Global Sensitivity Analysis for Randomized Trials with Competing Causes of Drop-out

Daniel O. Scharfstein

Department of Biostatistics

Johns Hopkins Bloomberg School of Public Health

May 31, 2007

Collaborators

Johns Hopkins

- Aristide Achy-Brou
- Weiwei Wang
- Aidan McDermott

Ortho-McNeil

- Bill Olson
- Joe Houlihan
- Frank Wiegand
- Steve Ascher

Problem

- Premature patient withdrawal (i.e., dropout) is a widespread problem in randomized clinical trials.
- Common reasons for dropout include lack of efficacy, adverse events, loss to follow-up, death, withdrawal of consent, and uncooperativeness.
- The resulting missing data in these trials complicates the evaluation of treatment effects.

Longitudinal Studies

- In longitudinal studies with assessments scheduled at fixed points in time after randomization, the target of inference is often a contrast between the treatment-specific means of outcomes at the final assesment time, in a counterfactual world where there is no premature patient withdrawal.
- Consistent estimation of this estimand requires non-parametrically *untestable* assumptions about how the drop-out mechanism relates to unobserable outcomes.

Assumptions

- Missing at random (MAR) assumption says that the hazard of dropout (for any reason) at vist t is unrelated to outcomes scheduled to be measured after $t-1$, conditional on observed outcomes (and possibly auxiliary factors) measured through $t-1$.
- Informative drop-out or missing not at random (MNAR) occurs when MAR fails. There will typically be a very large collection of plausible MNAR assumptions.
- Inferences about the estimand of interest may vary substantively across models.

Sensitivity Analysis

- It is natural to report the results of studies with potentially informative missing data in the form of a sensitivity analysis.
- FDA provides general guidance that "the sensitivity of the overall conclusions to various limitations of the data, *assumptions*, and analytic approaches to data analysis" should be reported.

Global Sensitivity Analysis

- Leamer (1985) defines a "global" sensitivity analysis strategy as one "in which a neighborhood of alternative assumptions is selected and the corresponding interval of inferences is identified."
- He considers conclusions to be sturdy "only if the neighborhood of assumptions is wide enough to be credible and the corresponding interval of inferences is narrow enough to be useful" and fragile "when an incredibly narrow set of assumptions is required to produce a usefully narrow set of conclusions."
- "Useful" is taken to mean clinically and statistically meaningful treatment effects.

Cornerstone

- Little and Rubin (1987), Rotnitzky *et al.* (1998), Molenberghs *et al.* (2004) have argued that a plausible MAR assumption should be the cornerstone of such a neighorbhood.
- The plausibility of the MAR assumption and the credibility of the neighborhood is necessarily a *subjective* assessement based on subject matter considerations.
- It is important to consider all the key factors scheduled to measured through time $t-1$ that make the decision to dropout due to a specific cause by those still on-study at that time, a random process, with cause-specific probabilities depending soley on these factors.

Neighborhood

- To define the neighborhood, it is useful to define a class of assumptions that are indexed by non-parametrically non-identified parameters that express deviations from the cornerstone assumption and for which a unique value of the parameters is equivalent to MAR.
- Subject matter experts can then constrain the set of parameters to a neighborhood.
- In practice, the parameterization of the class of assumptions should be continuous and high-dimensional enough to be credible, but low-dimensional enough to (1) facilitate expert evaluation and (2) display of results.

Inference

- There are two main paradigms for inference in the presence of missing data, one parametric and likelihood-based and the other semi-parametric and estimating function-based.

	Pros	Cons
Parametric	Efficient	Not Robust
	Handles Int. Missingness	Comp. Intensive
	Software	SA More Complex
Sem-parametric	Less Efficient	More Robust
	Doesn't handle Int. Missingness	Less Comp. Intensive
	SA Less Complex	New Software

Outline

- Diabetic polyneuropathy studies
- Data and Notation
- Semi-parametric model
- Imputation of Intermittent Missing Data
- Data Analysis
- Discussion/Take-home Points

Diabetic Polyneuropathy Studies

- Peripheral neuropathy is a common complication of diabetes.
- Diabetic peripheral polyneuropathy is characterized by damage to small-diameter sensory fibers in distal areas of the peripheral nervous system.
- Manifested by painful tingling or burning sensations in the hands and feet.
- Pain can be so severe that it compromises day-to-day actitivities and quality of life.

