mu(\widehat{P}) - \mu(P^*) &= \int D(\widehat{P})(o) d(\widehat{P} - P^*)(o) + Rem(\widehat{P}, P^*) \\ &= \frac{1}{n}\sum_{i=1}^{n} D(P^*)(O_i) + \int [D(\widehat{P})(o) - D(P^*)(o)] d(P_n - P^*)(o) \\ &\quad - \frac{1}{n}\sum_{i=1}^{n} D(\widehat{P})(O_i) + Rem(\widehat{P}, P^*) \,,\end{aligned}$$

where P_n denotes the empirical distribution based on $O_1, O_2, \ldots, O_n$. If $\widehat{P}$ is a sufficiently well-behaved estimator of P^*, it is often the case that the terms $\int [D(\widehat{P})(o) - D(P^*)(o)] d(P_n - P^*)(o)$ and $Rem(\widehat{P}, P^*)$ are asymptotically negligible. However, when $\widehat{P}$ involves smoothing, as in the setting considered in this paper, the term $n^{-1}\sum_{i=1}^{n} D(\widehat{P})(O_i)$ generally tends to zero too slowly to allow $\mu(\widehat{P})$ to be an asymptotically linear estimator of μ^*. Nonetheless, the corrected estimator

$$\widehat{\mu} = \mu(\widehat{P}) + \frac{1}{n}\sum_{i=1}^{n} D(\widehat{P})(O_i)$$

is regular and asymptotically linear with influence function $D(P^*)$, provided that the aforementioned terms are asymptotically negligible. Consequently, $\widehat{\mu}$ converges to μ^* in probability and $n^{1/2}(\widehat{\mu} - \mu^*)$ tends in distribution to a zero-mean Gaussian random variable with variance $\sigma^2 := \int D(P^*)(o)^2 dP^*(o)$. This estimator is, in fact, a direct generalization of the one-step Newton-Raphson procedure used in parametric settings to produce an asymptotically

efficient estimator. This correction approach was discussed early on by Ibragimov and Khasminskii (1981), Pfanzagl (1982) and Bickel (1982), among others.

An alternative estimation strategy would consist of employing targeted minimum loss-based estimation (TMLE) to reduce bias due to inadequate tuning (van der Laan and Rubin, 2006). TMLE proceeds by modifying the initial estimator $\widehat{P}$ into an estimator $\widetilde{P}$ that preserves the consistency of $\widehat{P}$ but also satisfies the equation $n^{-1}\sum_{i=1}^{n} D(\widetilde{P})(O_i) = 0$. As such, the TMLE-based estimator $\widetilde{\mu} := \mu(\widetilde{P})$ of μ^* does not require additional correction and is asymptotically efficient. In preliminary simulation studies (not shown here), we found no substantial difference between the TMLE $\widetilde{\mu}$ and our proposed one-step estimator $\widehat{\mu}$. In this case, we favor the latter because of its greater ease of implementation.

3.2.2 *Estimator based on canonical gradient: definition and properties.* In our problem, the one-step estimator can be constructed using any gradient D of the parameter μ defined on the model $\mathscr{M}_0$. Efficiency theory motivates the use of the canonical gradient, often called the efficient influence function, in the construction of the above estimator. The resulting estimator is then not only asymptotically linear but also asymptotically efficient relative to model $\mathscr{M}_0$. The canonical gradient can be obtained by projecting any other gradient onto the tangent space, defined at each $P \in \mathscr{M}_0$ as the closure of the linear span of all score functions of regular one-dimensional parametric models through P. A comprehensive treatment of efficiency theory can be found in Pfanzagl (1982) and Bickel et al. (1993).

In our analysis, we restrict our attention to the class of selection bias functions of the form $\rho_{k+1}(\overline{y}_k, y_{k+1}) = \alpha\rho(y_{k+1})$, where ρ is a specified function of y_{k+1} and α is a sensitivity analysis parameter. With this choice, $\alpha = 0$ corresponds to our benchmark assumption (SI-1), which is weaker than missing at random (MAR) but stronger than sequential ignorability (SI). For the parameter chosen, the canonical gradient $D^{\dagger}(P)$ relative to $\mathscr{M}_0$, suppressing

notational dependence on α, is given by

$$D^\dagger(P)(o) := a_0(y_0) + \sum_{k=0}^{K-1} r_{k+1} b_{k+1}(y_{k+1}, y_k) + \sum_{k=0}^{K-1} r_k \{1 - r_{k+1} - H_{k+1}(y_k)\} c_{k+1}(y_k) \ ,$$

where expressions for $a_0(y_0)$, b_{k+1} and c_{k+1} are given in Appendix A. In this paper we suggest the use of the following one-step estimator

$$\widehat{\mu} := \mu(\widehat{P}) + \frac{1}{n} \sum_{i=1}^{n} D^\dagger(\widehat{P})(O_i)$$

which stems from linearization (4), as formalized in the following lemma.

LEMMA 1: *For any $P \in \mathscr{M}_0$, the linearization*

$$\mu(P) - \mu(P^*) = \int D^\dagger(P)(o) d(P - P^*)(o) + Rem(P, P^*)$$

holds for a second-order remainder term $Rem(P, P^*)$ defined in Appendix B.

In the above lemma, the expression *second-order* refers to the fact that $Rem(P, P^*)$ can be written as a sum of the integral of the product of two error terms each tending to zero as P tends to P^*, that is,

$$Rem(P, P^*) = \sum_{k=0}^{K-1} \int u_k^*(o) \left\{\Psi_k(P)(o) - \Psi_k(P^*)(o)\right\} \left\{\Theta_k(P)(o) - \Theta_k(P^*)(o)\right\} dP^*(o) \quad (5)$$

for certain smooth operators $\Psi_0, \ldots, \Psi_{K-1}, \Theta_0, \ldots, \Theta_{K-1}$ and weight functions $u_0^*, \ldots, u_{K-1}^*$ that possibly depend on P^*. The proof of Lemma 1 follows from the derivations in Web Appendices A and B.

The proposed estimator is asymptotically efficient relative to model $\mathscr{M}_0$ under certain regularity conditions, as outlined below.

THEOREM 1: *If*

(a) $\int [D^\dagger(\widehat{P})(o) - D^\dagger(P^*)(o)] d(P_n - P^*)(o) = o_P(n^{-1/2})$, *and*
(b) $Rem(\widehat{P}, P^*) = o_P(n^{-1/2})$

then it holds that

$$\widehat{\mu} = \mu^* + \frac{1}{n} \sum_{i=1}^{n} D^\dagger(P^*)(O_i) + o_P(n^{-1/2})$$

and therefore $\widehat{\mu}$ is an asymptotically efficient estimator of μ^* relative to model $\mathscr{M}_0$.

This result not only justifies the use of $\widehat{\mu}$ in practice but also suggests that a Wald-type asymptotic $100 \times (1-\gamma)\%$ confidence interval for μ^* can be constructed as

$$\left(\widehat{\mu} - \frac{z_{\gamma/2}\widehat{\sigma}}{\sqrt{n}},\ \widehat{\mu} + \frac{z_{\gamma/2}\widehat{\sigma}}{\sqrt{n}}\right), \tag{6}$$

where $\widehat{\sigma}^2 := \frac{1}{n}\sum_{i=1}^{n} D^\dagger(\widehat{P})(O_i)^2$ is a consistent estimator of the asymptotic variance of $n^{1/2}(\widehat{\mu} - \mu^*)$ under mild conditions and $z_{\gamma/2}$ is the $(1-\gamma/2)$-quantile of the standard normal distribution.

Alternative sufficient conditions can be established to guarantee that conditions (a) and (b) of the theorem above hold. For example, a simple application of Lemma 19.24 of van der Vaart (2000) implies that condition (a) holds provided it can be established that

(i) $D^\dagger(\widehat{P})$ is a consistent estimator of $D^\dagger(P^*)$ in the $L_2(P^*)$-norm in the sense that

$$\int \left[D^\dagger(\widehat{P})(o) - D^\dagger(P^*)(o)\right]^2 dP^*(o) \xrightarrow{P} 0, \text{and}$$

(ii) for some P^*-Donsker class $\mathscr{F}$, $D^\dagger(\widehat{P})$ falls in $\mathscr{F}$ with probability tending to one.

Since our estimator $\widehat{P}$ is based on kernel regression, and is therefore consistent, condition (i) holds by a simple application of the continuous mapping theorem. Condition (ii) is standard in the analysis of estimators based on data-adaptive estimation of nuisance parameters – Giné and Nickl (2008) presents an excellent study of the conditions under which it is expected to hold. Condition (b) is satisfied as a result of the following argument. The use of cross-validation allows the optimal rate $n^{-2/5}$ to be achieved for the estimator $\widehat{P}$ since the latter is constructed using univariate kernel smoothers. By a repeated use of the Cauchy-Schwartz inequality on the various summands of $Rem(\widehat{P}, P^*)$ in (5), the continuous mapping theorem allows us to show that, since each term in $Rem(\widehat{P}, P^*)$ is a second-order difference involving smooth transformations of components of $\widehat{P}$ and P, $Rem(\widehat{P}, P^*)$ tends to zero

in probability at a rate faster than $n^{-1/2}$ under very mild conditions, including that the probabilities $\widehat{\pi}(Y_{j-1}, Y_j)$ are bounded away from zero with probability tending to one.

3.3 *Practical considerations in confidence interval construction*

For given α, there are many ways to construct confidence intervals for μ^*. As indicated above, an influence function-based asymptotic confidence interval is given by (6). In Section 5, we present the results of a simulation study in which this confidence interval construction results in poor coverage in moderately sized samples. The poor coverage can be explained in part by the fact that $\widehat{\sigma}^2$ can be severely downward biased in finite samples (Efron and Gong, 1983). This side effect of poor variance estimation may be alleviated by resorting to alternative pivots. The empirical likelihood methodology (Owen, 2001) is based on the influence function and forms a pivot whose signed square root is asymptotically standard normal without explicit variance estimation. Variance stabilization (Tibshirani, 1988; DiCiccio et al., 2006) aims to single out a suitable reparametrization of μ, say $h(\cdot)$, such that the asymptotic variance of $n^{1/2}\{h(\widehat{\mu}) - h(\mu)\}$ is exactly or approximately 1. However, simulation results (not reported) highlight that none of these procedures exhibit appreciably better coverage accuracy than (6) .

There is hope that resampling-based procedures may be used to improve performance. In considering such procedures, we must keep an eye on computational feasibility. A first idea is to consider the jackknife estimator for σ^2,

$$\widehat{\sigma}^2_{JK} := (n-1)\sum_{i=1}^{n}\{\widehat{\mu}^{(-i)} - \widehat{\mu}^{(\cdot)}\}^2$$

where $\widehat{\mu}^{(-i)}$ is the estimator of μ^* with the ith individual deleted from the dataset and $\widehat{\mu}^{(\cdot)} := \frac{1}{n}\sum_{i=1}^{n}\widehat{\mu}^{(-i)}$. This estimator is known to be conservative (Efron and Stein, 1981), but is the "method of choice if one does not want to do bootstrap computations" (Efron and Gong, 1983). Using the jackknife, confidence intervals take the form of (6) with $\widehat{\sigma}$ replaced

by $\widehat{\sigma}_{JK}$. Our simulation study in Section 5 demonstrates that these intervals perform better than interval (6) although some undercoverage is still present.

Another possible approach would be to utilize the Studentized bootstrap, wherein confidence intervals are formed by choosing cutpoints based on the distribution of

$$\left\{ \frac{\widehat{\mu}_{(b)} - \widehat{\mu}}{\widehat{se}(\widehat{\mu}_{(b)})} : b = 1, 2, \ldots, B \right\} \tag{7}$$

where $\widehat{\mu}_{(b)}$ is the estimator of μ^* based on the bth bootstrap dataset and $\widehat{se}(\widehat{\mu}_{(b)})$ is an estimator of the standard error of $\widehat{\mu}_{(b)}$. One can consider standard error estimators based on the influence function or jackknife. An equal-tailed $(1-\gamma)$ confidence interval takes the form $\big(\widehat{\mu} - t_{1-\gamma/2}\widehat{se}(\widehat{\mu}), \widehat{\mu} - t_{\gamma/2}\widehat{se}(\widehat{\mu})\big)$, where t_q is the qth quantile of (7). A symmetric $(1-\gamma)$ confidence interval takes the form $\big(\widehat{\mu} - t^*_{1-\gamma}\widehat{se}(\widehat{\mu}), \widehat{\mu} + t^*_{1-\gamma}\widehat{se}(\widehat{\mu})\big)$, where $t^*_{1-\gamma}$ is selected so that the sampling distribution of (7) assigns probability mass $1-\gamma$ between $-t^*_{1-\gamma}$ and $t^*_{1-\gamma}$.

We can either adopt a non-parametric or parametric approach to the bootstrap. The advantage of the non-parametric bootstrap is that it does not require a model for the distribution of the observed data. Since our analysis depends on correct specification of a semiparametric model and on estimation of such a model, it appears sensible to use this model to bootstrap the observed data. In our data analysis and simulation study, we use the estimated distribution of the observed data to generate bootstrapped observed datasets. Our simulation study in Section 5 suggests that the symmetric Studentized bootstrap with jackknifed standard errors performs best.

4. SCA-3004 Study

SCA-3004 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, international study designed to evaluate the efficacy and safety of once-monthly, injectable paliperidone palmitate (PP1M), as monotherapy or as an adjunct to pre-study mood stabilizers or antidepressants, relative to placebo (PBO) in delaying the time to relapse in patients

with schizoaffective disorder (SCA) (Fu et al., 2014). The study included multiple phases. After initial screening, an open-label phase consisted of a 13-week, flexible-dose, lead-in period and a 12-week, fixed-dose, stabilization period. Stable patients entered a 15-month, double-blind, relapse-prevention phase and were randomized (1:1) to receive either PP1M or placebo injections at baseline (Visit 0) and every 28 days (Visits 1–15). An additional clinic visit (Visit 16) was scheduled 28 days after the last scheduled injection. In the study, 170 and 164 patients were randomized to the PBO and PP1M arms, respectively. One placebo patient was removed because of excessive influence on the analysis – an expanded discussion can be found in Section 6.

The research question driving this maintenance-of-effect study was whether or not outcomes in patients with schizoaffective disorder are better maintained if they continued on treatment rather than being withdrawn from treatment and given placebo. Given the explanatory nature of the research question, an ideal study would follow all randomized patients through Visit 16 while maintaining them on their randomized treatment and examine symptomatic and functional outcomes at that time point. Since clinical relapse, largely determined by symptoms (e.g., Positive and Negative Symptom scale) and clinical response to symptoms (e.g., hospitalization), can have a major negative impact on the lives of participants and lead to irreversible harm, there is an ethical requirement that investigators and clinicians be highly vigilant, look for the first signs of relapse, and intervene to prevent adverse short-term and long-term outcomes. As a consequence, the study design required that patients who had signs of relapse be withdrawn from the study. Thus, follow-up clinical data were unavailable post-relapse. In addition to this source of missing data, some patients discontinued due to adverse events, withdrew consent or were lost to follow-up. In the trial, 38% and 60% of patients in the PBO and PP1M arms, respectively, were followed through Visit 16 ($p<0.001$).

We focus our analysis on patient function as measured by the Personal and Social Performance (PSP) scale. The PSP scale is a validated clinician-reported instrument that has been extensively used. It is scored from 1 to 100, with higher scores indicating better functioning based on evaluation of four domains (socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behaviors). It has been argued that a clinically meaningful difference in PSP scores is between 7 and 12 points (Patrick et al., 2009).

We seek to estimate, for each treatment group, the mean PSP at Visit 16 in the counterfactual world in which all patients are followed and treated through Visit 16. Since symptoms and function are correlated, the observed PSP data are likely to be a highly biased representation of the counterfactual world of interest. The mean PSP score among completers was 76.53 and 76.96 in the PBO and PP1M arms, respectively; the estimated difference is -0.43 (95% CI: -3.34 to 2.48), indicating a non-significant treatment effect (p=0.77).

In Figure 1, we display the treatment-specific trajectories of mean PSP score, stratified by last visit time. For patients who prematurely terminate the study, it is interesting to notice that there tends to be a worsening of mean PSP scores at the last visit on study.

[Figure 1 about here.]

Before implementing our proposed sensitivity analysis procedure, we implemented the approach of Scharfstein *et al.* (2014). For each treatment group, we modeled H^*_{k+1} using logistic regression with visit-specific intercepts and a common effect of Y_k. Additionally, we modeled F^*_{k+1} both using beta and truncated normal regression, each with visit-specific intercepts and a common effect of Y_k. Using estimates of the parameters from these models, we simulated 500,000 datasets for each treatment group. We compared the proportion dropping out before visit $k+1$ among those on study at visit k based on the actual and simulated datasets. We also compared the empirical distribution of PSP scores among those

on study at visit $k+1$ based on these datasets using the Kolmogorov-Smirnov statistics. The results for the simulations involving the truncated normal regression and beta regression models are shown in the first and second rows of Figure 2, respectively. The figure suggests that these models do not fit the observed data well. For both the truncated normal and beta regression models, inspection of the actual and simulated distribution of PSP scores at each study visit reveals large discrepancies. For the beta regression model, the contrast between the simulated and actual drop-out probabilities for the PP1M arm is particularly poor.

We contrast the fit of these models to the non-parametric smoothing approach proposed in this paper. For estimation of F^*_{k+1} and H^*_{k+1} based on data from the PBO arm, the optimal choices of λ_F and λ_H are 1.81 and 5.18, respectively. The corresponding optimal choices for the PP1M arm were 1.16 and 8.53. Using the estimated F^*_{k+1} and H^*_{k+1} and optimal choices of λ_F and λ_H, we simulated, as before, 500,000 observed datasets for each treatment group. The results of this simulation in comparison to the actual observed data is shown in the bottom row of Figure 2. In sharp contrast to the parametric modeling approach, the results show excellent agreement between the actual and simulated datasets. For each treatment group, inspection of the actual and simulated distribution of PSP scores at the study visit with the largest Kolmogorov-Smirnov statistics reveals only small discrepancies.

[Figure 2 about here.]

Under SI-1, that is, when $\alpha = 0$, the estimated counterfactual means of interest are 73.31 (95% CI: 69.71 to 76.91) and 74.52 (95% CI: 72.28 to 76.75) for the PBO and PP1M arms, respectively. The estimated treatment difference is -1.20 (95% CI: -5.34 to 2.93). Relative to the complete-case analysis, the SI-1 analysis corrects for bias in a direction that is anticipated: the estimated means under SI-1 are lower and, since there is greater drop-out in the PBO arm, there is a larger correction in that arm. As a consequence, the estimated treatment effect is more favorable to PP1M, although the 95% CI still includes 0. For comparative purposes, the

plug-in procedure produces estimates of the means that are slightly lower (73.79 and 74.63) and an estimated treatment difference that is slightly larger (-0.84). The logistic-truncated normal and logistic-beta models for the distribution of the observed data produce markedly different results under SI-1. For the logistic-truncated model the estimated means are 70.62 (95% CI: 67.01 to 74.24) and 74.68 (95% CI: 72.89 to 76.48) with an estimated difference of -4.06 (95% CI: -8.13 to 0.01); for the logistic-beta model, the estimated means are 64.42 (95% CI: 55.15 to 73.69) and 70.55 (95% CI: 67.53 to 73.56) with an estimated difference of -6.13 (95% CI: -15.96 to 3.71).

In our sensitivity analysis, we chose ρ as depicted in Figure 3. The shape of the function is chosen so that when comparing patients on the low end ($\leqslant 30$) and high end ($\geqslant 80$) of the PSP scale there is relatively less difference in the risk of drop-out than when comparing patients in the middle of the PSP scale (30-80). For example, consider two cohorts of patients who are on study through assessment k and have the same history of measured factors through that assessment. If the first and second cohort of patients have PSP scores at $k+1$ of 30 (40:50:60:70:80) and 20 (30:40:50:60:70), respectively, then the log odds ratio of dropping out between visits k and $k+1$ is α times 0.01 (0.18, 0.40, 0.30, 0.09, 0.01) for the first relative to the second cohort. When $\alpha > 0$ ($\alpha < 0$), patients with higher PSP scores are more (less) likely to drop out. Since lower PSP scores represent worse function, it is most plausible that $\alpha \leqslant 0$. For completeness, we ranged the treatment-specific α values from -20 to 20.

[Figure 3 about here.]

In Figure 4, we display the estimated treatment-specific mean PSP at Visit 16 as a function of α along with 95% pointwise confidence intervals. Figure 5 displays a contour plot of the estimated differences between mean PSP at Visit 16 for PBO versus PP1M for various treatment-specific combinations of α. The point (0,0) corresponds to the SI-1 assumption in both treatment arms. There are no treatment-specific combinations of α for which the

estimated treatment differences are clinically meaningful or statistically significant (at the 0.05 level). Figure 6 displays the estimated treatment-specific difference in mean PSP at Visit 16 between non-completers and completers as a function of α. For each treatment group and α, the estimated mean among non-completers is back-calculated from the estimated overall mean ($\widehat{\mu}$), the observed mean among completers ($\sum_i R_{K,i}Y_{K,i}/\sum_i R_{K,i}$) and the proportion of completers ($\sum_i R_{K,i}/n$). The differences in the negative range of α are in the clinically meaningful range, suggesting that the considered choices of the sensitivity analysis parameters are reasonable.

