

## Monthly Program Status Report – PROJECT

<b>Reporting Period:</b>	April 2014
<b>Contracting Agency:</b>	Food and Drug Administration (FDA)
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<b>Contract / Order:</b>	HHSF223201310230C
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<b>Project Team:</b>	Aidan McDermott (Computer Programmer)
<b>Description of Activity:</b>	A recent FDA-sponsored National Research Council Report recommended that "examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting." While the Report outlines a framework for conducting sensitivity analysis, there are two major problems with existing methods: (1) they have not been implemented in software packages and (2) they do not adequately address non-monotone missing data patterns (i.e., patients provide data irregularly). The objective of this project is to address these gaps by: 1) creating unified and coherent methods for global sensitivity analysis of clinical trials with monotone and non-monotone missing data, 2) developing free, open source and reproducible software in SAS and R to implement the methods, and 3) demonstrating the methods and software using real clinical trial data.

Project Health Check						
Health ▶	Budget	Schedule	Resources	Deliverables		
Notes ▶	Within Budget	On Schedule	Adequate	On Target		

Budget Tracking – (TOTAL CONTRACT CEILING)							
POP	Ceiling Remaining	Cumulative Funding	Year Funding (Year 1)	Spent to Date	Year Funding Remaining	Month Invoice	Funding Covers
Base	\$1,094,565	\$1,094,565	\$1,094,565	\$166,558.97 (*\$145,645.22 committed)	\$782,360.81	\$127,201.33	Salary, fringe, other expenses, and indirect costs

Activity Summary and Highlights
Over the last month, we have tested code for flexible sensitivity analysis methodology for monotone missing data. We continued to address the issue of under-coverage of standard confidence intervals. We identified an issue of bias of our estimation procedure in small sample sizes, which disappears as the sample size grows. We implemented a bootstrap bias correction procedure that removes a substantial amount of bias. While this bias reduction procedure improves the coverage properties of standard confidence intervals, we continue to see under-coverage. We are currently experimenting with other confidence interval procedures to correct this problem. Hall's percentile bootstrap indicates coverage closer to the nominal level.

Our article entitled “Global Sensitivity Analysis of Repeated Measures Studies with Informative Dropout: A Fully Parametric Approach” received a favorable review at *Statistics in Biopharmaceutical Research*.

An editorial we were asked to write entitled: “Prospective EHR-Based Clinical Trials: The Challenge of Missing Data” will appear in the *Journal of General Internal Medicine*.

Key Accomplishments	
Current Reporting Period	Planned for Next Period
<ul style="list-style-type: none"> <li>• Tested code for flexible sensitivity analysis methodology for monotone missing data.</li> <li>• Worked on bias of estimation procedure and under-coverage of confidence intervals.</li> <li>• Received favorable review of our <i>Statistics in Biopharmaceutical Research</i> article about sensitivity analysis.</li> <li>• An editorial we wrote about the challenge of missing data in prospective EHR-based clinical trials will appear in <i>Journal of General Internal Medicine</i>.</li> </ul>	<ul style="list-style-type: none"> <li>• Solve the confidence interval issue.</li> <li>• Initiate the Forum option on Website</li> <li>• Expand membership on Website</li> <li>• Post C code for flexible sensitivity analysis methodology for monotone missing data</li> </ul>

Issues and Risks					
Category	Priority	Status	Opened	Issue	Description
Contract (FDA)	1	Open	9/30/13	Intellectual Property	Revision to contract regarding intellectual property language.
Dissemination (FDA)	2	Closed	2/15/14	Website	FDA Personnel cannot connect to <a href="http://www.missingdatamatters.org">www.missingdatamatters.org</a> from their office computers.
Software (JHU)	1	Open	3/15/14	Coverage of Confidence Intervals	Simulations indicate that standard procedures for constructing confidence intervals are not providing adequate coverage with typical sample sizes.
Computing (JHU)	1	Open	4/21/14	Periods of slow performance of computing cluster	A new computing cluster was installed at Johns Hopkins. We are experiencing periods of slow performance on the cluster.

Other Activities
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<b>Attachments and References</b>
<ul style="list-style-type: none"><li>• Simulation Results Table</li><li>• <i>Journal of General Internal Medicine</i> Editorial</li></ul>