Topiramate

- Approved medication for the treatment of epileptic seizures, which operates by dampening neuronal hyperexcitability in the central nervous system.
- Hypothesized that topiramate might also dampen the excitability of nerves in peripheral nervous system.
- 3 placebo-controlled randomized trials were conducted to evaluate the efficacy of different doses of topiramate in reducing pain in patients with diabetic peripheral polyneuropathy.
- Two these studies had nearly identical designs.

NP 001 and 002

- Baseline and double-blind phases.
- Eligibility determined during the baseline phase.
- Prior to randomization, subjects must have been tapered off all background medications being used to treat neuropathic pain.
- During the baseline phase, all subjects were to have their diabetes controlled on a stable regimen of oral hypoglycemics, insulin, or diet alone.
- The double-blind phase included 2 periods: a 10 week titration period and a 12 week maintenance period.

- The primary efficacy variable was the pain score measured on a 100-mm Visual Analog Scale (VAS), where higher levels of VAS indicate worse pain.
- VAS scores were scheduled on day 1 of the baseline phases, every two weeks during titration, and then monthly during the maintenance phase. (8 follow-up assessments)
- Treatment effects were based on the difference in the mean VAS scores at the final follow-up visit.
- Adverse events and use of rescue medications was also scheduled to be monitored throughout the double-blind phase.
- The trials were not designed to follow patients after they discontinued their assigned therapy.

Premature Withdrawal

	Placebo ($n = 255$)		100 mg/day ($n = 128$)		200 mg/day ($n = 246$)		400 mg/day ($n = 257$)	
Completed	145	57%	66	52%	114	46%	108	42%
Withdrawn	110	43%	62	48%	132	54%	149	58%
Adverse Event	24	9%	22	17%	67	27%	79	31%
Lack of Efficacy	55	22%	18	14%	31	13%	32	12%
Other	31	12%	22	18%	34	14%	38	15%

Central Question

What is the difference in the mean VAS scores at the end of the double blind phase between topiramate at a specified dose level vs. placebo in the counterfactual world in which there was no premature withdrawal?

Censoring Terminology

A subject is said to be

- uncensored at assessment t if she has not prematurely withdrawn at or prior to assessment t $(t = 1, \ldots, 8)$.
- censored due adverse events by assessement t if she withdrew due to adverse events at or prior to assessment t.
- censored due to lack of efficacy by assessment t is she withdrew due to lack efficacy at or prior to assessment t.
- censored due to other reasons by assessment t is she withdrew due to other reasons at or prior to assessment t.

Notation

Let

- $X = 0$ if the subject is assigned to placebo, 1 if assigned to 100 mg/day, 2 if assigned to 200 mg/day, and 3 if assigned 400 mg/day.
- Z be baseline covariates including age, gender, length of diabetes prior to study entry, duration of polyneuropathy prior to study entry, study membership (NP 001 vs, NP 002), and region of care (US vs. Europe).
- V_t be the VAS score to be measured at assessment t.
- $Y = V_8$.

- $A_t = (RM_t, AE_t, P_t)$, where
  - RM_t is the percentage of days between assessment $t-1$ and t of rescue medication use
  - AE_t is the proportion of days between assessment $t-1$ and t on which an adverse event was experienced
  - P_t is the presence of parethesia between assessment $t-1$ and t all to be measured at assessment t

Notation

For $t = 1, \ldots, 8$, define

$$R_t = \begin{cases} 0 & \text{if subject is uncensored at assessment } t \\ 1 & \text{if subject is censored due adverse events by assessment } t \\ 2 & \text{if subject is censored due to lack of efficacy by assessment } t \\ 3 & \text{if subject is censored due to other reasons by assessment } t \end{cases}$$

Let

- $R_0 = 0$
- $C = 9$ if $R_8 = 0$ and $C = \min\{t : R_t \neq 0\}$, otherwise

Data

- V_t can be missing for some $1 \leq t \leq C-1$.
- Let M_t be the indicator of missing VAS score at assesement t, for $t = 1, \ldots, C-1$.
- Let

$$\begin{aligned} \overline{V}_t &= (V_0, \ldots, V_{t-1}) \\ \overline{A}_t &= (A_1, \ldots, A_{t-1}) \\ \overline{R}_t &= (R_1, ..., R_{t-1}) \\ \overline{M}_t &= (M_1, \ldots, M_{t-1}) \end{aligned}$$