[Figure 4 about here.]

[Figure 5 about here.]

[Figure 6 about here.]

5. Simulation study

As in our goodness-of-fit evaluation above, we simulated, using the estimated F_k^* and H_k^* and optimal choices of λ_F and λ_H, 1,000 datasets for each treatment group. For purposes of the simulation study, we treat the best fit to the observed data as the true data generating mechanism. We evaluate the performance of our procedures for various α values ranging from -10 to 10. The target for each α is the mean computed using formula (1).

The results of our simulation study are displayed in Tables 1 and 2. In Table 1, we report for each treatment group and each α the bias and mean-squared error (MSE) for the plug-in estimator $\mu(\widehat{P})$ and the one-step estimator $\widehat{\mu}$. The results show that the one-step estimator has less bias and lower MSE than the plug-in estimator, although the differences are not dramatic. In Table 2, we report, for each treatment group and each α, 95% confidence interval coverage for six confidence interval procedures: (1) normality-based confidence interval with influence function-based standard error estimator (Normal-IF); (2)

normality-based confidence interval with jackknife-based standard error estimator (Normal-JK); (3) equal-tailed, Studentized-t bootstrap confidence interval with influence function-based standard error estimator (Bootstrap-IF-ET); (4) equal-tailed, Studentized-t bootstrap confidence interval with jackknife-based standard error estimator (Bootstrap-JK-ET); (5) symmetric, Studentized-t bootstrap confidence interval with influence function-based standard error estimator (Bootstrap-IF-S); (6) symmetric, Studentized-t bootstrap confidence interval with jackknife-based standard error estimator (Bootstrap-JK-S). Bootstrapping was based on 1,000 datasets.

[Table 1 about here.]

[Table 2 about here.]

We found that the normality-based confidence interval with influence function-based standard error estimator underperformed for both treatment groups and all choices of the sensitivity analysis parameters. In general, the confidence interval procedures that used jackknife standard errors performed better than their counterparts that used the influence function-based standard error estimator. The symmetric, Studentized-t bootstrap confidence interval with jackknife-based standard error estimator (Bootstrap-JK-S) exhibited the most consistent performance across treatment groups and sensitivity analysis parameters.

Our simulation studies reveal some evidence of possible residual bias of the one-step estimator in the context considered. The latter is based upon the use of kernel smoothing in order to estimate the various conditional distribution functions required in the evaluation of μ. It may be possible to achieve better small-sample behavior by employing alternative conditional distribution function estimators with better theoretical properties – examples of such include the estimators described in Hall et al. (1999). An ensemble learning approach, such as the Super Learner (van der Laan et al., 2007), may also yield improved function estimators and decrease the residual bias of the resulting one-step estimator. Nevertheless, because the

construction of the one-step estimator relies on a first-order asymptotic representation, the benefits from improved function estimation may possibly be limited by the relatively small sample size investigated in this simulation study. The use of correction procedures based on higher-order asymptotic representations, as described in Robins et al. (2008), van der Vaart et al. (2014), Carone et al. (2014) and Díaz et al. (2016), for example, may lead to improved performance in smaller samples.

6. Discussion

In this paper, we have developed a semi-parametric method for conducting a global sensitivity analysis of repeated measures studies with monotone missing data. We have developed an open-source software package that implements the methods discussed in this paper. The package is called SAMON and can be found at `www.missingdatamatters.org`.

Our approach does not, as of yet, accommodate auxiliary covariates V_k scheduled to be measured at assessment k. Incorporating $\overline{V}_k$ into the conditioning arguments of Assumptions 1 and 2 can serve to increase the plausibility of these assumptions. In particular, $\overline{V}_k$ can be allowed to influence the decision, for patients on study at visit k, to drop out between visits k and $k+1$, and the unmeasured common causes of $Y_0, Y_1, \ldots, Y_K$ can be allowed to indirectly impact the decision to drop out through their relationship with $\overline{V}_k$. In the context of SCA-3004, it would be useful to incorporate the PANSS (Positive and Negative Symptom Scale) and CGI (Clinical Global Impressions) scores as auxiliary covariates as they are related to planned patient withdrawal as well as correlated with PSP. In future work, we plan to extend the methods developed here to accommodate auxiliary covariates. An extension that handles multiple reasons for drop-out is also worthwhile.

In this paper, we imposed a first-order Markovian assumption in modeling the distribution of the observed data. The plausibility of this assumption was considered in the data analysis as we have evaluated the goodness-of-fit of our model, as illustrated in the bottom row of

Figure 2. The Markovian assumption can be relaxed by incorporating the past history using (1) a specified function of the past history, (2) semiparametric single index models (Hall and Yao, 2005) or (3) recently developed methods in data adaptive non-parametric function estimation (van der Laan, 2015).

For given α, our estimator of μ^* is essentially an α-specific weighted average of the observed outcomes at visit K. As a result, it does not allow extrapolation outside the support of these outcomes. We found that one patient in the PBO arm who completed the study with the lowest observed PSP score at the final visit had a very large influence on the analysis. Under SI-1 and other values of α, this patient affected the estimated mean in the PBO group by more than 3 points. In contrast to our approach, a mixed modeling approach, which posits a multivariate normal model for the joint distribution of the full data, does allow extrapolation. Inference under this approach is valid under MAR and correct specification of the multivariate normality assumption. We found that this approach provides much more precise inference, yielding a statistically significant treatment effect in favor of PP1M (treatment effect = -4.7, 95% CI: -7.7 to -1.8). Further, this approach was insensitive to the PBO patient that we removed from our analysis. The disadvantages of the mixed model approach are its reliance on normality and the difficulty of incorporating it into global sensitivity analysis.

In SCA-3004 there is a difference, albeit not a statistically significant one, in baseline PSP score between treatment groups. The PBO arm has a lower baseline mean PSP score than the PP1M arm (71.2 vs. 72.9). Our method can easily address this imbalance by subtracting out this difference from our effect estimates or by formally modeling change from baseline. In either case, the treatment effect estimates would be less favorable to PP1M. It is notable that a mixed model analysis that models change from baseline does yield a statistically significant effect in favor of PP1M. It may also be of interest to adjust the treatment effect

estimates for other baseline covariates, either through regression or direct standardization. We will address this issue in future work. We also plan to develop methods for handling intermittent missing outcome data.

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Appendix A: Explicit Form of Canonical Gradient

The derivation of the canonical gradient is provided in Web Appendix A. Here, we present its explicit form.

Let $\pi_{k+1}(y_k, y_{k+1}) = [1 + \exp\{\ell_{k+1}(y_k) + \alpha\rho(y_{k+1})\}]^{-1}$, where

$$\ell_{k+1}(y_k) := \text{logit}\left\{H_{k+1}(y_k)\right\} - \log\left\{\int \exp\{\rho_{k+1}(\overline{y}_k, u)\} dF_{k+1}(u \mid y_k)\right\}.$$

Let $\pi(\overline{y}_K) = \prod_{k=0}^{K-1} \pi_k(y_k, y_{k+1})$,

$$w_{k+1}(y_k) = E\left[\exp\{\alpha\rho(Y_{k+1})\} \mid R_{k+1} = 1, Y_k = y_k\right],$$

and $g_{k+1}(y_{k+1}, y_k) = \{1 - H_{k+1}(y_k)\} w_{k+1}(y_k) + \exp\{\alpha\rho(y_{k+1})\} H_{k+1}(y_k)$.

The canonical gradient is expressed as

$$D^\dagger(P)(o) := a_0(y_0) + \sum_{k=0}^{K-1} r_{k+1} b_{k+1}(y_{k+1}, y_k) + \sum_{k=0}^{K-1} r_k \{1 - r_{k+1} - H_{k+1}(y_k)\} c_{k+1}(y_k)$$

where

$$a_0(y_0) \;=\; E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \,\middle|\, Y_0 = y_0\right] - \mu(P)$$

$$\begin{aligned} & b_{k+1}(y_{k+1}, y_k) \\ &= E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \,\middle|\, R_{k+1} = 1, Y_{k+1} = y_{y+1}, Y_k = y_k\right] - E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \,\middle|\, R_{k+1} = 1, Y_k = y_k\right] \\ &\quad + E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \left[\frac{\exp\{\alpha\rho(Y_{k+1})\}}{g_{k+1}(Y_{k+1}, Y_k)}\right] \,\middle|\, R_{k+1} = 1, Y_k = y_k\right] H_{k+1}(y_k) \left\{1 - \frac{\exp\{\alpha\rho(y_{k+1})\}}{w_{k+1}(y_k)}\right\} \end{aligned}$$

$$\begin{aligned} & c_{k+1}(y_k) \\ &= \quad E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \left[\frac{\exp\{\alpha\rho(Y_{k+1})\}}{g_{k+1}(Y_{k+1}, Y_k)}\right] \,\middle|\, R_k = 1, Y_k = y_k\right] \\ &\quad - E\left[\frac{R_K Y_K}{\pi(\overline{Y}_K)} \left[\frac{1}{g_{k+1}(Y_{k+1}, Y_k)}\right] \,\middle|\, R_k = 1, Y_k = y_k\right] w_{k+1}(y_k) \end{aligned}$$

Appendix B: Explicit Form of the Remainder Term

The derivation of the remainder term is provided in Web Appendix B. Here, we present its explicit form.

$$\begin{aligned} Rem(P, P^*) \;&=\; \mu(P) - \mu(P^*) + \int D^\dagger(P)(o) dP^*(o) \\ &=\; \sum_{k=0}^{K-1} Rem_{1,k}(P, P^*) + \sum_{k=1}^{K-1} Rem_{2,k}(P, P^*) + \sum_{k=2}^{K-1} Rem_{3,k}(P, P^*)\ , \end{aligned}$$

where we define

$$
\begin{aligned}
Rem_{1,k}(P,P^*) &:= E^*\left[R_k E^*\left[R_{k+1}e^{\alpha r(Y_{k+1})}\middle| R_k=1,Y_k\right] Rem_{1,k,1}(P,P^*)(O) Rem_{1,k,2}(P,P^*)(O)\right],\\
Rem_{1,k,1}(P,P^*)(O) &:= \frac{E\left[\frac{R_K Y_K e^{\alpha r(Y_{k+1})}}{\prod_{j\neq k+1}\pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right]}{E[R_{k+1}e^{\alpha r(Y_{k+1})}\,|\,R_k=1,Y_k]} - \frac{E^*\left[\frac{R_K Y_K e^{\alpha r(Y_{k+1})}}{\prod_{j=1}^k \pi_j(Y_{j-1},Y_j)\prod_{j=k+2}^K \pi_j^*(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right]}{E^*[R_{k+1}e^{\alpha r(Y_{k+1})}\,|\,R_k=1,Y_k]},\\
Rem_{1,k,2}(P,P^*)(O) &:= \frac{H^*_{k+1}(Y_k)}{E^*[R_{k+1}e^{\alpha r(Y_{k+1})}\,|\,R_k=1,Y_k]} - \frac{H_{k+1}(Y_k)}{E\left[R_{k+1}e^{\alpha r(Y_{k+1})}\,|\,R_k=1,Y_k\right]},\\
Rem_{2,k}(P,P^*) &:= E^*\left[R_k Rem_{2,k,1}(P,P^*)(O) Rem_{2,k,2}(P,P^*)(O)\right],\\
Rem_{2,k,1}(P,P^*)(O) &:= E^*\left[\frac{R_K Y_K}{\prod_{j=k+1}^K \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right] - E\left[\frac{R_K Y_K}{\prod_{j=k+1}^K \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right],\\
Rem_{2,k,2}(P,P^*)(O) &:= E\left[\frac{1}{\prod_{j=1}^k \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right] - E^*\left[\frac{1}{\prod_{j=1}^k \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right],\\
Rem_{3,k}(P,P^*) &:= E^*\left[R_k Rem_{3,k,1}(P,P^*)(O) Rem_{3,k,2}(P,P^*)(O)\right],\\
Rem_{3,k,1}(P,P^*)(O) &:= E^*\left[\frac{R_K Y_K}{\prod_{j=k+1}^K \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right] - E\left[\frac{R_K Y_K}{\prod_{j=k+1}^K \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k\right]\\
Rem_{3,k,2}(P,P^*)(O) &:= E\left[\frac{1}{\prod_{j=1}^k \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k,Y_{k-1}\right] - E^*\left[\frac{1}{\prod_{j=1}^k \pi_j(Y_{j-1},Y_j)}\middle| R_k=1,Y_k,Y_{k-1}\right].
\end{aligned}
$$

Under suitable norms and provided reasonable regularity conditions hold, each function $o \mapsto Rem_{j,k,i}(P,P^*)(o)$ tends to zero as P tends to P^*, illustrating thus that $Rem(P,P^*)$ is indeed a second-order term.

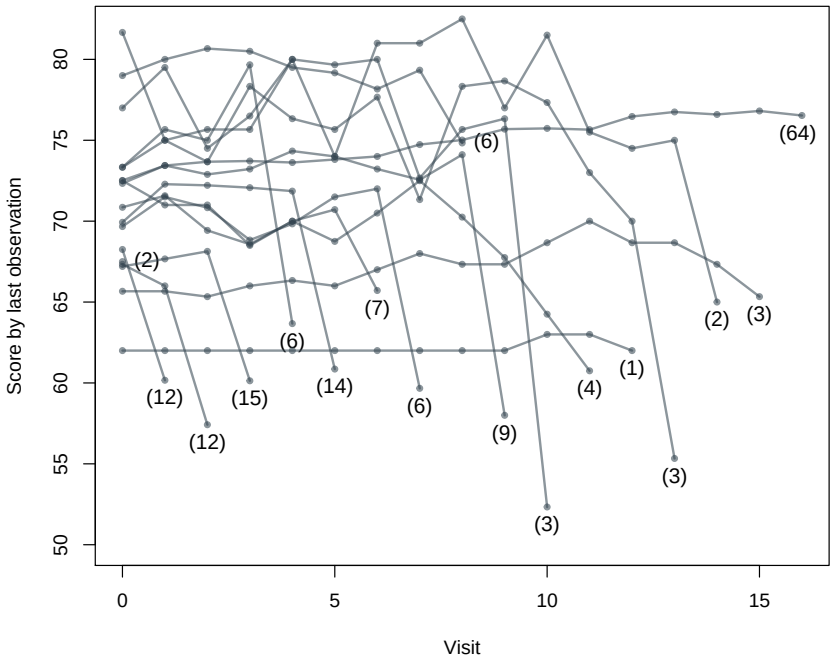
Appendix C: Proof of Theorem 1

We can write that

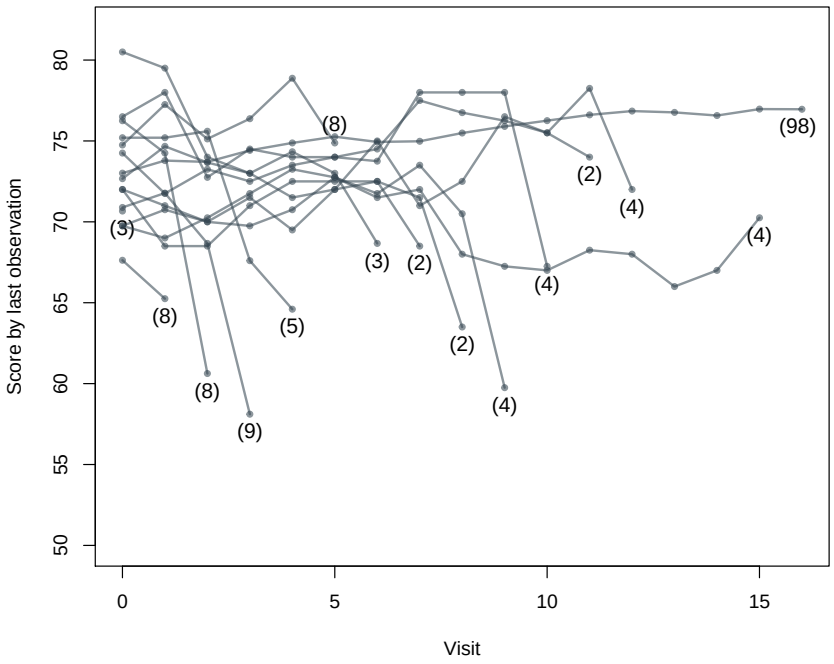
$$
\begin{aligned}
\widehat{\mu}-\mu^* &= \mu(\widehat{P})-\mu(P^*)+\frac{1}{n}\sum_{i=1}^n D^\dagger(\widehat{P})(O_i)\\
&= -\int D^\dagger(\widehat{P})(o)dP^*(o) + Rem(\widehat{P},P^*)+\frac{1}{n}\sum_{i=1}^n D^\dagger(\widehat{P})(O_i)\\
&= \frac{1}{n}\sum_{i=1}^n D^\dagger(P^*)(O_i)+\int\left[D^\dagger(\widehat{P})(o)-D^\dagger(P^*)(o)\right]d(P_n-P^*)(o)+Rem(\widehat{P},P^*).
\end{aligned}
$$

Under conditions (a) and (b), we obtain that $\widehat{\mu}$ is an asymptotically linear estimator of μ^* with influence function $D^\dagger(P^*)$. Since $D^\dagger(P^*)$ is the canonical gradient of μ at P^* relative to $\mathscr{M}_0$, we conclude that $\widehat{\mu}$ is asymptotically efficient relative to $\mathscr{M}_0$.

Figure 1: Treatment-specific trajectories of mean PSP scores, stratified by last visit time.



(a) Placebo



(b) PP1M

Figure 2: Left column: Comparison of the proportion dropping out before visit $k+1$ among those on study at visit k based on the actual and simulated datasets. Right column: Comparison, using the Kolmogorov-Smirnov statistics, of the empirical distribution of PSP scores among those on study at visit $k+1$ based on the actual and simulated datasets. First row: Logistic regression for conditional probabilities of drop-out and truncated normal regressions for outcomes; Second row: Logistic regression for conditional probabilities of drop-out and beta regressions for outcomes; Third row: Non-parametric smoothing for conditional probabilities of drop-out and for outcomes.

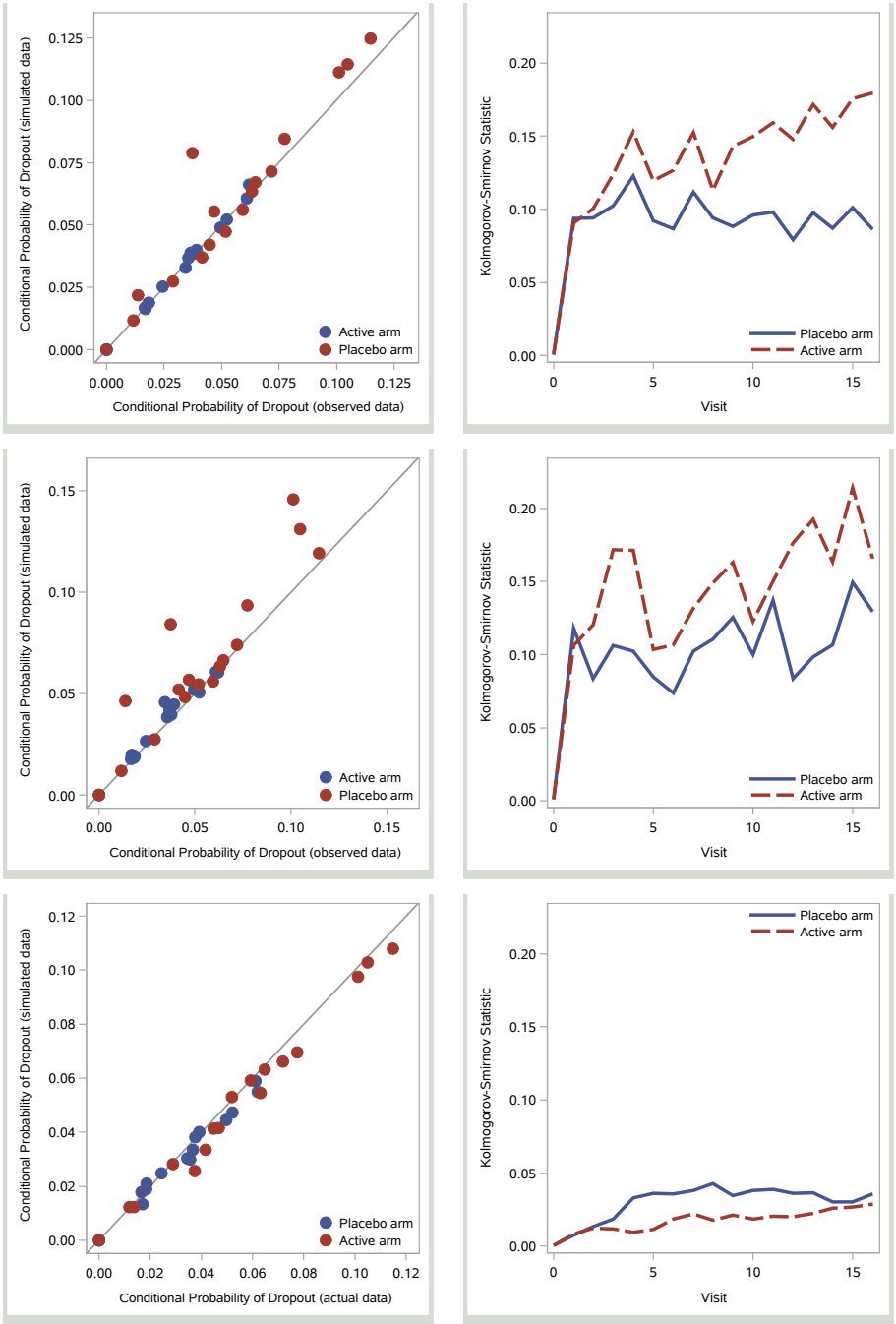


Figure 3: Selection bias function

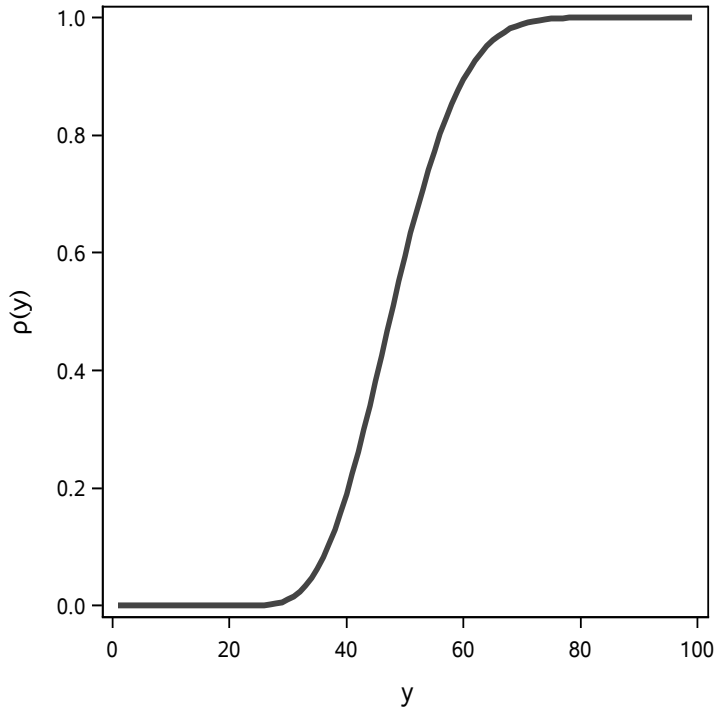


Figure 4: Treatment-specific mean PSP at Visit 16 as a function of α, along with 95% pointwise confidence intervals.