- Let $\bar{V}_C = (\bar{V}_{C,obs}, \bar{V}_{C,mis})$

- Let

$$
\begin{aligned}
F &= (X, Z, \bar{R}_9, \overline{M}_C, \overline{A}_9, \overline{V}_9) \\
O &= (X, Z, \bar{R}_9, \overline{M}_C, \overline{A}_C, \overline{V}_C) \\
O^{\dagger} &= (X, Z, \bar{R}_9, \overline{A}_C, \overline{M}_C, \overline{V}_{C,obs})
\end{aligned}
$$

Parameters of Interest

Let $\mu_x = E[Y|X = x]$. The goal is to use the observed data to draw inference about μ_x and

$$\Delta_x = \mu_x - \mu_0$$

for $x = 1, 2, 3$.

Strategy

1. Develop a procedure for drawing inference about μ_x if data O were observed on all subjects.

2. Develop an imputation procedure for "filling in" missing VAS scores prior to drop-out.

3. Put 1 and 2 together using Rubin's combining rules.

Identification of μ_x from F_O

$$\mu_x = E[Y|R_8 = 0, X = x]P[R_8 = 0|X = x] + \sum_{t=1}^{8}\sum_{j=1}^{3} E[Y|R_t - R_{t-1} = j, X = x]P[R_t - R_{t-1} = j|x = x]$$

$$f(y|R_t - R_{t-1} = j, X = x)$$

$$= \int \dots \int f(y|R_t - R_{t-1} = j, \overline{V}_t = \overline{v}_t, \overline{A}_t = \overline{a}_t, Z = z, X = x)$$

$$dF(\overline{v}_t, \overline{a}_t, z|R_t - R_{t-1} = j, X = x)$$

Assumption 1

- The decision to drop-out at time t due to cause j does not depend on the distal outcome Y, conditional on $\overline{V}_{t+1}$,$\overline{A}_t$, Z, $X = x$ and $R_{t-1} = 0$
- Clinicians have difficulty imagining and quantifying how a distal outcome would influence the decision to drop-out after controlling for the past factors and the outcome to be measured at time t.

Assumption 2 (Pattern-Mixture)

$$
\begin{aligned}
&f(v_t|R_t - R_{t-1} = j, \overline{V}_t, \overline{A}_t, Z, X = x) \\
&= \frac{f(v_t|R_t = 0, \overline{V}_t, \overline{A}_t, Z, X = x) \exp\left(q_{t,j}^{(x)}(v_t, \overline{V}_t, \overline{A}_t, Z)\right)}{E\left[\exp\left(q_{t,j}^{(x)}(V_t, \overline{V}_t, \overline{A}_t, Z)\right)|R_t = 0, \overline{V}_t, \overline{A}_t, Z, X = x\right]}
\end{aligned}
$$

- $q_{t,j}^{(x)}(v_t, \overline{V}_t, \overline{A}_t, Z)$ is a specified function of v_t, $\overline{V}_t$, $\overline{A}_t$, Z, and x to be elicited from subject matter experts and varied in a sensitivity analysis (more later).
- Under Assumptions 1 and 2, $f(y|R_t - R_{t-1} = j, \overline{V}_t, \overline{A}_t, Z, X = x)$ is identified.
- Therefore, μ_x and Δ_x are identified.

Selection Equivalence

Assumptions 1 and 2 are equivalent to assuming:

$$\log \left\{ \frac{P[R_t = j | R_{t-1} = 0, Y, \overline{V}_{t+1}, \overline{A}_t, Z, X = x]}{P[R_t = 0 | R_{t-1} = 0, Y, \overline{V}_{t+1}, \overline{A}_t, Z, X = x]} \right\}$$
$$= h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z) + q_{t,j}^{(x)}(\overline{V}_{t+1}, \overline{A}_t, Z)$$

where

$$h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z) = \log \left\{ \frac{P[R_t = j | R_{t-1} = 0, \overline{V}_t, \overline{A}_t, Z, X = x]}{P[R_t = 0 | R_{t-1} = 0, \overline{V}_t, \overline{A}_t, Z, X = x]} \right\} -$$
$$\log \left\{ E \left[\exp \left(q_{t,j}^{(x)}(V_t, \overline{V}_t, \overline{A}_t, Z) \right) | R_t = 0, \overline{V}_t, \overline{A}_t, Z, X = x \right] \right\}$$

- If $q_{t,j}^{(x)}(v_t, \overline{V}_t, \overline{A}_t, Z)$ is constant in v_t, then MAR holds; otherwise MNAR holds.

Selection Identification Formula for μ_x

$$\mu_x = E\left[\frac{I(R_8 = 0)Y}{\prod_{t=1}^{8}\left(1 + \sum_{j=1}^{3}\exp\{h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z) + q_{t,j}^{(x)}(\overline{V}_{t+1}, \overline{A}_t, Z)\}\right)^{-1}} \,\middle|\, X = x \right]$$

Curse of Dimensionality

- While the parameters of interest are non-parametrically identified, their identification relies on high dimensional conditional distributions which cannotbe well estimated in moderate sized samples.
- In order to draw inference, it is necessary to impose additional restrictions.

- From a pattern-mixture perspective, one would need to model
  1. V_t given $R_t = 0$,$\overline{V}_t$, $\overline{A}_t$, Z and X
  2. R_t given $R_{t-1} = 0$, $\overline{V}_t$, $\overline{A}_t$, Z, and X
  3. Z given X
  4. A_t given $R_t = 0$, $\overline{V}_{t+1}$, $\overline{A}_t$, Z, and X
  5. A_t given $R_t - R_{t-1} = j$, $\overline{V}_t$, $\overline{A}_t$, Z, and X
- From a selection perspective, one would only need to model $h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z)$. This can be done *directly* or by modeling 1 and 2 above.
- From the selection perspective there is no need to model the auxiliary variables.

Selection Perspective

We will assume that

$$h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z) = h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta}^*)$$

where $h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta})$ is a specified function of its arguments and $\boldsymbol{\eta}$ is a unknown parameter with true value $\boldsymbol{\gamma}^*$.

In our analysis, we assumed that

$$
\begin{aligned}
h_{t,1}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta}^*) &= \eta_{0,t,1} + \eta_{1,1} I(x=1) + \eta_{2,1} I(x=2) + \eta_{3,1} I(x=3) + \\
&\quad \eta_{4,1} RM_{t-1} + \eta_{5,1} AE_{t-1} + \eta_{6,1}(V_{t-1} - V_0) + \eta_{7,1}(V_{t-1} - V_{t-2}) \\
h_{t,2}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta}^*) &= \eta_{0,t,2} + \eta_{1,2} I(x=1) + \eta_{2,2} I(x=2) + \eta_{3,2} I(x=3) + \\
&\quad \eta_{4,2} RM_{t-1} + \eta_{5,2} AE_{t-1} + \eta_{6,2}(V_{t-1} - V_0) + \\
&\quad \eta_{7,2}(V_{t-1} - V_{t-2}) + \eta_{8,2} AE_{t-1}(V_{t-1} - V_0) + \\
&\quad \eta_{9,2} AE_{t-1}(V_{t-1} - V_{t-2}) \\
h_{t,3}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta}^*) &= \eta_{0,t,3} + \eta_{1,3} I(x=1) + \eta_{2,3} I(x=2) + \eta_{3,3} I(x=3) + \\
&\quad \eta_{4,3} RM_{t-1} + \eta_{5,3} AE_{t-1} + \eta_{6,3}(V_{t-1} - V_0) + \eta_{7,3}(V_{t-1} - V_{t-2})
\end{aligned}
$$

Parameterization of the Selection Bias Function, $q_{t,j}^{(x)}$

- It is not possible to explore the effect of all functions $q_{t,j}^{(x)}$ on inferences
- It is useful to parameterize $q_{t,j}^{(x)}$ by an interpretable parameter $\tau_j^{(x)}$, where $\tau_1^{(x)} = \tau_2^{(x)} = \tau_3^{(x)} = 0$ implies MAR and otherwise MNAR, for treatment group x.