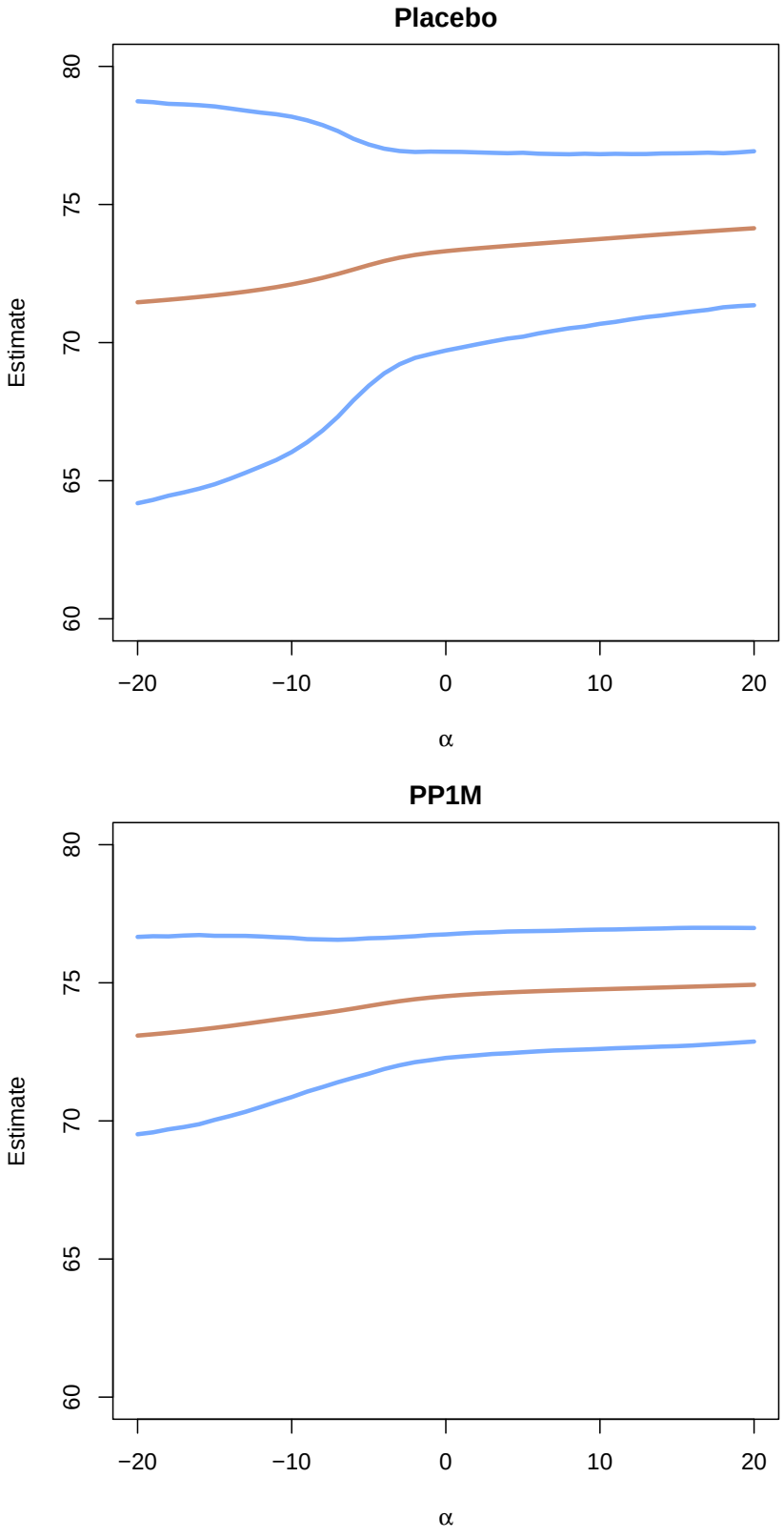


Figure 5: Contour plot of the estimated differences between mean PSP at Visit 16 for PBO vs. PP1M for various treatment-specific combinations of α.

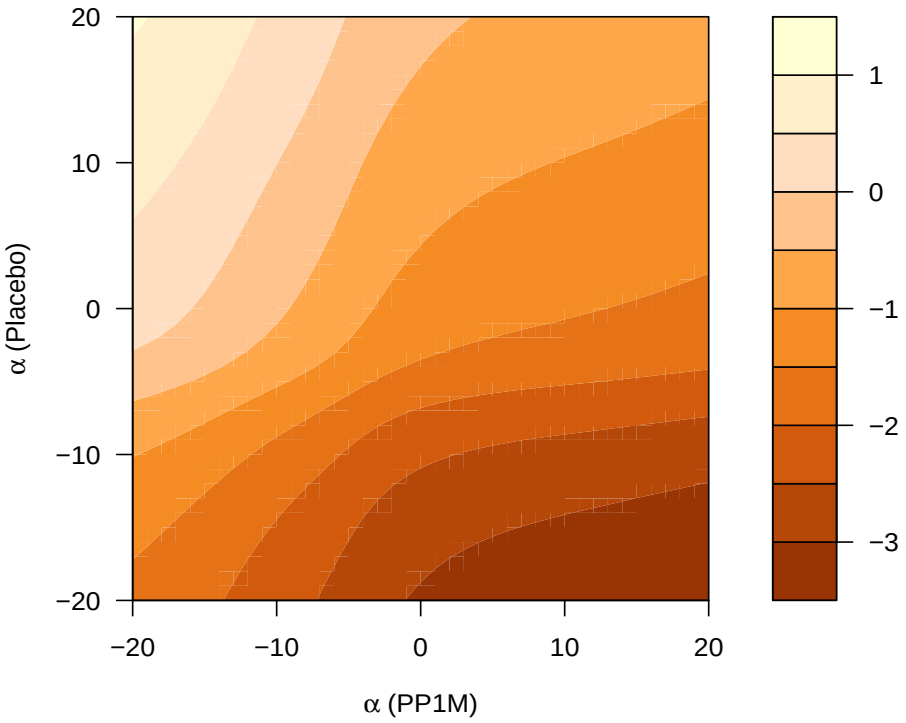


Figure 6: Treatment-specific differences between the mean PSP for non-completers and completers, as a function of α.

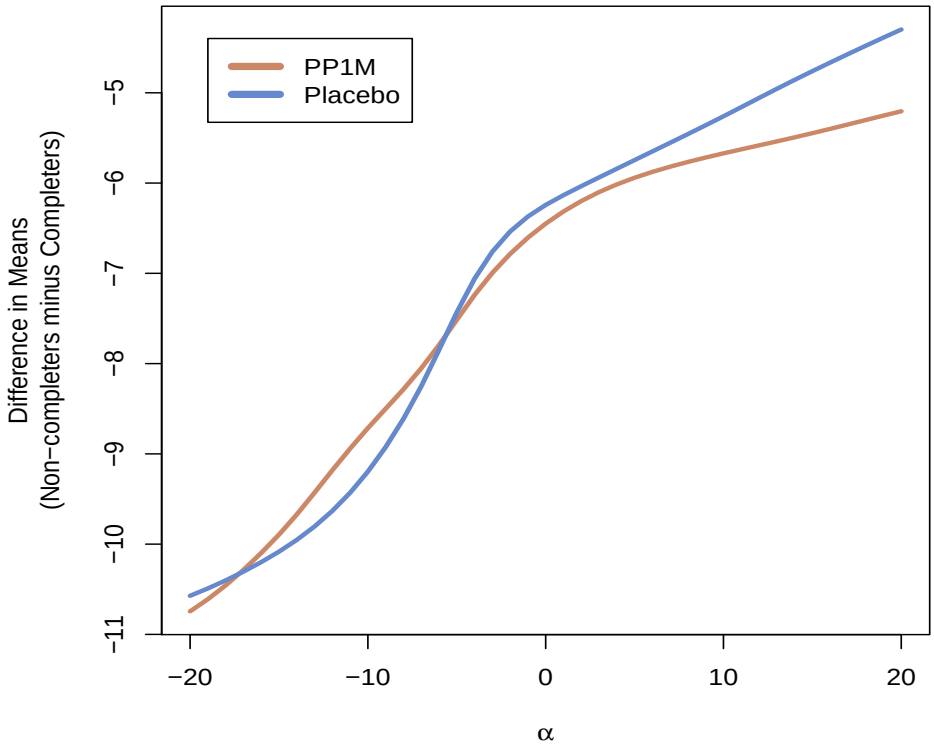


Table 1: Treatment-specific simulation results: Bias and mean-squared error (MSE) for the plug-in ($\mu(\widehat{P})$) and one-step ($\widehat{\mu}$) estimators, for various choices of α.

		PBO			PP1M		
α	Estimator	μ^*	Bias	MSE	μ^*	Bias	MSE
-10	$\mu(\widehat{P})$	72.89	0.76	1.75	73.76	0.41	1.36
	$\widehat{\mu}$		0.50	1.58		0.31	1.26
-5	$\mu(\widehat{P})$	73.38	0.52	1.42	74.25	0.26	1.14
	$\widehat{\mu}$		0.31	1.32		0.16	1.05
-1	$\mu(\widehat{P})$	73.74	0.38	1.23	74.59	0.17	1.02
	$\widehat{\mu}$		0.19	1.18		0.06	0.95
0	$\mu(\widehat{P})$	73.80	0.36	1.21	74.63	0.16	1.01
	$\widehat{\mu}$		0.18	1.17		0.08	0.95
1	$\mu(\widehat{P})$	73.84	0.35	1.19	74.67	0.18	1.01
	$\widehat{\mu}$		0.17	1.15		0.05	0.94
5	$\mu(\widehat{P})$	74.00	0.30	1.13	74.67	0.16	1.00
	$\widehat{\mu}$		0.13	1.11		0.04	0.93
10	$\mu(\widehat{P})$	74.15	0.24	1.08	74.84	0.15	0.97
	$\widehat{\mu}$		0.10	1.08		0.06	0.91

Table 2: Treatment-specific simulation results: Confidence interval coverage for the influence function (IF), Studentized bootstrap (SB), and fast double bootstrap (FDB) procedures, for various choices of α.

		PBO	PP1M
α	Procedure	Coverage	Coverage
-10	Normal-IF	86.1%	88.6%
	Normal-JK	92.1%	92.6%
	Bootstrap-IF-ET	90.2%	91.9%
	Bootstap-JK-ET	92.4%	93.7%
	Bootstap-IF-S	92.3%	92.7%
	Bootstap-JK-S	93.9%	94.3%
-5	Normal-IF	89.0%	91.7%
	Normal-JK	94.1%	94.2%
	Bootstrap-IF-ET	91.7%	92.6%
	Bootstap-JK-ET	93.6%	94.9%
	Bootstap-IF-S	94.1%	94.2%
	Bootstap-JK-S	95.1%	95.1%
-1	Normal-IF	90.8%	93.4%
	Normal-JK	94.9%	94.8%
	Bootstrap-IF-ET	91.0%	94.0%
	Bootstap-JK-ET	92.8%	94.9%
	Bootstap-IF-S	94.4%	94.7%
	Bootstap-JK-S	95.0%	95.3%
0	Normal-IF	90.7%	93.5%
	Normal-JK	95.0%	94.9%
	Bootstrap-IF-ET	92.8%	93.9%
	Bootstap-JK-ET	94.3%	95.0%
	Bootstap-IF-S	95.3%	94.7%
	Bootstap-JK-S	96.0%	95.1%
1	Normal-IF	90.9%	93.5%
	Normal-JK	94.9%	94.8%
	Bootstrap-IF-ET	92.8%	93.5%
	Bootstap-JK-ET	94.2%	95.0%
	Bootstap-IF-S	95.3%	94.6%
	Bootstap-JK-S	96.0%	95.2%
5	Normal-IF	91.5%	93.7%
	Normal-JK	94.6%	95.1%
	Bootstrap-IF-ET	92.6%	93.8%
	Bootstap-JK-ET	93.8%	94.7%
	Bootstap-IF-S	94.9%	95.1%
	Bootstap-JK-S	96.0%	95.5%
10	Normal-IF	92.1%	93.4%
	Normal-JK	94.8%	95.0%
	Bootstrap-IF-ET	92.9%	93.8%
	Bootstap-JK-ET	93.9%	94.8%
	Bootstap-IF-S	94.7%	95.0%
	Bootstap-JK-S	95.6%	95.4%

Web Appendix A

In this section, we derive the efficient influence function in the nonparametric model $\mathscr{M}$ (EIF) and in the Markov-restricted model $\mathscr{M}_0$ (EIF_0). To find EIF, we use the fact that the canonical gradient of target parameter is the efficient influence function in model $\mathscr{M}$ [1]. To find the EIF_0, we project EIF onto to tangent space for the $\mathscr{M}_0$.

Let P denote a distribution in $\mathscr{M}$, characterized by $P_k(\overline{y}_{k-1}) = P(R_k = 1|R_{k-1} = 0, \overline{Y}_{k-1} = \overline{y}_{kk-1})$, $F_k(y_k|\overline{y}_{k-1}) = P(Y_k \leq y_k|R_k = 1, \overline{Y}_{k-1} = \overline{y}_{k-1})$ and $F_0(y_0) = P(Y_0 \leq y_0)$. In what follows, expectations are taken with respect to P. Let $\{P_\eta : \eta\}$ denote a parametric submodel of $\mathscr{M}$ passing through P (i.e., $P_{\eta=0} = P$). Let $s(O)$ be the score for η evaluated at $\eta = 0$. Let $\mathcal{T}$ denote the tangent space of $\mathscr{M}$. The canonical gradient is defined as the unique element $D \in \mathcal{T}$ that satisfies

$$\frac{\partial}{\partial \eta}\mu(P_\eta)\big|_{\eta=0} = E[s(O)D(O)].$$

We consider parametric submodels, indexed by $\eta = (\epsilon_0, \varepsilon_k, \upsilon_k : k = 1, \ldots, K)$, characterized by

$$dF_{0,\eta_0} = dF_0(y_0)\left\{1 + \varepsilon_0 h_0(y_0)\right\} : \; E[h_0(Y_0)] = 0$$

$$dF_{k,\eta_k}(y_k|\overline{y}_{k-1}) = dF_k(y_k|\overline{y}_{k-1})\left\{1 + \varepsilon_k h_k(\overline{y}_k)\right\} : \; E[h_k(\overline{Y}_k)|R_k = 1, \overline{Y}_{k-1}] = 0$$

$$P_{k,\upsilon_k}(\overline{y}_{k-1}) = \frac{P_k(\overline{y}_{k-1})\exp\{\upsilon_k l_k(\overline{y}_{k-1})\}}{P_k(\overline{y}_{k-1})\exp\{\upsilon_k l_k(\overline{y}_{k-1})\} + 1 - P_k(\overline{y}_{k-1})} : \; l_k(\cdot) \text{ is any function of } \overline{y}_{k-1}$$

The associated score functions evaluated at $\eta = 0$ are $h_0(Y_0)$, $R_k h_k(\overline{Y}_k)$ and $R_{k-1}\{R_k - P_k(\overline{Y}_{k-1})\}l_k(\overline{Y}_{k-1})$.

The target parameter as a functional of P_η is

$$\mu(P_\eta) = \int \cdots \int y_K \prod_{j=1}^{K} \left\{ dF_j(y_j|\overline{y}_{j-1})\left\{1 + \varepsilon_j h_j(\overline{y}_j)\right\}\left\{\frac{P_j(\overline{y}_{j-1})\exp\{\upsilon_j l_j(\overline{y}_{j-1})\}}{P_j(\overline{y}_{j-1})\exp\{\upsilon_j l_j(\overline{y}_{j-1})\} + 1 - P_j(\overline{y}_{j-1})}\right\} + \frac{dF_j(y_j|\overline{y}_{j-1})\exp\{\alpha r(y_j)\}\left\{1 + \varepsilon_j h_j(\overline{y}_j)\right\}\left\{\frac{1-P_j(\overline{y}_{j-1})}{P_j(\overline{y}_{j-1})\exp\{\upsilon_j l_j(\overline{y}_{j-1})\}+1-P_j(\overline{y}_{j-1})}\right\}}{\int \exp\{\alpha r(y_j)\} dF_j(y_j|\overline{y}_{j-1})\left\{1 + \varepsilon_j h_j(\overline{y}_j)\right\}} \right\} dF_0(y_0)\left\{1 + \varepsilon_0 h_0(y_0)\right\}$$

In what follows, we represent $P_k(\overline{y}_{k-1})$, $dF_k(y_k|\overline{y}_{k-1})$, $dF_0(y_0)$, $\alpha r(y_k)$, $h_k(\overline{y}_k)$ and $l_k(\overline{y}_{k-1})$ by P_k, Q_k, Q_0, r_k, h_k and l_k, respectively. The derivative with respect to ε_0 (evaluated at $\eta = 0$) is $d\varepsilon_0(h_0)$ equal to

$$\int \cdots \int y_K \prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}\{1 - P_j\}}{\int \exp\{\alpha r_j\} Q_j} \right\} Q_0 h_0$$

The derivative with respect to ε_k (evaluated at $\eta = 0$) is $d\varepsilon_k(h_k)$ equal to

$$\int \cdots \int y_K \prod_{j \neq k} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}\{1 - P_j\}}{\int \exp\{\alpha r(y_j) Q_j\}} \right\} \times \left\{ Q_k P_k h_k + \frac{\left\{\int \exp\{\alpha r_k\} Q_k\right\} \exp\{\alpha r_k\} Q_k h_k - Q_k \exp\{\alpha r_k\} \int \exp\{\alpha r_k\} Q_k h_k}{\{\int \exp\{\alpha r_k\} Q_k\}^2}(1 - P_k) \right\} Q_0$$

The derivative with respect to υ_k (evaluated at $\eta = 0$) is $d\upsilon_k(l_k)$ equal to

$$\int \cdots \int y_K \prod_{j \neq k}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1 - P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\} \left\{ Q_k \left\{P_k(1 - P_k) l_k\right\} - \frac{Q_k \exp(r_k)\left\{P_k(1 - P_k) l_k\right\}}{\left\{\int \exp(r_k) Q_k\right\}} \right\} Q_0$$

Any element of can be expressed as $\mathcal{T}$ can be expressed as

$$a(Y_0) + \sum_{k=1}^{K} R_k b_k(\overline{Y}_k) + \sum_{k=1}^{K} R_{k-1}(R_k - P_k) c_k(\overline{Y}_{k-1})$$

where $E[a(Y_0)] = 0$, $E[b_j(\overline{Y}_j)|R_j = 1, \overline{Y}_{j-1}] = 0$ and $c_j(\cdot)$ is any function of $\overline{Y}_{j-1}$. We need to find functions $a(Y_0)$,$b_k(\overline{Y}_k)$ and $c_k(\overline{Y}_{k-1})$ such that

$$E[a(Y_0)h_0(Y_0)] = d\varepsilon_0(h_0)$$

$$E[R_k b_k(\overline{Y}_k)h_k(\overline{Y}_k)] = d\varepsilon_k(h_k)$$

$$E[R_{k-1}(R_k - P_k)^2 c_k(\overline{Y}_{k-1})l_k(\overline{Y}_{k-1})] = d\nu_k(l_k)$$

First, notice that

$$E[a_0(Y_0)h_0(Y_0)] = \int_{y_0} a_0(y_0)h_0(y_0)Q_0$$

and

$$d\varepsilon_0(h_0) = \int_{y_0} \left\{ \int \cdots \int y_K \prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\} \right\} h_0 Q_0$$

Thus, $E[a_0^*(Y_0)h_0(Y_0)] = d\varepsilon_0(h_0)$ where

$$a_0^*(Y_0) = \int_{y_1} \cdots \int_{y_K} y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \prod_{j=1}^{K} Q_j P_j = E\left[\frac{R_K Y_K}{\prod_{j=1}^{K} \left(1 + \exp\left\{ g_j(\overline{Y}_{j-1}) + \alpha r(Y_j) \right\}\right)^{-1}} \middle| Y_0 \right]$$

with $g_k = \log\left(\{1-P_k\}/P_k\right) - \log \int \exp(r_k) Q_k$. Note that $a_0^*(Y_0)$ does not have mean zero; it actually has mean μ. We can substract out its mean to obtain $a_0(Y_0) = a_0^*(Y_0) - \mu$; note that $E[a_0(Y_0)h_0(Y_0)] = d\varepsilon_0(h_0)$.