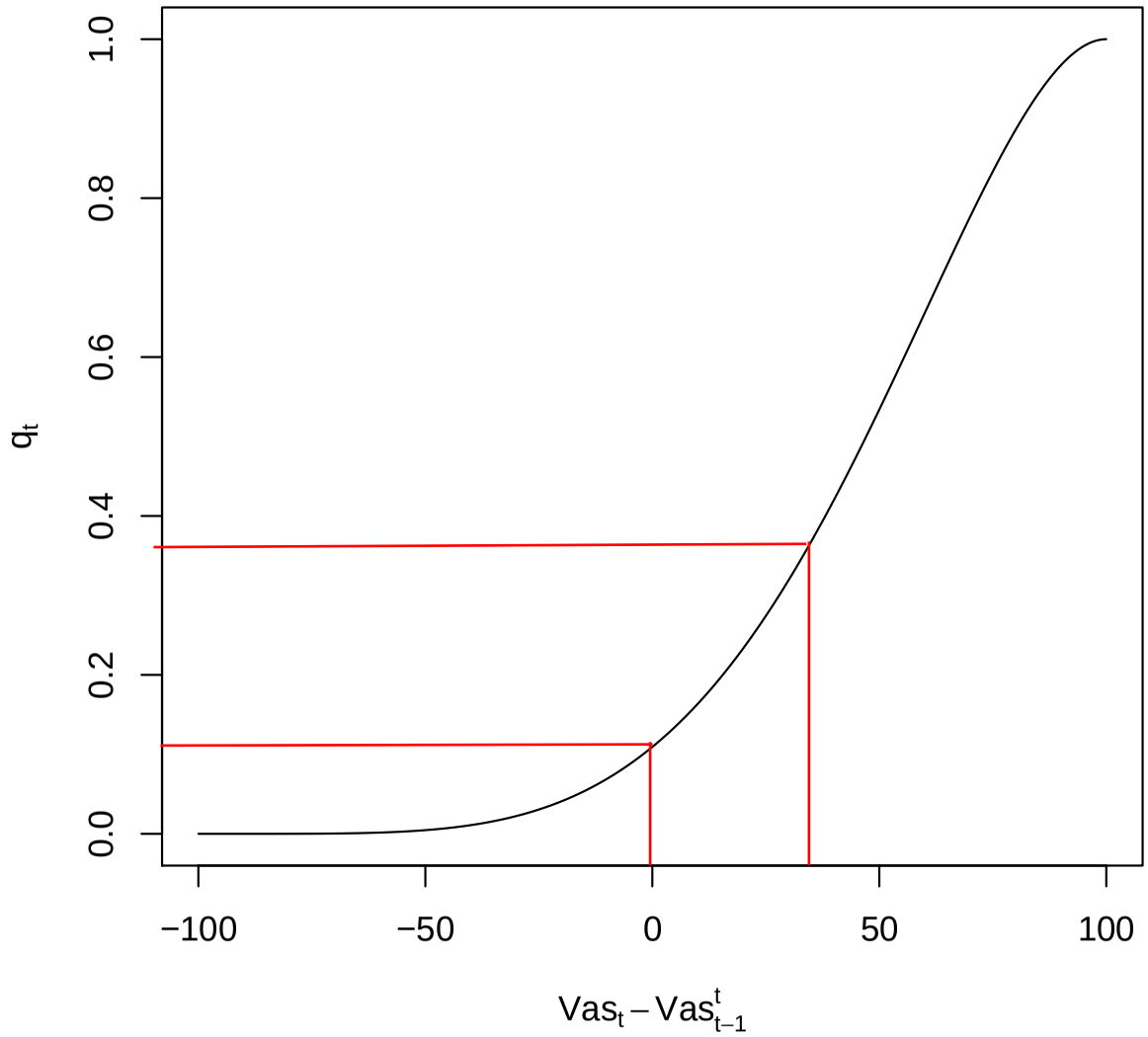
In our analysis, we assume that

- $q_{t,1}^{(x)} = 0$ (AE)
- $q_{t,3}^{(x)}$ (Other reasons)
-

$$q_{t,2}^{(x)}(\overline{V}_{t+1}, \overline{A}_t, Z) = \tau_2^{(x)} q(\{V_t - V_{t-1}^t\}/200 + 1/2)$$

where

$$V_{t-1}^t = \min(\max(2V_{t-1} - V_{t-2}, 0), 100)$$


1.0
0.8
0.6
0.4
0.2
0.0
q_t
−100
−50
0
50
100
$Vas_t - Vas_{t-1}^t$

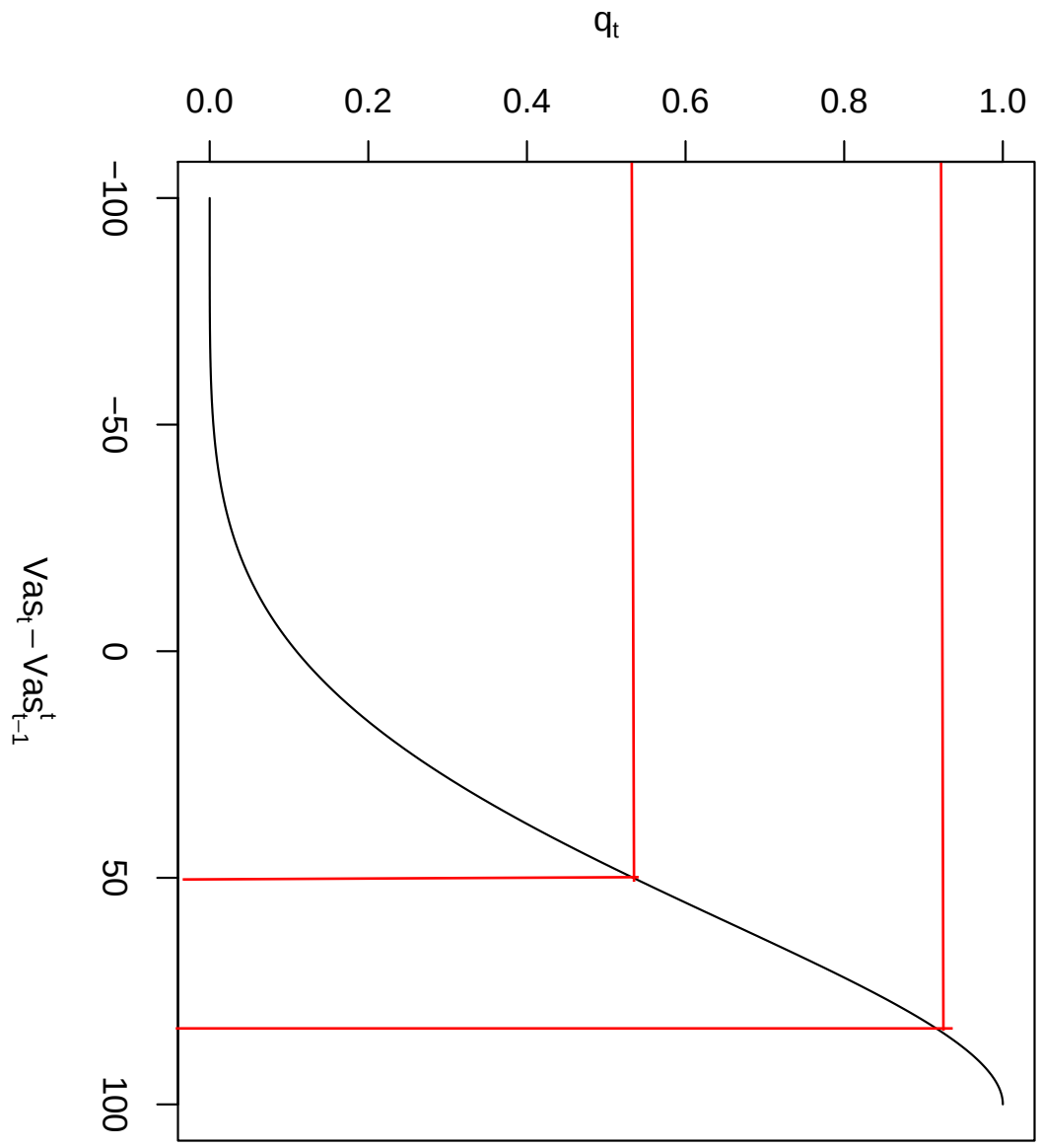
Interpretation $\tau_2^{(x)}$

Consider two people who are on-study at time $t-1$ and have the same exact covariate history through time $t-1$.