Second, notice that

$$E\left[R_k b_k(\overline{Y}_k) h_k(\overline{Y}_k)\right] = \int_{y_0} \cdots \int_{y_k} b_k(\overline{y}_k) h_k(\overline{y}_k) \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0$$

and

$$\begin{aligned}
&d\varepsilon_k(h_k) \\
&= \int_{y_0} \cdots \int_{y_k} \int_{y_{k+1}} \cdots \int_{y_K} \left\{ y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \right\} \left\{ \prod_{j=k+1}^{K} Q_j P_j \right\} \\
&\qquad \left\{ h_k - \frac{\exp\{\alpha r_k\}(1-P_k) \int_{y_k^*} \exp\{\alpha r_k^*\} Q_k^* h_k^*}{P_k \left\{ \int \exp\{\alpha r_k\} Q_k \right\}^2 + \exp\{\alpha r_k\}(1-P_k) \int \exp\{\alpha r_k\} Q_k} \right\} \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0 \\
&= \int_{y_0} \cdots \int_{y_k} \int_{y_{k+1}} \cdots \int_{y_K} \left\{ y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \right\} \left\{ \prod_{j=k+1}^{K} Q_j P_j \right\} h_k \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0 - \\
&\quad \int_{y_0} \cdots \int_{y_{k-1}} \int_{y_k} \int_{y_{k+1}} \cdots \int_{y_K} \left\{ y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \right\} \left\{ Q_k \prod_{j=k+1}^{K} Q_j P_j \right\} \\
&\qquad \left\{ \frac{\exp\{\alpha r_k\}(1-P_k) \int_{y_k^*} \exp\{\alpha r_k^*\} Q_k^* h_k^*}{P_k \left\{ \int \exp\{\alpha r_k\} Q_k \right\}^2 + \exp\{\alpha r_k\}(1-P_k) \int \exp\{\alpha r_k\} Q_k} \right\} \left\{ P_k \prod_{j=1}^{k-1} Q_j P_j \right\} Q_0 \\
&= \int_{y_0} \cdots \int_{y_k} \left[\int_{y_{k+1}} \cdots \int_{y_K} \left\{ y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \right\} \left\{ \prod_{j=k+1}^{K} Q_j P_j \right\} \right] h_k \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0 - \\
&\quad \int_{y_0} \cdots \int_{y_{k-1}} \int_{y_k^*} \left[\int_{y_k} \int_{y_{k+1}} \cdots \int_{y_K} \left\{ y_K \frac{\prod_{j=1}^{K} \left\{ Q_j P_j + \frac{Q_j \exp\{\alpha r_j\}(1-P_j)}{\int \exp\{\alpha r_j\} Q_j} \right\}}{\prod_{j=1}^{K} Q_j P_j} \right\} \left\{ Q_k \prod_{j=k+1}^{K} Q_j P_j \right\} \right. \\
&\qquad \left. \left\{ \frac{\exp\{\alpha r_k\}(1-P_k)}{P_k \left\{ \int \exp\{\alpha r_k\} Q_k \right\}^2 + \exp\{\alpha r_k\}(1-P_k) \int \exp\{\alpha r_k\} Q_k} \right\} \right] \exp\{\alpha r_k^*\} h_k^* \left\{ Q_k^* P_k \prod_{j=1}^{k-1} Q_j P_j \right\} Q_0 \\
&= \int_{y_0} \cdots \int_{y_k} E\left[\frac{R_K Y_K}{\prod_{j=1}^{K} \left(1 + \exp\left\{ g_j(\overline{Y}_{j-1}) + \alpha r(Y_j) \right\}\right)^{-1}} \middle| R_k = 1, \overline{Y}_k = \overline{y}_k \right] h_k \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0 - \\
&\quad \int_{y_0} \cdots \int_{y_k} E\left[\frac{R_K Y_K}{\prod_{j=1}^{K} \left(1 + \exp\left\{ g_j(\overline{Y}_{j-1}) + \alpha r(Y_j) \right\}\right)^{-1}} \right. \\
&\qquad \left. \left\{ \frac{\exp\{\alpha r_k\}(1-P_k)}{P_k \left\{ \int \exp\{\alpha r_k\} Q_k \right\}^2 + \exp\{\alpha r_k\}(1-P_k) \int \exp\{\alpha r_k\} Q_k} \right\} \middle| R_k = 1, \overline{Y}_{k-1} = \overline{y}_{k-1} \right] \exp\{\alpha r_k\} h_k \left\{ \prod_{j=1}^{k} Q_j P_j \right\} Q_0
\end{aligned}$$

Thus $E\left[R_k b_k^*(\overline{Y}_k)h_k(\overline{Y}_k)\right] = d\varepsilon_k(h_k)$, where

$$
\begin{aligned}
&b_k^*(\overline{Y}_k) \\
&= E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}|R_k=1,\overline{Y}_k\right] - \\
&\quad E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}\left\{\frac{\exp(r_k)\,(1-P_k)}{P_k\left\{\int\exp\{\alpha r_k\}Q_k\right\}^2+\exp\{\alpha r_k\}(1-P_k)\int\exp\{\alpha r_k\}Q_k}\right\}|R_k=1,\overline{Y}_{k-1}\right]\times \\
&\qquad\qquad \exp\{\alpha r_k\}
\end{aligned}
$$

Note that $b_k^*(\overline{Y}_k)$ does not have mean 0 given $R_k = 1$ and $\overline{Y}_{k-1}$. We can substract out $E[b_k^*(\overline{Y}_k)|R_k = 1, \overline{Y}_{k-1}]$ to obtain $b_k(\overline{Y}_k)$

$$
\begin{aligned}
&= E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}|R_k=1,\overline{Y}_k\right] - E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}|R_k=1,\overline{Y}_{k-1}\right] - \\
&\quad E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}\left\{\frac{\exp(\alpha r_k)\,(1-P_k)}{P_k\left\{\int\exp\{\alpha r_k\}Q_k\right\}^2+\exp\{\alpha r_k\}(1-P_k)\int\exp\{\alpha r_k\}Q_k}\right\}|R_k=1,\overline{Y}_{k-1}\right]\times \\
&\qquad\qquad \exp\{\alpha r_k\}+ \\
&\quad E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}\left\{\frac{\exp(\alpha r_k)\,(1-P_k)}{P_k\left\{\int\exp\{\alpha r_k\}Q_k\right\}^2+\exp\{\alpha r_k\}(1-P_k)\int\exp\{\alpha r_k\}Q_k}\right\}|R_k=1,\overline{Y}_{k-1}\right]\times \\
&\qquad\qquad E\left[\exp\{\alpha r_k\}|R_k=1,\overline{Y}_{k-1}\right]
\end{aligned}
$$

Note that $E\left[R_k b_k(\overline{Y}_k)h_k(\overline{Y}_k)\right] = d\varepsilon_k(h_k)$ since $E\left[h(Y_k)|R_k = 1, \overline{Y}_{k-1}\right] = 0$.

Third, notice that

$$
E[R_{k-1}(R_k - P_k)^2 c_k(\overline{Y}_{k-1})l_k(\overline{Y}_{k-1})] = \int_{y_0}\cdots\int_{y_{k-1}} c_k(\overline{y}_{k-1})P_k(1-P_k)l_k(\overline{y}_{k-1})\left\{\prod_{j=1}^{k-1}Q_jP_j\right\}Q_0
$$

and

$$
\begin{aligned}
&d\upsilon_k(l_k) \\
&= \int_{y_0}\cdots\int_{y_{k-1}}\left[\int_{y_k}\cdots\int_{y_K} y_K \frac{\prod_{j=1}^K\left\{Q_jP_j+\frac{Q_j\exp\{\alpha r_j\}(1-P_j)}{\int\exp\{\alpha r_j\}Q_j}\right\}}{\prod_{j=1}^K Q_jP_j}\frac{Q_k-\frac{Q_k\exp\{\alpha r_k\}}{\{\int\exp\{\alpha r_k\}Q_k\}}}{Q_kP_k+\frac{Q_k\exp\{\alpha r_k\}(1-P_k)}{\int\exp\{\alpha r_k\}Q_k}}\left\{\prod_{j=k}^K Q_jP_j\right\}\right]\times \\
&\qquad\qquad P_k(1-P_k)l_k\left\{\prod_{j=1}^{k-1}Q_jP_j\right\}Q_0
\end{aligned}
$$

Thus,

$$
c_k(\overline{Y}_{k-1}) = E\left[\frac{R_K Y_K}{\prod_{j=1}^K \left(1+\exp\left\{g_j(\overline{Y}_{j-1})+\alpha r(Y_j)\right\}\right)^{-1}}\left\{\frac{1-\frac{\exp\{\alpha r_k\}}{\{\int\exp\{\alpha r_k\}Q_k\}}}{P_k+\frac{\exp\{\alpha r_k\}(1-P_k)}{\int\exp\{\alpha r_k\}Q_k}}\right\}\middle|\, R_{k-1}=1,\overline{Y}_{k-1}\right]
$$

This completes the derivation of EIF.

The tangent space for $\mathscr{M}_0$, $\mathcal{T}_0$, has elements of the form:

$$
\tilde{a}(Y_0) + \sum_{k=1}^K R_k\tilde{b}_k(Y_k, Y_{k-1}) + \sum_{k=1}^K R_{k-1}(R_k - P_k)\tilde{c}_k(Y_{k-1})
$$

where $E[\tilde{a}(Y_0)] = 0$ and $E[\tilde{b}_k(Y_k, Y_{k-1})|R_k = 1, Y_{k-1}] = 0$. The projection of EIF onto $\mathcal{T}_0$ has $\tilde{a}(Y_0) = a(Y_0)$, $\tilde{b}_k(Y_k, Y_{k-1}) = E[b_k(\overline{Y}_k)|R_k = 1, Y_k, Y_{k-1}]$ and $\tilde{c}_k(Y_{k-1}) = E[c_k(\overline{Y}_{k-1})|R_{k-1} = 1, Y_{k-1}]$. This completes the derivation of EIF_0

References

[1] P.J. Bickel, C.A.J. Klaassen, Y. Ritov, and J. Wellner. *Efficient and Adaptive Estimation for Semiparametric Models.* Springer-Verlag, 1998.

Web Appendix B

In this section, we derive an expression for $Rem(P, P^*) = \mu(P) - \mu(P^*) - \int D(P)(o)d(P - P^*)$. To start, we note that we can write

$$\mu(P^*) = \sum_{k=1}^{K} \left\{ E^* \left[\left(\frac{1}{\pi_k^*(Y_{k-1}, Y_k)} - \frac{1}{\pi_k(Y_{k-1}, Y_k)} \right) \frac{R_K Y_K}{\prod_{l=1}^{k-1} \pi_l(Y_{l-1}, Y_l) \prod_{l=k+1}^{K} \pi_l^*(Y_{l-1}, Y_l)} \right] \right\} + E^* \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \right]$$

Using this expression, we can write

$$\begin{aligned}
Rem(P, P^*) = &- \sum_{k=1}^{K} \left\{ E^* \left[\left(\frac{1}{\pi_k^*(Y_{k-1}, Y_k)} - \frac{1}{\pi_k(Y_{k-1}, Y_k)} \right) \frac{R_K Y_K}{\prod_{l=1}^{k-1} \pi_l(Y_{l-1}, Y_l) \prod_{l=k+1}^{K} \pi_l^*(Y_{l-1}, Y_l)} \right] \right\} - \\
& E^* \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \right] + E^* \left[E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| Y_0 \right] \right] + \\
& \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| R_k = 1, Y_k, Y_{k-1} \right] \right] - \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| R_k = 1, Y_{k-1} \right] \right] + \\
& \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_k = 1, Y_{k-1} \right] H_k(Y_{k-1}) \right] - \\
& \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_k = 1, Y_{k-1} \right] H_k(Y_{k-1}) \frac{\exp\{\alpha r(Y_k)\}}{w_k(Y_{k-1})} \right] + \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} \{1 - R_k - H_k(Y_{k-1})\} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] \right] - \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} \{1 - R_k - H_k(Y_{k-1})\} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{1}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] w_k(Y_{k-1}) \right]
\end{aligned}$$

Let $E_k(Y_{k-1}) = E\left[R_k \exp\{\alpha r(Y_k)\} \,|\, R_{k-1} = 1, Y_{k-1}\right]$. Through the properties of conditional expectations, we can write

$$\begin{aligned}
Rem(P, P^*) = &- \sum_{k=1}^{K} \left\{ E^* \left[R_{k-1} \left(\frac{H_k^*(Y_{k-1})}{E_k^*(Y_{k-1})} - \frac{H_k(Y_{k-1})}{E_k(Y_{k-1})} \right) E^* \left[\frac{R_K Y_K \exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1} \pi_l(Y_{l-1}, Y_l) \prod_{l=k+1}^{K} \pi_l^*(Y_{l-1}, Y_l)} \middle| R_{k-1} = 1, Y_{k-1} \right] \right] \right\} - \\
& E^* \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \right] + E^* \left[E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| Y_0 \right] \right] + \\
& \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| R_k = 1, Y_k, Y_{k-1} \right] \right] - \sum_{k=1}^{K} E^* \left[R_{k-1} \frac{1 - H_k^*(Y_{k-1})}{1 - H_k(Y_{k-1})} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \middle| R_{k-1} = 1, Y_{k-1} \right] \right] + \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} \frac{1 - H_k^*(Y_{k-1})}{1 - H_k(Y_{k-1})} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] H_k(Y_{k-1}) \right] - \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] H_k(Y_{k-1}) \frac{E_k^*(Y_{k-1})}{E_k(Y_{k-1})} \right] + \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} \frac{\{H_k^*(Y_{k-1}) - H_k(Y_{k-1})\}}{H_k(Y_{k-1})} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{\exp\{\alpha r(Y_k)\}}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] H_k(Y_{k-1}) \right] - \\
& \sum_{k=1}^{K} E^* \left[R_{k-1} \left\{ \frac{H_k^*(Y_{k-1}) - H_k(Y_{k-1})}{1 - H_k(Y_{k-1})} \right\} E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1}, Y_l)} \left[\frac{1}{g_k(Y_k, Y_{k-1})} \right] \middle| R_{k-1} = 1, Y_{k-1} \right] E_k(Y_{k-1}) \right]
\end{aligned}$$

Using the fact that $\frac{1}{\pi_k(Y_{k-1},Y_k)} = 1 + \frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\exp\{\alpha r(Y_k)\}$, we can write

$$
\begin{aligned}
&Rem(P,P^*)\\
&= -\sum_{k=1}^{K}\left\{E^*\left[R_{k-1}\left(\frac{H_k^*(Y_{k-1})}{E_k^*(Y_{k-1})} - \frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right)E^*\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l^*(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\right]\right\} -\\
&\quad E^*\left[\frac{R_KY_K}{\prod_{l=1}^{K}\pi_l(Y_{l-1},Y_l)}\right] + E^*\left[E\left[\frac{R_KY_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, Y_0\right]\right] + E^*\left[E\left[\frac{R_KY_K\exp\{\alpha r(Y_1)\}}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, Y_0\right]\frac{H_1(Y_0)}{E_1(Y_0)}\right] +\\
&\quad \sum_{k=1}^{K}E^*\left[R_kE\left[\frac{R_KY_K}{\prod_{l=1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right]\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\frac{1-H_k^*(Y_{k-1})}{1-H_k(Y_{k-1})}E\left[\frac{R_KY_K}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\frac{1-H_k^*(Y_{k-1})}{1-H_k(Y_{k-1})}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right] +\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\frac{1-H_k^*(Y_{k-1})}{1-H_k(Y_{k-1})}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\frac{E_k^*(Y_{k-1})}{E_k(Y_{k-1})}\right] +\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\left\{\frac{H_k^*(Y_{k-1})-H_k(Y_{k-1})}{H_k(Y_{k-1})}\right\}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\left\{\frac{H_k^*(Y_{k-1})-H_k(Y_{k-1})}{1-H_k(Y_{k-1})}\right\}E\left[\frac{R_KY_K}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\right]
\end{aligned}
$$

Cancelling and combining terms, we obtain

$$
\begin{aligned}
&Rem(P,P^*)\\
&= -\sum_{k=1}^{K}\left\{E^*\left[R_{k-1}\left(\frac{H_k^*(Y_{k-1})}{E_k^*(Y_{k-1})} - \frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right)E^*\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l^*(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\right]\right\} -\\
&\quad E^*\left[\frac{R_KY_K}{\prod_{l=1}^{K}\pi_l(Y_{l-1},Y_l)}\right] + E^*\left[E\left[\frac{R_KY_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, Y_0\right]\right] + E^*\left[E\left[\frac{R_KY_K\exp\{\alpha r(Y_1)\}}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, Y_0\right]\frac{H_1(Y_0)}{E_1(Y_0)}\right] +\\
&\quad \sum_{k=1}^{K}E^*\left[R_kE\left[\frac{R_KY_K}{\prod_{l=1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right]\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}E\left[\frac{R_KY_K}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\right] -\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\frac{E_k^*(Y_{k-1})}{E_k(Y_{k-1})}\right] +\\
&\quad \sum_{k=1}^{K}E^*\left[R_{k-1}\left\{\frac{H_k^*(Y_{k-1})-H_k(Y_{k-1})}{H_k(Y_{k-1})}\right\}E\left[\frac{R_KY_K\exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1}\pi_l(Y_{l-1},Y_l)\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_{k-1}=1,Y_{k-1}\right]\frac{H_k(Y_{k-1})}{E_k(Y_{k-1})}\right]
\end{aligned}
$$

Through further algebraic manipulation, we obtain that $Rem(P,P^*) = Rem_1(P,P^*) + Rem_2(P,P^*)$, where

$$
\begin{aligned}
&Rem_1(P,P^*) \\
&= -\sum_{k=1}^{K} \left\{ E^* \left[R_{k-1} E_k^*(Y_{k-1}) \left(\frac{H_k^*(Y_{k-1})}{E_k^*(Y_{k-1})} - \frac{H_k(Y_{k-1})}{E_k(Y_{k-1})} \right) \right.\right. \\
&\qquad \left.\left. \left\{ \frac{E^* \left[\frac{R_K Y_K \exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1} \pi_l(Y_{l-1},Y_l) \prod_{l=k+1}^{K} \pi_l^*(Y_{l-1},Y_l)} \middle| R_{k-1}=1, Y_{k-1} \right]}{E_k^*(Y_{k-1})} - \frac{E \left[\frac{R_K Y_K \exp\{\alpha r(Y_k)\}}{\prod_{l=1}^{k-1} \pi_l(Y_{l-1},Y_l) \prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_{k-1}=1, Y_{k-1} \right]}{E_k(Y_{k-1})} \right\} \right] \right\}
\end{aligned}
$$

and

$$
Rem_2(P,P^*) = -E^* \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1},Y_l)} \right] + \sum_{k=1}^{K} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k, Y_{k-1} \right] \right] - \sum_{k=1}^{K-1} E^* \left[R_k E \left[\frac{R_K Y_K}{\prod_{l=1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right]
$$

Notice that $Rem_1(P,P^*)$ is second order. It remains to show that $Rem_2(P,P^*)$ is second order. In our derivation, we use the fact that, for $k = 1, \ldots, K-1$,

$$
E \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k, Y_{k-1} \right] = E \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right]
$$

and

$$
\begin{aligned}
&E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right] \\
&= E^* \left[R_{k+1} E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_{k+1}=1, Y_{k+1}, Y_k \right] \right] \\
&= E^* \left[\frac{R_{k+1}}{\pi_{k+1}(Y_k,Y_{k+1})} E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+2}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_{k+1}=1, Y_{k+1} \right] \right] \\
&= E^* \left[R_{k+1} E \left[\frac{1}{\prod_{l=1}^{k+1} \pi_l(Y_{l-1},Y_l)} \middle| R_{k+1}=1, Y_{k+}, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+2}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_{k+1}=1, Y_{k+1} \right] \right]
\end{aligned}
$$

We can write

$$
\begin{aligned}
Rem_2(P,P^*) = &- E^* \left[R_1 E^* \left[\frac{1}{\pi_1(Y_1,Y_0)} \middle| R_1=1, Y_1 \right] E^* \left[\frac{R_K Y_K}{\prod_{l=2}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_1=1, Y_1 \right] \right] + \\
&E^* \left[R_1 E^* \left[\frac{1}{\pi_1(Y_1,Y_0)} \middle| R_1=1, Y_1 \right] E \left[\frac{R_K Y_K}{\prod_{l=2}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_1=1, Y_1 \right] \right] - \\
&E^* \left[R_1 E \left[\frac{1}{\pi_1(Y_1,Y_0)} \middle| R_1=1, Y_1 \right] E \left[\frac{R_K Y_K}{\prod_{l=2}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_1=1, Y_1 \right] \right] + \\
&\sum_{k=2}^{K} E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k, Y_{k-1} \right] E \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right] - \\
&\sum_{k=2}^{K-1} E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right]
\end{aligned}
$$

We add the following zero terms to $Rem_2(P,P^*)$:

$$
\begin{aligned}
A(P,P^*) = &\sum_{k=1}^{K-1} \left\{ E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right] - \right. \\
&\left. E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right] \right\} \\
= &\sum_{k=1}^{K-1} E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right] - \\
&\sum_{k=2}^{K} E^* \left[R_k E \left[\frac{1}{\prod_{l=1}^{k} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k, Y_{k-1} \right] E^* \left[\frac{R_K Y_K}{\prod_{l=k+1}^{K} \pi_l(Y_{l-1},Y_l)} \middle| R_k=1, Y_k \right] \right]
\end{aligned}
$$

$$B(P,P^*) = \sum_{k=2}^{K-1} \Bigg\{ E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right]\Bigg\} +$$
$$\Bigg\{ E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right]\Bigg\}$$

So,

$$Rem_2(P,P^*) = - E^*\left[R_1 E^*\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\, R_1=1,Y_1\right] E^*\left[\frac{R_K Y_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_1=1,Y_1\right]\right] +$$
$$E^*\left[R_1 E^*\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\, R_1=1,Y_1\right] E\left[\frac{R_K Y_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_1=1,Y_1\right]\right] -$$
$$E^*\left[R_1 E\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\, R_1=1,Y_1\right] E\left[\frac{R_K Y_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_1=1,Y_1\right]\right] +$$
$$E^*\left[R_1 E\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\, R_1=1,Y_1\right] E^*\left[\frac{R_K Y_K}{\prod_{l=2}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_1=1,Y_1\right]\right] +$$
$$\sum_{k=2}^{K} E^*\left[R_k E\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$\sum_{k=2}^{K-1} E^*\left[R_k E\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] +$$
$$\sum_{k=2}^{K-1} E^*\left[R_k E\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$\sum_{k=2}^{K} E^*\left[R_k E\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] +$$
$$\sum_{k=2}^{K-1} \Bigg\{ E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E^*\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right]\Bigg\} +$$
$$\Bigg\{ E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right] -$$
$$E^*\left[R_k E^*\left[\frac{1}{\prod_{l=1}^{k}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k,Y_{k-1}\right] E\left[\frac{R_K Y_K}{\prod_{l=k+1}^{K}\pi_l(Y_{l-1},Y_l)}\,\middle|\, R_k=1,Y_k\right]\right]\Bigg\}$$

Through algebra,

$$
\begin{aligned}
Rem_2(P,P^*) = &- E^*\left[R_1\left\{E^*\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\,R_1=1,Y_1\right]-E\left[\frac{1}{\pi_1(Y_1,Y_0)}\,\middle|\,R_1=1,Y_1\right]\right\}\right. \\
&\qquad \left.\left\{E^*\left[\frac{R_KY_K}{\prod_{l=2}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_1=1,Y_1\right]-E\left[\frac{R_KY_K}{\prod_{l=2}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_1=1,Y_1\right]\right\}\right] + \\
&\sum_{k=2}^{K-1}E^*\left[R_k\left\{E^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]-E\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]\right\}\right. \\
&\qquad \left.\left\{E^*\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]-E\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right\}\right] - \\
&\sum_{k=2}^{K-1}E^*\left[R_kE\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]E\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right] + \\
&\sum_{k=2}^{K-1}E^*\left[R_kE\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]E^*\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right] - \\
&\sum_{k=2}^{K-1}E^*\left[R_kE^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]E^*\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right] + \\
&\sum_{k=2}^{K-1}E^*\left[R_kE^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]E\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right]
\end{aligned}
$$

We now use the fact that, for all $k=2,\ldots,K-1$ and $f_k(Y_k)$,

$$
E^*\left[R_kE^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]f_k(Y_k)\right]=E^*\left[R_kE^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]f_k(Y_k)\right]
$$

to conclude that

$$
\begin{aligned}
Rem_2(P,P^*) = &-\sum_{k=1]}^{K-1}E^*\left[R_k\left\{E^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]-E\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right\}\right. \\
&\qquad \left.\left\{E^*\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]-E\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right\}\right] + \\
&\sum_{k=2}^{K-1}E^*\left[R_k\left\{E^*\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]-E\left[\frac{1}{\prod_{l=1}^k\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k,Y_{k-1}\right]\right\}\right. \\
&\qquad \left.\left\{E^*\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]-E\left[\frac{R_KY_K}{\prod_{l=k+1}^K\pi_l(Y_{l-1},Y_l)}\,\middle|\,R_k=1,Y_k\right]\right\}\right]
\end{aligned}
$$

In this form, it is easy to see that $Rem_2(P,P^*)$ is second order.

Global Sensitivity Analysis of Clinical Trials with Missing Patient Reported Outcomes

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Abstract

Randomized trials with patient reported outcomes are commonly plagued by missing data. The analysis of such trials relies on untestable assumptions about the missing data mechanism. To address this issue, it has been recommended that the sensitivity of the trial results to assumptions should be a mandatory reporting requirement. In this paper, we describe a formal methodology for conducting sensitivity analysis of randomized trials in which outcomes are scheduled to be measured at fixed points in time after randomization and some subjects prematurely withdraw from study participation. Our methods are motivated by a placebo-controlled randomized trial designed to evaluate a treatment for bipolar disorder. We present a comprehensive data analysis and a simulation study to evaluate the performance of our methods. A software package entitled SAMON (R and SAS versions) that implements our methods is available at www.missingdatamatters.org.

1 Introduction

Missing outcome data are a widespread problem in clinical trials, including those with patient-reported outcomes. Since such outcomes require active engagement of patients and patients, while encouraged, are not required to remain or provide data while on-study, high rates of missing data can be expected.

To understand the magnitude of this issue, we reviewed all randomized trials [1] reporting five major patient-reported outcomes (SF-36, SF-12, Patient Health Questionnaire-9, Kansas City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire) published in five leading general medical journals (*New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, *British Medical Journal*, *PLoS One*) between January 1, 2008 and January 31, 2017. We identified 145 studies, which are summarized in Table 3. There is large variation in the percentages of missing data, with 78.6% of studies reporting percentages greater than 10%, 43.4% greater than 20% and 24.8% greater than 30%. Fielding *et al.* conducted a similar review of clinical trials reporting quality of life outcomes in four of these journals during 2005/6 and found a comparable distribution of missing data percentages. Given the quality of these journals, it is likely that the percentages reported in Fielding *et al.* and in Table 1 are an optimistic representation of percentages of missing data across the universe of clinical trials with patient-reported outcomes published in the medical literature.

[1] We focused on randomized trials in which patients in each treatment group were scheduled to be interviewed at a common set of post baseline assessment times. We excluded crossover trials, 10 trials in which patients were at high risk of death during the scheduled follow-up period, and 6 studies which did not report follow-up rates at the assessment times.

Missing outcome data complicates the inferences that can be drawn about treatment effects. While unbiased estimates of treatment effects can be obtained from trials with no missing data, this is no longer true when data are missing on some patients. The essential problem is that inference about treatment effects relies on *unverifiable* assumptions about the nature of the mechanism that generates the missing data. While we may know the reasons for missing data, we do not know the distribution of outcomes for patients with missing data, how it compares to that of patients with observed data and whether differences in these distributions can be explained by the observed data.

It is widely recognized that the way to address the problem caused by missing outcome data is to posit varying assumptions about the missing data mechanism and evaluate how inference about treatment effects is affected by these assumptions. Such an approach is called "sensitivity analysis." A 2010 National Research Council (NRC) report entitled "The Prevention and Treatment of Missing Data in Clinical Trials" and a follow-up manuscript published in the *New England Journal of Medicine* recommends:

> Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.

Li *et al.* (2012) echoed this recommendation (see Standard 8) in their PCORI sponsored report entitled "Minimal Standards in the Prevention and Handling of Missing Data in Observational and Experimental Patient Centered Outcomes Research".

The set of possible assumptions about the missing data mechanism is very large and cannot be fully explored. As discussed in Scharfstein *et al.* (2014), there are, broadly speaking, three main approaches to sensitivity analysis: ad-hoc, local and global.

- Ad-hoc sensitivity analysis involves analyzing data using a few different analytic methods (e.g., last or baseline observation carried forward, complete or available case analysis, mixed models, imputation) and evaluating whether the resulting inferences are consistent. The problem with this approach is that consistency of inferences across the various methods does not imply that there are no reasonable assumptions under which the inference about the treatment effect is different.

- Local sensitivity analysis (Verbeke *et al.*, 2001; Copas and Eguchi, 2001; Troxel, Ma and Heitjan, 2004; Ma, Troxel and Heitjan, 2005) evaluates whether inferences are robust in a small neighborhood around a reasonable benchmark assumption, such as the classic missing at random assumption (Little and Rubin, 2014). Unfortunately, this approach does not address whether the inferences are robust to plausible assumptions outside of the local neighborhood.

- Global sensitivity analysis (Rotnitzky, Robins and Scharfstein, 1998; Scharfstein, Rotnitzky and Robins, 1999; Robins, Rotnitzky and Scharfstein, 2000; Rotnitzky *et al.*, 2001; Daniels and Hogan, 2008) emphasized in Chapter 5 of the NRC report, evaluates robustness of results across a much broader range of assumptions that include a reasonable benchmark assumption and a collection of additional assumptions that trend toward best and worst case assumptions. From this analysis, it can be determined how much deviation from the benchmark assumption is required in order for the inferences to change. If the deviation is judged to be sufficiently far from the benchmark assumption, then greater credibility is lent to the benchmark analysis; if not, the benchmark analysis can be considered to be fragile. Some researchers have dubbed this approach "tipping point analysis" (Yan, Lee and Li, 2009; Campbell, Pennello and Yue, 2011).

In this paper, we consider randomized clinical trials in which patient-reported outcomes are scheduled to be measured at baseline (prior to randomization) and at a fixed number of post-baseline assessment times. We assume that some patients discontinue participation prior to the final assessment time and that all outcomes are observed while the patients are on-study. This assumption implies that there is no intermittent missing outcome data. We discuss a method and associated software for conducting global sensitivity analysis of such trials. We explicate our methodology in the context of a randomized trial designed to evaluate the efficacy of quetiapine fumarate for the treatment of patients with bipolar disorder.

2 Quetiapine Bipolar Trial

The Quetiapine Bipolar trial was a multi-center, placebo-controlled, double-dummy study in which patients with bipolar disorder were randomized equally to one of three treatment arms: placebo, Quetiapine 300 mg/day or Quetiapine 600 mg/day (Calabrese *et al.*, 2005). Randomization was stratified by type of bipolar disorder: 1 or 2. A key secondary patient-reported endpoint was the short-form version of the Quality of Life Enjoyment Satisfaction Questionnaire (QLESSF, Endicott *et al.*, 1993), which was scheduled to be measured at baseline, week 4 and week 8.[2]

In this paper, we will focus on the subset of 234 patients with bipolar 1 disorder who were randomized to either the placebo (n=116) or 600 mg/day (n=118) arms.[3] We seek to compare the mean QLESSF outcomes at week 8 between these two treatment groups, in a world in which there are no missing outcomes. Unfortunately, this comparison is complicated because patients prematurely withdrew from the study. Figure 1 displays the treatment-specific trajectories of mean QLESSF scores, stratified by last available measurement. Notice that only 65 patients (56%) in placebo arm and 68 patients (58%) in the 600mg/day arm had a complete set of QLESSF scores. Further, the patients with complete data tend to have higher average QLESSF scores, suggesting that a complete-case analysis could be biased.

3 Global Sensitivity Analysis

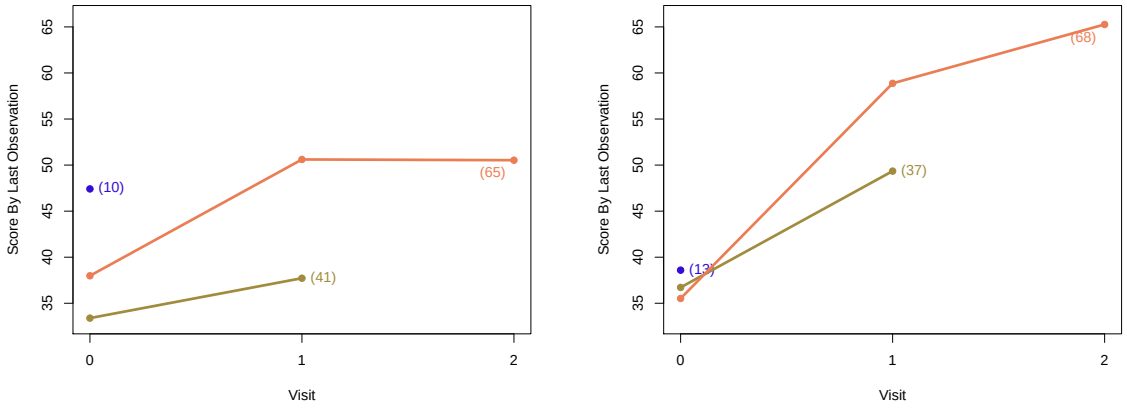
Chapter 5 of the NRC report [90] lays out a general framework for global sensitivity analysis. In this framework, inference about treatment effects requires two types of assumptions: (i) untestable assumptions about the distribution of outcomes among those with missing data and (ii) testable assumptions that serve to increase the efficiency of estimation (see Figure 2[4]). Type (i) assumptions are required to "identify" parameters of interest: identification means that one can mathematically express parameters of interest (e.g., treatment arm-specific means, treatment effects) in terms of the distribution of the observed data. In other words, if one were given the distribution of the observed data and given a type (i) assumption, then one could compute the value of the parameter of interest (see arrows in Figure 2). In the absence of identification, one cannot learn the value of the parameter of interest based only on knowledge of the distribution of the observed data. Identification implies that the parameters of interest can, *in theory*, be estimated if the sample size is large enough.

[2]Data were abstracted from the clinical study report available at http://psychrights.org/research/Digest/NLPs/Seroquel/UnsealedSeroquelStudies/. The number of patients that were abstracted does not exactly match the number of patients reported in Calabrese *et al.*, 2005.

[3]These sample sizes exclude three randomized patients - one from placebo and two from 600 mg/day Quetiapine. From each group, one patient was removed because of undue influence on the analysis. In the 600 mg/day Quetiapine arm, one patient had incomplete questionaire data at baseline.

[4]A model is a set of distributions, which we represent by circles in Figure 2.

Figure 1: Treatment-specific (left: placebo; right: 600 mg/day Quetiapine) trajectories of mean QLESSF scores, stratified by last available measurement. Blue, brown and orange represent the trajectories of patients last seen at visits 0, 1 and 2, respectively. The number in parentheses at the end of each trajectory represents the number of associated patients.



There are an infinite number of ways of positing type (i) assumptions. It is impossible to consider all such assumptions. A reasonable way of positing these assumptions is to

(a) stratify individuals with missing outcomes according to the data that were able to be collected on them and the occasions at which the data were collected, and

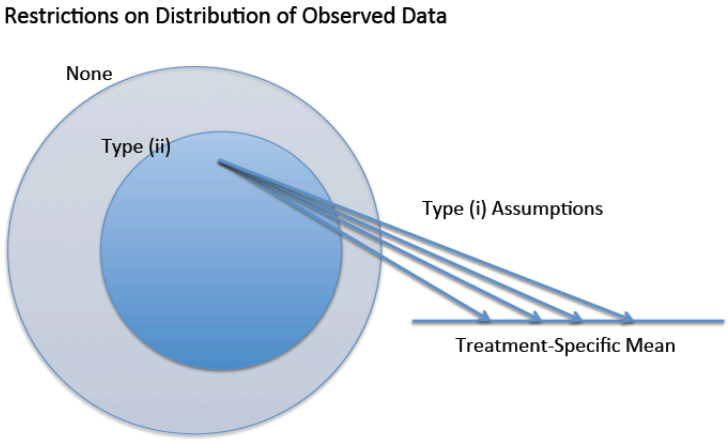
(b) separately for each stratum, hypothesize a connection (or link) between the distribution of the missing outcomes with the distribution of these outcomes for patients who share the same recorded data and for whom the distribution is identified.

The connection that is posited in (b) is a type (i) assumption. The problem with this approach is that the stratum of people who share the same recorded data will typically be very small (e.g., the number of patients who share exactly the same baseline data will be very small). As a result, it is necessary to draw strength across strata by "smoothing." Smoothing is required because, *in practice*, we are not working with large enough sample sizes. Without smoothing, the data analysis will not be informative because the uncertainty (i.e., standard errors) of the parameters of interest will be too large to be of substantive use. Thus, it is necessary to impose type (ii) smoothing assumptions (represented by the inner circle in Figure 2). Type (ii) assumptions are testable (i.e., place restrictions on the distribution of the observed data) and should be scrutinized via model checking.

The global sensitivity framework proceeds by parameterizing (i.e., indexing) the connections (i.e., type (i) assumptions) in (b) above via sensitivity analysis parameters. The parameterization is configured so that a specific value of the sensitivity analysis parameters (typically set to zero) corresponds to a benchmark connection that is considered reasonably plausible and sensitivity analysis parameters further from the benchmark value represent more extreme departures from the benchmark connection.

The global sensitivity analysis strategy that we propose is focused on separate inferences for each treatment arm, which are then combined to evaluate treatment effects. Until the last part of this section, our focus will be on estimation of the mean outcome at week 8 (in a world without

Figure 2: Schematic representation of the global sensitivity analysis framework. Circles represent modeling restrictions placed on the distribution of the observed data, with the outer circle indicating no restrictions and the inner circle indicating type (ii) restrictions. The arrows indicate a mappings from the distribution of the observed data to the true mean, which depends on the type (i) assumptions.



missing outcomes) for one of the treatment groups and we will suppress reference to treatment assignment.

3.1 Notation and Data Structure

Let Y_0, Y_1 and Y_2 denote the QLESSF scores scheduled to be collected at baseline, week 4 and week 8, respectively. Let R_k be the indicator that Y_k is observed. We assume $R_0 = 1$ and that $R_k = 0$ implies $R_{k+1} = 0$ (i.e., missingness is monotone). We refer to a patient as on-study at visit k if $R_k = 1$, as discontinued prior to visit k if $R_k = 0$ and last seen at visit $k-1$ if $R_{k-1} = 1$ and $R_k = 0$. We define Y_k^{obs} to be equal to Y_k if $R_k = 1$ and equal to nil if $R_k = 0$.

The observed data for an individual are $O = (Y_0, R_1, Y_1^{obs}, R_2, Y_2^{obs})$, which is drawn from some distribution P^* contained within a set of distributions $\mathcal{M}$ (to be discussed later). Throughout, the superscript $*$ will be used to denote the true value of the quantity to which it is appended. Any distribution $P \in \mathcal{M}$ can be represented in terms of the following distributions: $f(Y_0)$, $P[R_1 = 1|Y_0]$, $f(Y_1|R_1 = 1, Y_0)$, $P[R_2 = 1|R_1 = 1, Y_1, Y_0]$ and $f(Y_2|R_2 = 1, Y_1, Y_0)$.

We assume that n independent and identically distributed copies of O are observed. The goal is to use these data to draw inference about $\mu^* = E^*[Y_2]$. When necessary, we will use the subscript i to denote data for individual i.

3.2 Benchmark Assumption (Missing at Random)

Missing at random (Little and Rubin, 2014) is a widely used assumption for analyzing longitudinal studies with missing outcome data. To understand this assumption, we define the following strata:

- $A_0(y_0)$: patients last seen at visit 0 with $Y_0 = y_0$.
- $B_1(y_0)$: patients on-study at visit 1 with $Y_0 = y_0$.
- $A_1(y_1, y_0)$: patients last seen at visit 1 with $Y_1 = y_1$ and $Y_0 = y_0$.

- $B_2(y_1, y_0)$: patients on-study at visit 2 with $Y_1 = y_1$ and $Y_0 = y_0$.

Missing at random posits the following type (i) "linking" assumptions:

- For all y_0, the distribution of Y_1 and Y_2 for patients in strata $A_0(y_0)$ is the same as the distribution of Y_1 and Y_2 for patients in strata $B_1(y_0)$
- For all y_0, y_1, the distribution of Y_2 for patients in strata $A_1(y_1, y_0)$ is the same as the distribution of Y_2 for patients in strata $B_2(y_1, y_0)$

Mathematically, we can express these assumptions as follows:

$$f^*(Y_1, Y_2| \underbrace{R_1 = 0, Y_0 = y_0}_{A_0(y_0)}) = f^*(Y_1, Y_2| \underbrace{R_1 = 1, Y_0 = y_0}_{B_1(y_0)}) \text{ for all } y_0 \tag{1}$$

and

$$f^*(Y_2| \underbrace{R_2 = 0, R_1 = 1, Y_1 = y_1, Y_0 = y_0}_{A_1(y_1,y_0)}) = f^*(Y_2| \underbrace{R_2 = 1, Y_1 = y_1, Y_0 = y_0}_{B_2(y_1,y_0)}) \text{ for all } y_1, y_0 \tag{2}$$

Using Bayes' rule, we can re-write these expressions as:

$$P^*[R_1 = 0|Y_2 = y_2, Y_1 = y_1, Y_0 = y_0] = P^*[R_1|Y_0 = y_0] \tag{3}$$

and

$$P^*[R_2 = 0|R_1 = 1, Y_2 = y_2, Y_1 = y_1, Y_0 = y_0] = P^*[R_2 = 0|R_1 = 1, Y_1 = y_1, Y_0 = y_0] \tag{4}$$

Written in this way, missing at random implies that the drop-out process is stochastic with the following properties:

- The decision to discontinue the study before visit 1 is like the flip of a coin with probability depending on the value of the outcome at visit 0.
- For those on-study at visit 1, the decision to discontinue the study before visit 2 is like the flip of a coin with probability depending on the value of the outcomes at visits 1 and 0.

Under missing at random, μ^* is identified. That is, it can be expressed as a function of the distribution of the observed data. Specifically,

$$\mu^* = \mu(P^*) = \int_{y_0} \int_{y_1} \int_{y_2} y_2 dF_2^*(y_2|y_1, y_0) dF_1^*(y_1|y_0) dF_0^*(y_0) \tag{5}$$

where $F_2^*(y_2|y_1, y_0) = P^*[Y_2 \leq y_2|R_2 = 1, Y_1 = y_1, Y_0 = y_0]$, $F_1^*(y_1|y_0) = P^*[Y_1 \leq y_1|R_1 = 1, Y_0 = y_0]$ and $F_0^*(y_0) = P^*[Y_0 \leq y_0]$.

Before proceeding to the issue of estimation, we will build a class of assumptions around the missing at random assumption using a modeling device called exponential tilting (Barndorff-Nielsen and and Cox, 1979).

3.3 Missing Not at Random and Exponential Tilting

To build a class of missing not at random assumptions, consider Equation (1) of the missing at random assumption. This equation is equivalent to the following two assumptions:

$$f^*(Y_2|\underbrace{R_1=0,Y_1=y_1,Y_0=y_0}_{A_0(y_1,y_0)}) = f^*(Y_2|\underbrace{R_1=1,Y_1=y_1,Y_0=y_0}_{B_1(y_1,y_0)}) \text{ for all } y_0,y_1 \tag{6}$$

and

$$f^*(Y_1|\underbrace{R_1=0,,Y_0=y_0}_{A_0(y_0)}) = f^*(Y_1|\underbrace{R_1=1,Y_0=y_0}_{B_1(y_0)}) \text{ for all } y_0 \tag{7}$$

where

- $A_0(y_1,y_0) \subset A_0(y_0)$: patients last seen at visit 0 with $Y_0=y_0$ and $Y_1=y_1$.
- $B_1(y_1,y_0) \subset B_1(y_0)$: patients on-study at visit 1 with $Y_0=y_0$ and $Y_1=y_1$.

Equation (6) posits the following type (i) "linking" assumption:

- For all y_0 and y_1, the distribution of Y_2 for patients in strata $A_0(y_1,y_0)$ is the same as the distribution of Y_2 for patients in strata $B_1(y_1,y_0)$

It has been referred to as the "non-future" dependence assumption (Diggle and Kenward, 1994) because it implies that R_1 (i.e., the decision to drop-out before visit 1) is independent of Y_2 (i.e., the future outcome) after conditioning on the Y_0 (i.e., the past outcome) and Y_1 (i.e., the most recent outcome). We will retain this assumption.

Next, we impose the following exponential tilting "linking" assumptions:

$$f^*(Y_1|\underbrace{R_1=0,Y_0=y_0}_{A_0(y_0)}) \propto f^*(Y_1|\underbrace{R_1=1,Y_0=y_0}_{B_1(y_0)})\exp\{\alpha r(Y_1)\} \text{ for all } y_0 \tag{8}$$

$$f^*(Y_2|\underbrace{R_2=0,R_1=1,Y_1=y_1,Y_0=y_0}_{A_1(y_1,y_0)}) \propto f^*(Y_2|\underbrace{R_2=1,Y_1=y_1,Y_0=y_0}_{B_2(y_1,y_0)})\exp\{\alpha r(Y_2)\} \text{ for all } y_0,y_1 \tag{9}$$

where $r(\cdot)$ is a specified function which we will assume to be an increasing function of its argument and α is a sensitivity analysis parameter. The missing not at random class of assumptions that we propose involves Equations (6), (8) and (9), where $r(\cdot)$ is considered fixed and α is a sensitivity analysis parameter that serves as the class index. Importantly, notice how (8) reduces to (7) and (9) reduces to (2) when $\alpha=0$. Thus, when $\alpha=0$, the MAR assumption is obtained. When $\alpha>0$ (<0), notice that (8) and (9) imply

- For all y_0, the distribution of Y_1 for patients in strata $A_0(y_0)$ is weighted more heavily (i.e., tilted) to higher (lower) values than the distribution of Y_1 for patients in strata $B_1(y_0)$
- For all y_0,y_1, the distribution of Y_2 for patients in strata $A_1(y_1,y_0)$ is weighted more heavily weighted (i.e., tilted) to higher (lower) values than the distribution of Y_2 for patients in strata $B_2(y_1,y_0)$

The amount of "tilting" increases with the magnitude of α.

Using Bayes' rule, we can re-write expressions (6), (8) and (9) succinctly as:

$$\text{logit } P^*[R_1=0|Y_2=y_2,Y_1=y_1,Y_0=y_0] = l_1^*(y_0)+\alpha r(y_1) \tag{10}$$

and

$$\text{logit } P^*[R_2 = 0|R_1 = 1, Y_2 = y_2, Y_1 = y_1, Y_0 = y_0] = l_2^*(y_1, y_0) + \alpha r(y_2) \tag{11}$$

where

$$l_1^*(y_0; \alpha) = \text{logit } P^*[R_1 = 0|Y_0 = y_0] - \log E^*[\exp\{\alpha r(Y_1)\}|R_1 = 1, Y_0 = y_0]$$

and

$$\begin{aligned} l_2^*(y_1, y_0; \alpha) &= \text{logit } P^*[R_2 = 0|R_1 = 1, Y_1 = y_1, Y_0 = y_0] - \\ &\quad \log E^*[\exp\{\alpha r(Y_2)\}|R_2 = 1, Y_1 = y_1, Y_0 = y_0] \end{aligned}$$

Written in this way, the drop-out process is stochastic with the following properties:

- The decision to discontinue the study before visit 1 is like the flip of a coin with probability depending on the value of the outcome at visit 0 *and*, in a specified way, the value of the outcome at visit 1.
- For those on-study at visit 1, the decision to discontinue the study before visit 2 is like the flip of a coin with probability depending on the value of the outcomes at visits 1 and 0 *and*, in a specified way, the value of the outcome at visit 2.

For given α, μ^* is identified. Specifically, $\mu^* = \mu(P^*; \alpha)$ equals

$$\begin{aligned} &\int_{y_0}\int_{y_1}\int_{y_2} y_2 \left\{ dF_2^*(y_2|y_1, y_0)\{1 - H_2^*(y_1, y_0)\} + \frac{dF_2^*(y_2|y_1, y_0)\exp\{\alpha r(y_2)\}}{\int_{y_2'} dF_2^*(y_2'|y_1, y_0)\exp\{\alpha r(y_2')\}} H_2^*(y_1, y_0) \right\} \times \\ &\qquad \left\{ dF_1^*(y_1|y_0)\{1 - H_1^*(y_0)\} + \frac{dF_1^*(y_1|y_0)\exp\{\alpha r(y_1)\}}{\int_{y_1'} dF_1^*(y_1'|y_0)\exp\{\alpha r(y_1')\}} H_1^*(y_0) \right\} dF_0^*(y_0) \end{aligned} \tag{12}$$

where $H_2^*(y_1, y_0) = P^*[R_2 = 0|R_1 = 1, Y_1 = y_1, Y_0 = y_0]$ and $H_1^*(y_0) = P^*[R_1 = 0|Y_0 = y_0]$

4 Inference

For given α, formula (12) shows that μ^* depends on $F_2^*(y_2|y_1, y_0)$, $F_1^*(y_1|y_0)$, $H_2^*(y_1, y_0)$ and $H_1^*(y_0)$. Thus, it is natural to consider estimating μ^* by "plugging in" estimators of $F_2^*(y_2|y_1, y_0)$, $F_1^*(y_1|y_0)$, $F_0^*(y_0)$, $H_2^*(y_1, y_0)$ and $H_1^*(y_0)$ into (12). How can we estimate these latter quantities? With the exception of $F_0^*(y_0)$, it is tempting to think that we can use non-parametric procedures to estimate these quantities. For example, a non-parametric estimate of $F_2^*(y_2|y_1, y_0)$ would take the form:

$$\widehat{F}_2(y_2|y_1, y_0) = \frac{\sum_{i=1}^n R_{2,i} I(Y_{2,i} \leq y_2) I(Y_{1,i} = y_1, Y_{0,i} = y_0)}{\sum_{i=1}^n R_{2,i} I(Y_{1,i} = y_1, Y_{0,i} = y_0)}$$

This estimator will perform very poorly (i.e., have high levels of uncertainly in moderate sample sizes) because the number of subjects who complete the study (i.e., $R_2 = 1$) and are observed to have outcomes at visits 1 and 0 exactly equal to y_1 and y_0 will be very small and can only be expected to grow very slowly as the sample size increases. As a result, a a plug-in estimator of μ^* that uses such non-parametric estimators will perform poorly. We address this problem in three ways.

4.1 Testable Assumptions

First we make the estimation task slightly easier by assuming that

$$F_2^*(y_2|y_1, y_0) = F_2^*(y_2|y_1) \tag{13}$$

and

$$H_2^*(y_1, y_0) = H_2^*(y_1) \tag{14}$$

That is, (13) states that, among subjects who complete the study, information about Y_0 does not provide any information about the distribution of Y_2 above and beyond information about Y_1 and (14) states that, among subjects on-study at visit 1, information about Y_0 does not influence of the risk of dropping out before visit 2 above and beyond information about Y_1. These assumptions are, with large enough samples, testable from the observed data. As such, we distinguish them from type (i) assumptions and refer to them as type (ii) assumptions.

4.2 Kernel Smoothing with Cross-Validation

Second we estimate $F_2^*(y_2|y_1)$, $F_1^*(y_1|y_0)$, $H_2^*(y_1)$ and $H_1^*(y_0)$ using kernel smoothing techniques. To motivate this idea, consider the following non-parametric estimate of $F_2^*(y_2|y_1)$

$$\widehat{F}_2(y_2|y_1) = \frac{\sum_{i=1}^n R_{2,i} I(Y_{2,i} \leq y_2) I(Y_{1,i} = y_1)}{\sum_{i=1}^n R_{2,i} I(Y_{1,i} = y_1)}$$

This estimator will still perform poorly, although better than $\widehat{F}_2(y_2|y_1, y_0)$, since there will be at least as many completers with Y_1 values equal to y_1 than completers with Y_1 *and* Y_0 values equal to y_1 and y_0, respectively. To improve its performance, we replace $I(Y_{1,i} = y_1)$ by $\phi\left(\frac{Y_{1,i}-y_1}{\lambda_{F_2}}\right)$, where $\phi(\cdot)$ is the density function for a standard normal random variable and λ_{F_2} is a tuning parameter. For fixed λ_{F_2}, let

$$\widehat{F}_2(y_2|y_1; \sigma_{F_2}) = \frac{\sum_{i=1}^n R_{2,i} I(Y_{2,i} \leq y_2) \phi\left(\frac{Y_{1,i}-y_1}{\lambda_{F_2}}\right)}{\sum_{i=1}^n R_{2,i} \phi\left(\frac{Y_{1,i}-y_1}{\lambda_{F_2}}\right)}$$

This estimator allows *all* completers to contribute, not just those with Y_1 values equal to y_1; it assigns weight to completers according to how far their Y_1 values are from y_1, with closer values assigned more weight. The larger λ_{F_2}, the larger the influence of values of Y_1 further from y_1 on the estimator. As $\lambda_{F_2} \to \infty$, the contribution of each completer to the estimator becomes equal, yielding bias but low variance. As $\lambda_{F_2} \to 0$, only completers with Y_1 values equal to y_1 contribute, yielding low bias but high variance.

To address the bias-variance trade-off, cross validation (Hall, Racine and Li, 2004) is typically used to select λ_{F_2}. In cross validation, the dataset is randomly divided into J (typically, 10) approximately equal parts. Each part is called a validation set. Let V_j be the indices of the subjects in the jth validation set. Let n_j be the associated number of subjects. Let $\widehat{F}_2^{(j)}(y_2|y_1; \lambda_{F_2})$ be the estimator of $F_2^*(y_2|y_1)$ based on the dataset that excludes the jth validation set (referred to as the jth training set). If λ_{F_2} is a good choice then one would expect

$$CV_{F_2^*(\cdot|\cdot)}(\lambda_{F_2}) = \frac{1}{J}\sum_{j=1}^{J}\left\{\frac{1}{n_j}\sum_{i\in V_j} R_{2,i} \underbrace{\int \left\{I(Y_{2,i} \leq y_2) - \widehat{F}_2^{(j)}(y_2|Y_{1,i}; \lambda_{F_2})\right\}^2 d\widehat{F}_2^{\circ}(y_2)}_{\text{Distance for } i \in V_j}\right\} \tag{15}$$

will be small, where $\widehat{F}_2^{\circ}(y_2)$ is the empirical distribution of Y_2 among subjects on-study at visit 2. In (15), the quantity in the vertical braces is a measure of how well the estimator of $F_2(y_2|y_1)$ based on the jth training set "performs" on the jth validation set. For each individual i in the jth validation set with an observed outcome at visit 2, we measure, by the quantity above the horizontal brace in (15), the distance (or loss) between the collection of indicator variables $\{I(Y_{2,i} \leq y_2) : d\widehat{F}_2^{\circ}(y_2) > 0\}$ and the corresponding collection of predicted values $\{\widehat{F}_2^{(j)}(y_2|Y_{1,i}; \lambda_{F_2}) : d\widehat{F}_2^{\circ}(y_2) > 0\}$. The distance for each of these individuals are then summed and divided by the number of subjects in the jth validation set. Finally, an average across the J validation/training sets is computed. We can then estimate $F_2^*(y_2|y_1)$ by $\widehat{F}_2(y_2|y_1; \widehat{\lambda}_{F_2})$, where $\widehat{\lambda}_{F_2} = \text{argmin } CV_{F_2^*(\cdot|\cdot)}(\lambda_{F_2})$.

Using this idea, we can estimate $F_1^*(y_1|y_0)$ by

$$\widehat{F}_1(y_1|y_0; \widehat{\sigma}_{F_1}) = \frac{\sum_{i=1}^n R_{1,i} I(Y_{1,i} \leq y_1) \phi\left(\frac{Y_{0,i}-y_0}{\widehat{\sigma}_{F_1}}\right)}{\sum_{i=1}^n R_{1,i} \phi\left(\frac{Y_{0,i}-y_0}{\widehat{\sigma}_{F_1}}\right)}$$

where $\widehat{\sigma}_{F_1}$ is the minimizer of

$$CV_{F_1^*(\cdot|\cdot)}(\sigma_{F_1}) = \frac{1}{J}\sum_{j=1}^{J}\left\{\frac{1}{n_j}\sum_{i\in V_j} R_{1,i}\int\left\{I(Y_{1,i} \leq y_1) - \widehat{F}_1^{(j)}(y_1|Y_{0,i}; \sigma_{F_1})\right\}^2 d\widehat{F}_1^{\circ}(y_1)\right\}$$

and $\widehat{F}_1^{\circ}(y_1)$ is the empirical distribution of Y_1 among subjects on-study at visit 1. Further, we estimate $H_k^*(y_{k-1})$ $(k = 1, 2)$ by

$$\widehat{H}_k(y_{k-1}; \widehat{\sigma}_{H_k}) = \frac{\sum_{i=1}^n R_{k-1,i}(1 - R_{k,i}) \phi\left(\frac{Y_{k-1,i}-y_{k-1}}{\widehat{\sigma}_{H_k}}\right)}{\sum_{i=1}^n R_{k-1,i} \phi\left(\frac{Y_{k-1,i}-y_{k-1}}{\widehat{\sigma}_{H_k}}\right)}$$

where $\widehat{\sigma}_{H_k}$ is the minimizer of

$$CV_{H_k^*(\cdot)}(\sigma_{H_k}) = \frac{1}{J}\sum_{j=1}^{J}\left\{\frac{1}{n_j}\sum_{i\in V_j} R_{k-1,i}\{1 - R_{k,i} - \widehat{H}_k^{(j)}(Y_{k-1,i}; \widehat{\sigma}_{H_k})\}\widehat{H}_k^{\circ}\right\}$$

and $\widehat{H}_k^{\circ}$ is the proportion of individual with drop out between visits $k-1$ and k among those on-study at visit $k-1$.

4.3 Correction Procedure

The cross-validation procedure for selecting tuning parameters achieves optimal finite-sample bias-variance trade-off for the quantities requiring smoothing, i.e., the conditional distribution functions $F_k^*(y_k|y_{k-1})$ and probability mass functions $H_k^*(y_{k-1})$. This optimal trade-off is usually not optimal for estimating μ^*. In fact, the plug-in estimator of μ^* could possibly suffer from excessive and asymptotically non-negligible bias due to inadequate tuning. This may prevent the plug-in estimator from enjoying regular asymptotic behavior, upon which statistical inference is generally based. In particular, the resulting estimator may have a slow rate of convergence, and common methods for constructing confidence intervals, such as the Wald and bootstrap intervals, can have poor coverage properties. Thus, our third move is to "correct" the plug-in estimator. Specifically, the goal is to construct an estimator that is "asymptotically linear" (i.e., can be expressed as the average of i.i.d. random variables plus a remainder term that is asymptotically negligible).

We now motivate the correction procedure. Let $\mathcal{M}$ be the class of distributions for the observed data O that satisfy constraints (13) and (14). It can be shown that, for $P \in \mathcal{M}$,

$$\mu(P;\alpha) - \mu(P^*;\alpha) = -E^*[\psi_P(O;\alpha) - \psi_{P^*}(O;\alpha)] + \text{Rem}(P, P^*;\alpha), \tag{16}$$

where $\psi_P(O;\alpha)$ is a "derivative" of $\mu(\cdot;\alpha)$ at P and $\text{Rem}(P, P^*;\alpha)$ is a "second-order" remainder term which converges to zero as P tends to P^*. This derivative is used to quantify the change in $\mu(P;\alpha)$ resulting from small perturbations in P; it also has mean zero (i.e., $E^*[\psi_{P^*}(O;\alpha)] = 0$). The remainder term is second order in the sense that it can be written as or bounded by the product of terms involving differences between (functionals of) P and P^*.

Equation (16) plus some simple algebraic manipulation teaches us that

$$\underbrace{\mu(\widehat{P};\alpha)}_{\text{Plug-in}} - \mu(P^*;\alpha) = \frac{1}{n}\sum_{i=1}^{n} \psi_{P^*}(O_i;\alpha) - \frac{1}{n}\sum_{i=1}^{n} \psi_{\widehat{P}}(O_i;\alpha) \tag{17}$$

$$+\frac{1}{n}\sum_{i=1}^{n}\{\psi_{\widehat{P}}(O_i;\alpha) - \psi_{P^*}(O_i;\alpha) - E^*[\psi_{\widehat{P}}(O;\alpha) - \psi_{P^*}(O;\alpha)]\} \tag{18}$$

$$+\text{Rem}(\widehat{P}, P^*;\alpha) \tag{19}$$

where $\widehat{P}$ is the estimated distribution of P^* discussed in the previous section. Under smoothness and boundedness conditions, term (18) will be $o_{P^*}(n^{-1/2})$ (i.e., will converge in probabity to zero even when it is multipled by $\sqrt{n}$). Provided $\widehat{P}$ converges to P^* at a reasonably fast rate, term (19) will also be $o_{P^*}(n^{-1/2})$. The second term in (17) prevents us from concluding that the plug-in estimator can be essentially represented as an average of i.i.d terms plus $o_{P^*}(n^{-1/2})$ terms. However, by adding the second term in (17) to the plug-in estimator, we can construct a "corrected" estimator that does have this representation. Formally, the corrected estimator is

$$\tilde{\mu}_\alpha = \underbrace{\mu(\widehat{P};\alpha)}_{\text{Plug-in}} + \frac{1}{n}\sum_{i=1}^{n} \psi_{\widehat{P}}(O_i;\alpha)$$

The practical implication is that $\tilde{\mu}_\alpha$ converges in probability to μ^* and

$$\sqrt{n}\,(\tilde{\mu}_\alpha - \mu^*) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} \psi_{P^*}(O_i;\alpha) + o_{P^*}(1)$$

With this representation, we see that $\psi_{P^*}(O;\alpha)$ is the so-called influence function. By the central limit theorem, we then know that $\sqrt{n}\,(\tilde{\mu}_\alpha - \mu^*)$ converges to a normal random variable with mean 0 and variance $\sigma_\alpha^2 = E^*[\psi_{P^*}(O;\alpha)^2]$. The asymptotic variance can be estimated by $\tilde{\sigma}_\alpha^2 = \frac{1}{n}\sum_{i=1}^{n} \psi_{\widehat{P}}(O_i;\alpha)^2$. A $(1-\gamma)\%$ Wald-based confidence interval for $\mu^*(\alpha)$ can be constructed as $\tilde{\mu}(\alpha) \pm z_{1-\gamma/2}\tilde{\sigma}_\alpha/\sqrt{n}$, where z_q is the qth quantile of a standard normal random variable.

The efficient influence function in model $\mathcal{M}$ is presented in Appendix A.

4.4 Confidence interval construction

For given α, there are many ways to construct confidence intervals for μ^*. Above, we discussed the Wald-based technique. In Section 6, we present the results of a simulation study in which this technqiue results in poor coverage in moderately sized samples. The poor coverage can be explained

in part due to the fact that $\tilde{\sigma}(\alpha)^2$ can be severely downward biased in finite samples (Efron and Gong, 1983).

Resampling-based procedures may be used to improve performance. A first idea is to consider the jackknife estimator for σ^2_α:

$$\tilde{\sigma}^2_{JK,\alpha} = (n-1)\sum_{i=1}^{n}\{\tilde{\mu}^{(-i)}_\alpha - \tilde{\mu}^{(\cdot)}_\alpha\}^2$$

where $\tilde{\mu}^{(-i)}_\alpha$ is the estimator of μ^* with the ith individual deleted from the dataset and $\tilde{\mu}^{(\cdot)}_\alpha = \frac{1}{n}\sum_{i=1}^{n}\tilde{\mu}^{(-i)}_\alpha$. This estimator is known to be conservative (Efron and Stein, 1981), but is the "method of choice if one does not want to do bootstrap computations" (Efron and Gong, 1983). Using the jackknife estimator of the variance, one can construct a Wald confidence interval with $\tilde{\sigma}_\alpha$ replaced by $\tilde{\sigma}_{JK,\alpha}$. Our simulation study in Section 6 demonstrates that these latter intervals perform better, but still have coverage lower than desired.

Another idea is to use studentized-t bootstrap. Here, confidence intervals are formed by choosing cutpoints based on the distribution of

$$\left\{\frac{\tilde{\mu}^{(b)}_\alpha - \tilde{\mu}_\alpha}{\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right)} : b = 1, 2, \ldots, B\right\} \tag{20}$$

where $\tilde{\mu}^{(b)}_\alpha$ is the estimator of μ^* based on the bth bootstrap dataset and $\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right)$ is an estimator of the standard error of $\tilde{\mu}^{(b)}_\alpha$ (e.g., $\tilde{\sigma}_\alpha/\sqrt{n}$ or $\tilde{\sigma}_{JK,\alpha}/\sqrt{n}$) . An equal-tailed confidence interval takes the form:

$$\left(\tilde{\mu}_\alpha - t_{1-\gamma/2}\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right), \tilde{\mu}_\alpha - t_{\gamma/2}\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right)\right),$$

where t_q is the qth quantile of (20). A symmetric confidence interval takes the form:

$$\left(\tilde{\mu}_\alpha - t^*_{1-\gamma}\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right), \tilde{\mu}_\alpha + t^*_{1-\gamma}\tilde{se}\left(\tilde{\mu}^{(b)}_\alpha\right)\right),$$

where $t^*_{1-\gamma}$ is selected so that $(1-\gamma)$ of the distribution of (20) is between $-t^*_{1-\gamma}$ and $t^*_{1-\gamma}$.

In terms of bootstrapping, there are two main choices: non-parametric and parametric. The advantage of non-parametric bootstrap is that it does not require a model for the distribution of the observed data. Since our analysis depends on correct specification and on estimation of such a model, it makes sense to use this model to bootstrap observed datasets. In our data analysis and simulation study, we use the estimated distribution of the observed data to generate bootstrapped observed datasets.

Our simulation study in Section 6 shows that the symmetric studentized-t bootstrap with jackknife standard errors performs best. We used this procedure in our data analysis.

5 Analysis of Quetiapine Trial

The first step of the analysis is to estimate the smoothing parameters and assess the goodness of fit of our models for H^*_j (drop-out) and F^*_j (outcome). We assumed a common smoothing parameter for the H^*_j $(j = 1, 2)$ models and a common smoothing parameter for F^*_j $(j = 1, 2)$ models; F^*_0 was estimated by its empirical distribution. The estimated smoothing parameters for the drop-out (outcome) model are 11.54 (6.34) and 9.82 (8.05) for the placebo and 600 mg arms, respectively. In

the placebo arm, the observed percentages of last being seen at visits 0 and 1 among those at risk at these visits are 8.62% and 38.68%, respectively. Estimates derived from the estimated model for the distribution of the observed data are 7.99% and 38.19%, respectively. For the 600 mg arm, the observed percentages are 11.02% and 35.24% and the model-based estimates are 11.70% and 35.08%. In the placebo arm, the Kolmogorov-Smirnov distances between the empirical distribution of the observed outcomes and the model-based estimates of the distribution of outcomes among those on-study at visits 1 and 2 are 0.013 and 0.033, respectively. In the 600 mg arm, these distances are 0.013 and 0.022. These results suggest that our model for the observed data fits the observed data well.

Under missing at random, the estimated values of μ^* are 46.45 (95% CI: 42.35,50.54) and 62.87 (95% CI: 58.60,67.14) for the placebo and 600 mg arms, respectively. The estimated difference between 600 mg and placebo is 16.42 (95% 10.34, 22.51), which represents both a statistically and clinically significant improvement in quality of life in favor of Quetiapine. [5]

In our sensitivity analysis, we set $r(y) = y$ and ranged the sensitivity analysis parameter from -10 and 10 in each treatment arm.[6] Figure 3 presents treatment-specific estimates (along with 95% pointwise confidence intervals) of μ^* as a function of α. To help interpret the sensitivity analysis parameter, Figure 4 displays treatment-specific differences between the estimated mean QLESSF at Visit 2 among non-completers and the estimated mean among completers, as a function of α. For example, when $\alpha = -10$ non-completers are estimated to have more than 20 points lower quality of life than completers; this holds for both treatment arms. In contrast, when $\alpha = 10$ non-completers are estimated to have 6 and 11 points higher quality of life than completers in the placebo and Quetiapine arms, respectively. The plausibility of α can be judged with respect the plausibility of these differences. In this setting, it may be considered unreasonable that completers are worse off in terms of quality of life than non-completers, in which case α should be restricted to be less than 6 in the placebo arm and less than 3 in the Quentiapine arm.

Figure 5 displays a contour plot of the estimated differences between mean QLESSF at Visit 2 for Quentiapine vs. placebo for various treatment-specific combinations of the sensitivity analysis parameters. The point (0,0) corresponds to the MAR assumption in both treatment arms. The figure shows that the differences are statistically significant (represented by dots) in favor of Quetiapine at almost all combinations of the sensitivity analysis parameters. Only when the sensitivity analysis are highly differential (e.g., α(placebo) = 8 and α(Quetaipine) = -8) are the differences no longer statistically significant. This figure shows that conclusions under MAR are highly robust.

6 Simulation Study

To evaluate the statistical properties of our proposed procedure, we conducted a realistic simulation study that mimics the data structure in the Quetiapine study. We generated 2500 placebo and Quetiapine datasets using the estimated distributions of the observed data from the Quentiapine study as the true data generating mechanisms. For given treatment-specific α, these true data generating mechanisms can be mapped to a true value of μ^*. For each dataset, the sample size was to set to 116 and 118 in the placebo and Quetiapine arms, respectively.

Table 1 reports bias and mean-squared error for the plug-in and corrected estimators, as a function of α. The bias tends to be low for both estimators and the mean-squared error is lower for the corrected estimators, except at extreme values of α.

[5] All confidence intervals are symmetric studentized-t bootstrap with jackknife standard errors.

[6] According to Dr. Dennis Rivicki and Dr. Jean Endicott, there is no evidence to suggest that there is a differential effect of a unit change in QLESSF on the hazard of drop-out based on its location on the scale.

Figure 3: Treatment-specific (left: placebo; right: 600 mg/day Quentiapine) estimates (along with 95% pointwise confidence intervals) of μ^* as a function of α.

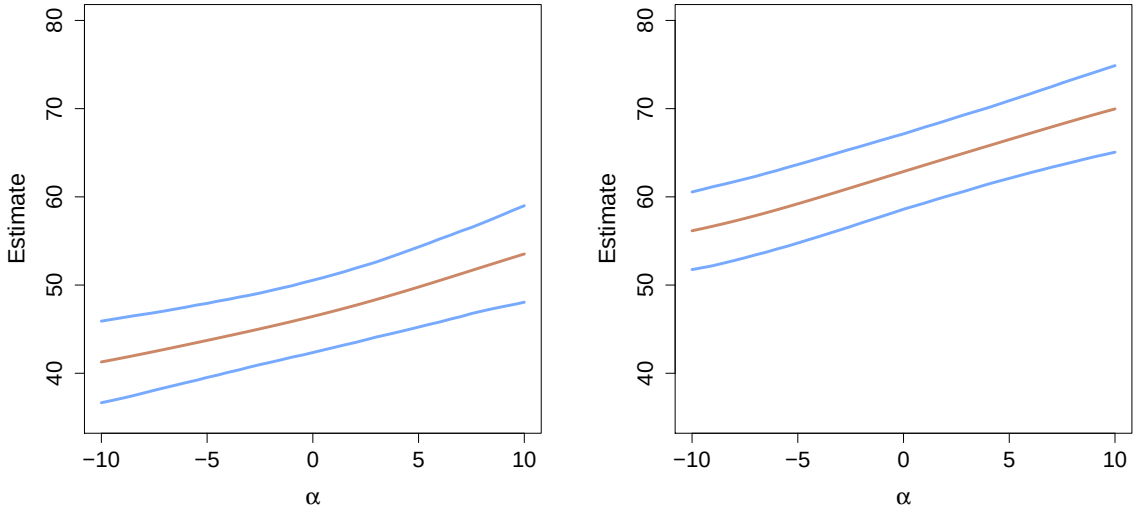


Table 2 reports the coverage properties of six difference methods for constructing confidence intervals: (1) Wald with influence function standard errors (Wald-IF), (2) Wald with jackknife standard errors (Wald-JK), (3) equal-tailed studentized parametric bootstrap with influence function standard errors (Bootstrap-IF-ET), (4) equal-tailed studentized parametric bootstrap with jackknife standard errors (Bootstrap-JK-ET), (5) symmetric studentized parametric bootstrap with influence function standard errors (Bootstrap-IF-S) and (6) symmetric studentized parametric bootstrap with jackknife standard errors (Bootstrap-JK-S); 2000 parametric bootstraps were used. The results demonstrate that using jackknife standard errors is superior to influence function standard errors. In this simulation, the best performing procedures are Wald with jackknife standard errors and symmetric studentized parametric bootstrap with jackknife standard errors, with the latter experiencing, for some values of α, coverages 1-2% higher than nominal levels. In other simulations (reported elsewhere), we have found that Wald with jacknife standard errors can have lower than nominal levels of coverage. Thus, we recommend using symmetric studentized parametric bootstrap with jackknife standard errors.

7 Discussion

Our review of leading medical journals demonstrated that missing data are a common occurrence in randomized trials with patient-reported outcomes. As per the 2010 NRC report, it is essential to evaluate the robustness of trial results to untestable assumptions about the underlying missing data mechanism. In this paper, we have presented a methodology for conducting global (as opposed to ad-hoc or local) sensitivity analysis of trials in which (1) outcomes are scheduled to be measured at fixed points after randomization and (2) missing data are monotone. While we developed our method in the context of a motivating example with two post-baseline measurements, it naturally generalizes to studies with more measurements. Our sensitivity analysis is anchored around the commonly used missing at random assumption. We have developed a software package called SAMON to implement our procedure. R and SAS versions of the software are available at

Figure 4: Treatment-specific differences between the estimated mean QLESSF at Visit 2 among non-completers and the estimated mean among completers, as a function of α.

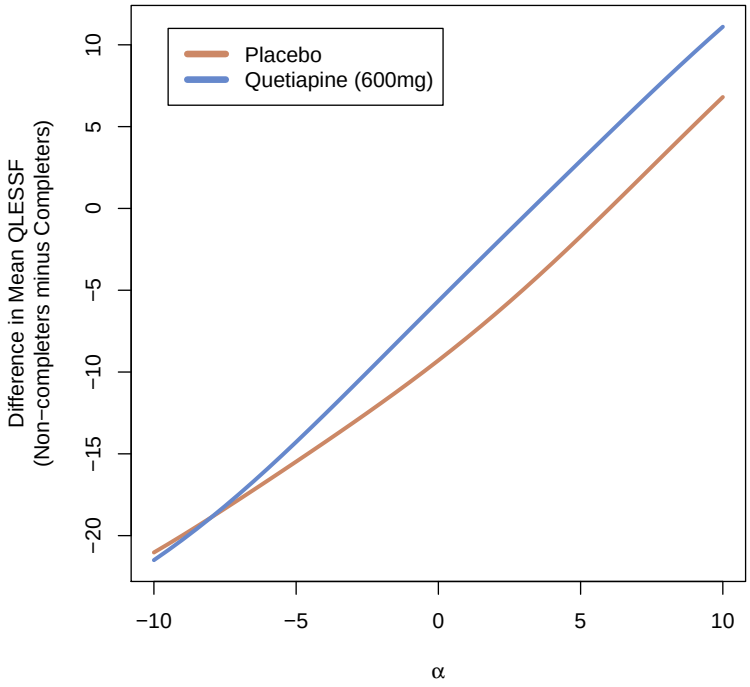


Figure 5: Contour plot of the estimated differences between mean QLESSF at Visit 2 for Quentiapine vs. placebo for various treatment-specific combinations of the sensitivity analysis parameters. The point (0,0) corresponds to the MAR assumption in both treatment arms.

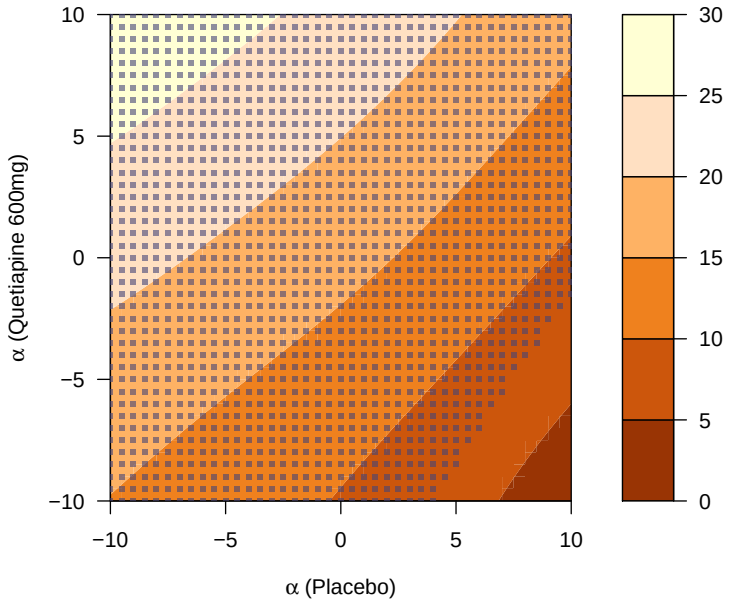


Table 1: Treatment- and α-specific simulation results: Bias and mean-squared error (MSE) for the plug-in ($\mu(\widehat{P};\alpha)$) and corrected ($\widetilde{\mu}_\alpha$) estimators, for various choices of α.

		Placebo			Quetiapine		
α	Estimator	μ^*	Bias	MSE	μ^*	Bias	MSE
-10	Plug-in	40.85	0.02	4.43	56.07	0.40	4.69
	Corrected		0.43	4.56		0.42	4.72
-5	Plug-in	43.45	0.05	4.29	59.29	0.34	4.55
	Corrected		0.27	4.26		0.24	4.35
-1	Plug-in	46.02	0.28	4.34	62.58	0.50	4.39
	Corrected		0.18	4.22		0.14	4.00
0	Plug-in	46.73	0.36	4.44	63.42	0.55	4.36
	Corrected		0.17	4.27		0.14	3.95
1	Plug-in	47.45	0.43	4.57	64.25	0.59	4.32
	Corrected		0.16	4.36		0.15	3.92
5	Plug-in	50.48	0.66	5.33	67.34	0.59	4.20
	Corrected		0.14	5.11		0.19	4.15
10	Plug-in	54.07	0.51	5.78	70.51	0.07	4.02
	Corrected		0.04	6.30		-0.05	4.66

`www.missingdatamatters.org`.

We have found that our procedure can be sensitive to outliers. In fact, we discarded two patients (one from each treatment arm) from the Quetiapine Study because of their undue influence. In the placebo arm, the patient was a completer and had baseline, visit 1 and visit 2 raw scores of 17, 26 and 48, respectively. At $\alpha = 10$, the scaled absolute DFBETA for this observation was 2.75 with the next largest absolute DFBETA being 1.13. In the Quetiapine arm, the patient was a completer and had baseline, visit 1 and visit 2 raw scores of 31, 29 and 18, respectively. At $\alpha = -10$, the scaled absolute DFBETA for this observation was 3.20 with the next largest absolute DFBETA being 0.52. One way to address the issue of outliers would be the robustify the influence function using ideas from the robust statistics literature (Huber and Ronchetti, 2009).

Our procedure does not currently handle intermittent missing data. In many randomized trials, intermittent missing data is usually a second order concern. We propose imputing intermittent observations, under a reasonable assumption (see, for example, Robins, 1997) to create a monotone data structure and then apply the methods outlined in this paper with proper accounting for uncertainty in the imputation process.

We believe that the methods and software that we have developed should be applied to all trials with missing outcome data, including but limited to those that are patient-reported. Trial results that are sensitive to untestable assumptions about the missing data mechanism should be viewed with skepticism, while greater credence should be given those that exhibit robustness. Our methods are not a substitute for study designs and procedures that minimize missing data.

Table 2: Treatment- and α-specific simulation results: Confidence interval coverage for (1) Wald with influence function standard errors (Wald-IF), (2) Wald with jackknife standard errors (Wald-JK), (3) equal-tailed studentized parametric bootstrap with influence function standard errors (Bootstrap-IF-ET), (4) equal-tailed studentized parametric bootstrap with jackknife standard errors (Bootstrap-JK-ET), (5) symmetric studentized parametric bootstrap with influence function standard errors (Bootstrap-IF-S) and (6) symmetric studentized parametric bootstrap with jackknife standard errors (Bootstrap-JK-S); 2000 parametric bootstraps were used.

		Placebo	Quetiapine
α	Procedure	Coverage	Coverage
-10	Wald-IF	91.5%	90.5%
	Wald-JK	95.0%	94.6%
	Bootstrap-IF-ET	94.3%	93.8%
	Bootstap-JK-ET	94.4%	93.4%
	Bootstap-IF-S	95.2%	94.6%
	Bootstap-JK-S	95.0%	94.6%
-5	Wald-IF	93.5%	92.9%
	Wald-JK	95.0%	94.8%
	Bootstrap-IF-ET	95.2%	94.6%
	Bootstap-JK-ET	94.8%	94.6%
	Bootstap-IF-S	95.4%	95.2%
	Bootstap-JK-S	95.1%	95.2%
-1	Wald-IF	93.9%	94.2%
	Wald-JK	94.9%	95.4%
	Bootstrap-IF-ET	95.1%	94.8%
	Bootstap-JK-ET	95.1%	94.6%
	Bootstap-IF-S	95.3%	96.4%
	Bootstap-JK-S	95.1%	96.3%
0	Wald-IF	93.8%	94.0%
	Wald-JK	95.0%	95.4%
	Bootstrap-IF-ET	94.6%	94.5%
	Bootstap-JK-ET	94.6%	94.6%
	Bootstap-IF-S	95.5%	96.6%
	Bootstap-JK-S	95.2%	96.7%
1	Wald-IF	93.3%	93.7%
	Wald-JK	95.1%	95.5%
	Bootstrap-IF-ET	94.6%	94.6%
	Bootstap-JK-ET	94.6%	94.6%
	Bootstap-IF-S	95.5%	96.5%
	Bootstap-JK-S	95.2%	96.5%
5	Wald-IF	90.8%	91.3%
	Wald-JK	95.3%	95.7%
	Bootstrap-IF-ET	93.2%	91.6%
	Bootstap-JK-ET	93.8%	93.0%
	Bootstap-IF-S	95.5%	95.4%
	Bootstap-JK-S	95.8%	96.4%
10	Wald-IF	85.4%	87.8%
	Wald-JK	94.9%	94.5%
	Bootstrap-IF-ET	88.2%	87.0%
	Bootstap-JK-ET	92.2%	89.7%
	Bootstap-IF-S	94.6%	93.9%
	Bootstap-JK-S	95.5%	95.1%

Table 3: List of Studies

Study	Indication	Journal	Endpoint	n	Follow-Up	Missing Data (%)
Berende (2016)	Lyme Disease	NEJM	SF-36	280	14 wks.	6.8%
Cohen (2011)	Cardiac Surgey	NEJM	SF-36	1800	1,6,12 mos.	9.5%-9.7%
Frobell (2010)	ACL Injury	NEJM	SF-36	141	3,6,12,24 mos.	14.2%-14.9%
Ghogawala (2016)	Lumbar Spondylolisthesis	NEJM	SF-36	66	1.5, 3, 6, 12, 24, 36, 48 mos.	12.1% - 31.8%
Khan (2008)	Heart Failure	NEJM	MLHFQ	81	6 mos.	0.0%
Kirkley (2008)	Oseteoarthritis	NEJM	SF-36	188	3,6,12,18, 24 mos.	9.6%-21.3%
Mark (2009)	Myocardial Infarction	NEJM	SF-36	951	4,12,24 mos.	12.4%-18.7%
Montalban (2016)	Multiple Sclerosis	NEJM	SF-36	732	120 wks.	21.3%
Temel (2010)	Metastatic Lung Cancer	NEJM	PHQ-9	151	12 wks.	31.1%
Wang (2010)	Fibromyalgia	NEJM	SF-36	66	12,24 wks.	7.6%-10.6%
Weinstein (2008)	Spinal Stenosis	NEJM	SF-36	289	1.5,3,6,12,24 mos.	11.8%-23.5%
Chalder (2015)	Chronic Fatigue Syndrome	Lancet-P	SF-36	641	52 wks.	14.0%
Christensen (2016)	Insomnia/Depression	Lancet-P	PHQ-9	1149	6 wks., 6 mos.	49.4%-56.1%
Fernandez-Rhodes (2011)	Spinal & Bulbar Muscular Atrophy	Lancet-N	SF-36	50	24 mos.	14.0%
Ganz (2015)	Ductal Carcinoma In Situ	Lancet	SF-12	1193	Every 6 mos. thru 54 mos.	4.9%-35.2%
Goudie (2014)	COPD	Lancet-RM	SF-36	120	12 wks.	5.8%
Hegarty (2013)	Intimate Partner Violence	Lancet	SF-12	272	6,12 mos.	30.9%-32.0%
McMillan (2014)	Sleep Apnoea	Lancet-RM	SF-36	278	3,12 mos.	11.9%-16.9%
Middelton (2011)	Stroke	Lancet	SF-36	1126	90 days	10.4%
Pareyson (2011)	Charcot-Marie-Tooth Disease	Lancet-N	SF-36	277	24 mos.	20.2%
Patel (2016)	Depression	Lancet	PHQ-9	495	3 mos.	5.9%
Richards (2016)	Depression	Lancet	PHQ-9	440	6, 12, 18 mos.	13.6% - 19.1%
Sharpe (2015)	Chronic Fatigue Syndrome	Lancet-P	SF-36	481	12,24,52,134 wks.	25.0%-26.1%
Salisbury (2016)	Depression	Lancet-P	PHQ-9	609	4,8,12 mos.	13.8%-15.4%
Wardlaw (2009)	Vertebral Fracture	Lancet	SF-36	300	1,3,6,12 mos.	13.0%-25.0%
White (2011)	Chronic Fatigue Syndrome	Lancet	SF-36	641	12, 24, 52 wks.	4.4%-5.6%
Wilkins (2015)	Localized Prostate Cancer	Lancet-O	SF-36	2100	24 mos.	31.2%
Witt (2008)	Parkinson's	Lancet-N	SF-36	156	6 mos.	21.2%
Ahimastos (2013)	Peripheral Artery Disease	JAMA	SF-36	212	6 mos.	5.7%
Bekelman (2015)	Heart Failure	JAMA-IM	KCCQ	392	3,6,12 mos.	10.2%-15.6%
Berk (2013)	Familial Amyloid Polyneuropathy	JAMA	SF-36	130	1,2 yrs.	32.3%-47.7%
Chibanda (2016)	Mental Disorders	JAMA	PHQ-9	573	6 mos.	9.1%
Curtis (2013)	Quality of Communication	JAMA	SF-12	472	10 mos.	58.9%
Dixon (2012)	Obstructive Sleep Apnea	JAMA	SF-36	60	2 yrs.	13.3%
Dobscha (2009)	Musculoskeletal Pain	JAMA	PHQ-9	401	3,6,12 mos.	3.0%-9.7%
Emmelot-Vonk (2008)	Low Testosterone	JAMA	SF-36	237	3,6 mos.	5.1%-12.7%
Engel (2016)	PTSD/Depression	JAMA-IM	SF-12	660	3,6,12 mos.	6.4%-12.1%
Fakhry (2015)	Intermittent Claudication	JAMA	SF-36	212	12 mos.	8.0%
Flynn (2009)	Heart Failure	JAMA	KCCQ	2331	3,6,9,12,24,36 mos.	12.6%-75.4%

Continued on next page

Table 3 – *Continued from previous page*

Study	Indication	Journal	Endpoint	n	Follow-Up	Missing Data (%)
Frank (2016)	Huntington Disease	JAMA	SF-36	90	12 wks.	<10%
Goldberg (2015)	Acute Sciatica	JAMA	SF-36	269	3,52 wks.	0.7%-13.0%
Halperin (2014)	Diabetes	JAMA-S	SF-36	43	1 yr.	11.6%
Hare (2012)	Ischemic Cardiomyopathy	JAMA	MLHFQ	31	3,6,12 mos.	9.7%-22.6%
Huffman (2014)	Depression/Anxiety	JAMA-IM	SF-12	183	24 wks.	6.0%
Kitzman (2016)	Heart Failure	JAMA	MLHFQ	100	20 wks.	8.0%
Klevens (2012)	Intimate Partner Violence	JAMA	SF-12	2700	1 yr.	12.4%
Kravitz (2013)	Depression	JAMA	SF-12	603	12 wks.	22.6%
Kroenke (2009)	Pain and Depression	JAMA	SF-36	250	1,3,6,12 mos.	4.0%-18.0%
Kroenke (2010)	Depression	JAMA	SF-36	405	1,3,6,12 mos.	12.6%-33.6%
Lautenschlager (2008)	Alzheimer's Disease	JAMA	SF-36	170	18 mos.	21.8%
LeBlanc (2015)	Depression	JAMA-IM	PHQ-9	301	3,6 mos.	60.8%-62.5%
Lenze (2009)	Anxiety	JAMA	SF-36	177	12 wks.	22.6%
Marklund (2015)	Sleep	JAMA-IM	SF-36	96	4 mos.	5.2%
Martin (2016)	Weight Loss	JAMA-IM	SF-36	220	12, 24 mos.	9.1%-13.6%
McDermott (2009)	Peripheral Artery Disease	JAMA	SF-36	156	6 mos.	19.2%
McDermott (2013)	Peripheral Artery Disease	JAMA	SF-36	194	6 mos.	8.2%
McFall (2010)	PTSD	JAMA	PHQ-9	943	3,6,9,12,15,18 mos.	12.4%-21.4%
Mohr (2012)	Depression	JAMA	PHQ-9	325	4,9, 14,18 wks.	9.2%-13.2%
Morey (2009)	Weight Control	JAMA	SF-36	641	12 mos.	12.9%
Poole (2013)	Peripheral Artery Disease	JAMA	SF-36	159	3,6 mos.	6.9%-18.2%
Rahman (2016)	Psychological Distress	JAMA	PHQ-9	346	3 mos.	12.4%
Richardson (2014)	Depression	JAMA	PHQ-9	101	6,12 mos.	18.8%-20.8%
Rollman (2009)	Depression	JAMA	SF-36	302	2,4,8 mos.	14.6%-16.6%
Stanley (2009)	Anxiety	JAMA	SF-12	134	3,6,9,12,15 mos.	14.2%-31.3%
Sullivan (2013)	Diabetes	JAMA-P	PHQ-9	2977	20,40 mos.	6.8%-11.1%
Tiwari (2010)	Initimate Partner Violence	JAMA	SF-12	200	3,9 mos.	0.0%
Wall (2014)	Intracranial Hypertension	JAMA-N	SF-36	165	6 mos.	23.6%
Walsh (2015)	Physical Rehabilitation	JAMA - IM	SF-12	240	3,6,12 mos.	17.9%-35.4%
Weisner (2016)	Addiction	JAMA-P	PHQ-9	503	6 mos.	9,.5%
Weiss (2015)	Diabetic Retinopathy Prevention	JAMA-O	PHQ-9	206	6 mos.	13.1%
Adamsen (2009)	Cancer	BMJ	SF-36	269	6 wks.	12.6%
Anguera (2016)	Depression	BMJ-I	PHQ-9	626	4,8,12 wks.	55.4%-69.8%
Arnold (2009)	Chest Pain	BMJ	SF-36	700	1 mo.	29.4%
Barnhoorn (2015)	Pain	BMJ-O	SF-36	56	3,6,9 mos.	3.6%-5.4%
Bruhn (2013)	Chronic Pain	BMJ-O	SF-12	196	6 mos.	33.7%-34.2%
Burton (2012)	Unexplained Symptoms	BMJ-O	PHQ-9	32	12 wks.	18.8%
Busse (2016)	Tibial Fractures	BMJ	SF-36	501	6,12,18,26,38,52 wks.	5.2% - 39.9%
Cartwright (2013)	Chronic Conditions	BMJ	SF-12	1573	4,12 mos.	37.3%-38.1%

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Study	Indication	Journal	Endpoint	n	Follow-Up	Missing Data (%)
Cohen (2009)	Trochanteric Pain	BMJ	SF-36	65	1,3 mos.	4.6%-46.2%
Coventry (2015)	Chronic Conditions	BMJ	PHQ-9	387	4 mos.	16.0%
Cuthbertson (2009)	Trauma	BMJ	SF-36	286	6,12 mos.	25.9%-34.6%
Dijk-De Vries (2015)	Diabetes Care	BMJ-O	264	SF-12	4,12 mos.	11.7%-15.5%
Dumville (2009)	Leg Ulcers	BMJ	SF-12	267	12 mos.	47.9%
El-Khoury (2015)	Fall Prevention	BMJ	SF-36	706	12,24 mos.	15.2%-19.5%
Fisher (2015)	Postpartum Mental Disorders	BMJ-O	400	SF-36	26 wks.	9.0%
Frobell (2013)	ACL Injury	BMJ	SF-36	121	5 yrs.	0.8%
Gilbody (2015)	Depression	BMJ	PHQ-9	691	4,12,24 mos.	23.9%-33.3%
Grande (2015)	Care Giving	BMJ S & PC	SF-12	681	4.5 mos.	1.8%
Griffin (2014)	Fractures	BMJ	SF-36	151	2 yrs.	23.2%
Hellum (2011)	Back Pain	BMJ	SF-36	179	1.5,3,6,12,24 mos.	7.8%-22.3%
Holzel (2016)	Depression/Back Pain	BMJ-O	PHQ-9	435	2 mos.	33.8%
Jenkinson (2009)	Knee Pain	BMJ	SF-36	389	24 mos.	18.8%
Khalafallah (2012)	Pregnancy	BMJ-O	SF-36	196	4 wks.	35.7%
Koek (2009)	Psoriasis	BMJ	SF-36	196	End of Therapy	6.1%
Lawton (2008)	Inactive Women	BMJ	SF-36	1089	12,24 mos.	7.4%-10.6%
Ly (2014)	Depression	BMJ-O	PHQ-9	81	2,6 mos.	11.1%-14.8%
Mansikkamaki (2015)	Menopause	BMJ-O	SF-36	176	0.5, 2.5, 4 yrs.	15.3% - 46.0%
McClellan (2012)	Soft Tissue Injury	BMJ-O	SF-12	372	2,8 wks.	40.1%-42.7%
Mordin (2014)	Cervical Dystonia	BMJ-O	SF-36	116	8 wks.	28.4%
Morrell (2009)	Postnatal Depression	BMJ	SF-12	4084	1.5,6,12 mos.	36.2%-58.9%
Murphy (2009)	Heart Disease	BMJ	SF-12	903	18 mos.	28.1%
Oerkild (2012)	Coronary Heart Disease	BMJ-O	SF-12	40	3,6,12 mos.	5.0%-10.0%
Patel (2009)	Osteoarthritis	BMJ	SF-36	812	4,12 mos.	38.2%-40.5%
Richards (2013)	Depression	BMJ	PHQ-9	581	4,12 mos.	13.7%-14.7%
Simkiss (2013)	Parenting Skills	BMJ-O	SF-12	286	9 mos.	19.2%
Walters (2013)	COPD	BMJ-O	SF-36	182	6,12 mos.	13.7%-15.4%
Williams (2009)	Gastrointestinal Endoscopy	BMJ	SF-36	1888	1, 30, 365 days	23.3%-32.7%
Adler (2013)	Depression	PLoS	SF-12	44	6 wks.	15.9%
Andreeva (2014)	Cardiovascular Disease	PLoS	SF-36	2501	3 yrs.	21.0%
Benda (2015)	Heart Failure	PLoS	SF-36	24	12 wks.	29.2%
Bergmann (2014)	Ischemic Heart Disease	PLoS	SF-36	213	3 mos.	15.0%
Conboy (2016)	Gulf War Illness	PLoS	SF-36	104	2,4,6 mos.	13.6% - 19.4%
Cooley (2009)	Anxiety	PLoS	SF-36	87	12 wks.	17.2%
Favrat (2014)	Iron Deficiency	PLoS	SF-12	294	56 days	3.7%
Francois (2015)	Alcohol Dependence	PLoS	SF-36	667	12,24 wks.	18.6%-39.7%
Gavi (2014)	Fibromyalgia	PLoS	SF-36	80	16 wks.	17.5%
Gine-Garriga (2013)	Chronic Conditions	PLoS	SF-12	362	3,6,12 mos.	12.7%-16.0%

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Study	**Indication**	**Journal**	**Endpoint**	n	**Follow-Up**	**Missing Data (%)**
Glozier (2013)	Depression, Cardiovascular Disease	PLoS	PHQ-9	562	12 wks.	4.3%
Hsu (2015)	Frozen Shoulder	PLoS	SF-36	72	6 mos.	8.3%
Kenealy (2015)	Chronic Conditions	PLoS	SF-36	171	6 mos.	11.7%
Kim (2014)	Chronic Knee Osteoarthritis	PLoS	SF-36	212	5 wks.	8.5%
Kogure (2015)	Back Pain	PLoS	SF-36	186	6 mos.	3.8%
Lambert (2016)	Leprosy	PLoS - NTD	SF-36	73	28 wks.	20.5%
Lau (2015)	Metabolic Syndrome	PLoS	SF-36	173	12 wks.	11.0%
MacPherson (2013)	Depression/Co-Morbid Pain	PLoS-M	PHQ-9	755	3,6,9,12 mos.	18.7%-24.6%
Lei (2016)	Parkinson's Disease	PLoS	SF-12	15	3 wks.	0.0%
Mead (2011)	Stroke	PLoS	SF-36	1400	64 wks.	22.9%
Merom (2016)	Falls	PLoS	SF-12	530	12 mos.	21.9%
Miyagawa (2013)	Narcolepsy	PLoS	SF-36	30	16 wks.	6.7%
Mohr (2013)	Depression	PLoS	PHQ-9	102	12 wks.	13.7%
Morgan (2013)	Depression	PLoS	PHQ-9	1736	3,6 wks.	55.5%-66.9%
Musiat (2014)	Mental Health	PLoS	PHQ-9	1047	6,12 wks.	50.3%-61.7%
Nagayama (2016)	Aging	PLoS	SF-36	54	4 mos.	18.5%
Ramly (2014)	Vitamin D Deficiency	PLoS	SF-36	192	6,12 mos.	6.8%-10.9%
Small (2014)	Postpartum Health	PLoS	SF-36	18424	2 yrs.	62.9%
Strayer (2012)	Chronic Fatigue	PLoS	SF-36	234	40 wks.	17.1%
Stuby (2015)	Distal Radius Fracture	PLoS	SF-36	29	3 mos.	0.0%
Therkelsen (2016)	Ulcerative Colitis	PLoS	SF-36	62	3 wks.	19.4%
Therkelsen (2016)	Crohn's Disease	PLoS	SF-36	76	3 wks.	34.2%
Titov (2010)	Depression	PLoS	PHQ-9	141	Post Tx., 4 mos.	17.0%-29.2%
Titov (2013)	Depression	PLoS	PHQ-9	274	3 mos.	40.1%
Titov (2014)	Depression	PLoS	PHQ-9	274	12 mos.	42.7%
van Gemert (2015)	Weight Control	PLoS	SF-36	243	4 mos.	11.1%
Younge (2015)	Heart Disease	PLoS	SF-36	324	3 mos.	20.1%
Zonneveld (2012)	Unexplained Symptoms	PLoS	SF-36	162	3 mos, 3,12 mos Post Tx.	17.9%-47.3%

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Appendix A: Influence Function

Let

$$\pi^*(y_0, y_1, y_2; \alpha) = [(1 + \exp\{l_1^*(y_0; \alpha) + \alpha r(y_1)\})(1 + \exp\{l_2^*(y_1; \alpha) + \alpha r(y_2)\})]^{-1}$$
$$w_1^*(y_0; \alpha) = E^* \left[\exp\{\alpha r(Y_1)\} \mid R_1 = 1, Y_0 = y_0\right],$$
$$w_2^*(y_1; \alpha) = E^* \left[\exp\{\alpha r(Y_2)\} \mid R_2 = 1, Y_1 = y_1\right],$$
$$g_1^*(y_0, y_1; \alpha) = \{1 - H_1^*(y_0)\} w_1^*(y_0; \alpha) + \exp\{\alpha r(y_1)\} H_1^*(y_0).$$
$$g_2^*(y_1, y_2; \alpha) = \{1 - H_2^*(y_1)\} w_2^*(y_1; \alpha) + \exp\{\alpha r(y_2)\} H_2^*(y_1).$$

Using semiparametric theory (Tsiatis, 2006), the efficient influence function in model $\mathcal{M}$ can be computed as:

$$\begin{aligned}\psi_{P^*}(O; \alpha) \quad := \quad & a_0^*(Y_0; \alpha) + R_1 b_1^*(Y_0, Y_1; \alpha) + R_2 b_2^*(Y_1, Y_2; \alpha) + \\ & \{1 - R_1 - H_1^*(Y_0)\} c_1^*(Y_0; \alpha) + R_1 \{1 - R_2 - H_2^*(Y_1)\} c_2^*(Y_1; \alpha)\end{aligned}$$

where

$$\begin{aligned}
a_0^*(Y_0) &= E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \,\middle|\, Y_0 \right] - \mu(P^*; \alpha) \\
b_1^*(Y_0, Y_1; \alpha) &= E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \,\middle|\, R_1 = 1, Y_1, Y_0 \right] - E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \,\middle|\, R_1 = 1, Y_0 \right] \\
&\quad + E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{\exp\{\alpha r(Y_1)\}}{g_1^*(Y_0, Y_1; \alpha)} \right] \,\middle|\, R_1 = 1, Y_0 \right] H_1^*(Y_0) \left\{ 1 - \frac{\exp\{\alpha r(Y_1)\}}{w_1^*(Y_0; \alpha)} \right\} \\
b_2^*(Y_1, Y_2; \alpha) &= E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \,\middle|\, R_2 = 1, Y_2, Y_1 \right] - E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \,\middle|\, R_2 = 1, Y_1 \right] \\
&\quad + E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{\exp\{\alpha r(Y_2)\}}{g_2^*(Y_1, Y_2; \alpha)} \right] \,\middle|\, R_2 = 1, Y_1 \right] H_2^*(Y_1) \left\{ 1 - \frac{\exp\{\alpha r(Y_2)\}}{w_2^*(Y_1; \alpha)} \right\} \\
c_1^*(Y_0) &= E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{\exp\{\alpha r(Y_1)\}}{g_1^*(Y_0, Y_1; \alpha)} \right] \,\middle|\, Y_0 \right] \\
&\quad - E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{1}{g_1^*(Y_0, Y_1; \alpha)} \right] \,\middle|\, Y_0 \right] w_1^*(Y_0; \alpha) \\
c_2^*(Y_1) &= E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{\exp\{\alpha r(Y_2)\}}{g_2^*(Y_1, Y_2; \alpha)} \right] \,\middle|\, R_1 = 1, Y_1 \right] \\
&\quad - E^* \left[\frac{R_2 Y_2}{\pi^*(Y_0, Y_1, Y_2; \alpha)} \left[\frac{1}{g_2^*(Y_1, Y_2; \alpha)} \right] \,\middle|\, R_1 = 1, Y_1 \right] w_2^*(Y_1; \alpha)
\end{aligned}$$