- Person 1: Difference of 30 between actual VAS and projected.
- Person 0: No difference between actual and projected

$\tau_2^{(x)} = 0.2$ is the difference between the log relative risk of dropping out due to lack of efficacy vs. remaining on study, for Person 1 vs. Person 0.

- If $\tau_2^{(x)} = 0$, no difference (MAR)
- If $\tau_2^{(x)} = 1$, then $\exp(0.2) = 1.22$ ratio of relative risks.
- If $\tau_2^{(x)} = 1.5$, then $\exp(1.5 * 0.2) = 1.35$ ratio of relative risks.


q_t
0.0
0.2
0.4
0.6
0.8
1.0
$Vas_t - Vas^t_{t-1}$
−100
−50
0
50
100

Interpretation $\tau_2^{(x)}$

Consider two people who are on-study at time $t-1$ and have the same exact covariate history through time $t-1$.

- Person 1: Difference of 80 between actual VAS and projected.
- Person 0: Difference of 50 between actual and projected

$\tau_2^{(x)} = 0.35$ represents the difference between the log relative risk of dropping out due to lack of efficacy vs. remaining on study for Person 1 vs. Person 0.

- If $\tau_2^{(x)} = 0$, no difference (MAR)
- If $\tau_2^{(x)} = 1$, then $\exp(0.35) = 1.42$ ratio of relative risks.
- If $\tau_2^{(x)} = 1.5$, then $\exp(1.5 * 0.35) = 1.69$ ratio of relative risks.

Estimation of η

Solve the estimating equation for $\widehat{\boldsymbol{\eta}}$

$$E_n[\sum_{t=1}^{8}\sum_{j=1}^{3}[I(R_t = j) - I(R_t = 0)\exp(h_{t,j}^{(X)}(\overline{V}_t, \overline{A}_t, Z; \boldsymbol{\eta}) + q_{t,j}^{(X)}(\overline{V}_{t+1}, \overline{A}_t, Z))]\phi_{t,j}^{(X)}(\overline{V}_t, \overline{A}_t, Z)] = 0$$

where $\phi_{t,j}^{(X)}(\overline{V}_t, \overline{A}_t, Z)$ is a function that has the same dimension as $\boldsymbol{\eta}$.

Estimation of μ_x

$$\widehat{\mu}_x = E_n \left[\frac{I(R_8 = 0)Y}{\prod_{t=1}^{8} \left(1 + \sum_{j=1}^{3} \exp\{h_{t,j}^{(x)}(\overline{V}_t, \overline{A}_t, Z; \widehat{\boldsymbol{\eta}}) + q_{t,j}^{(x)}(\overline{V}_{t+1}, \overline{A}_t, Z)\}\right)^{-1}} \,\middle|\, X = x \right]$$

- Standard errors found by stacking estimating equations and using sandwich variance formula.

Missing VAS Scores Prior to Drop-out

Assessment	Treatment	# On Study	# Missing	% Missing
1†	Placebo	255	67	26.3%
	100 mg/day	128	38	29.7%
	200 mg/day	246	65	26.4%
	400 mg/day	257	64	24.9%
2	Placebo	248	7	2.8%
	100 mg/day	114	5	4.4%
	200 mg/day	225	17	7.6%
	400 mg/day	227	15	6.6%
3†	Placebo	231	44	19.0%
	100 mg/day	103	23	22.3%
	200 mg/day	197	40	20.3%
	400 mg/day	202	43	21.3%
4	Placebo	221	19	8.6%
	100 mg/day	96	9	9.4%
	200 mg/day	176	14	8.0%
	400 mg/day	187	19	10.2%

Assessment	Treatment	# On Study	# Missing	% Missing
5	Placebo	208	7	3.4%
	100 mg/day	89	4	4.5%
	200 mg/day	157	4	2.5%
	400 mg/day	156	6	3.8%
6	Placebo	188	13	6.9%
	100 mg/day	81	9	11.1%
	200 mg/day	141	9	6.4%
	400 mg/day	137	6	4.4%
7	Placebo	170	8	4.7%
	100 mg/day	73	4	5.5%
	200 mg/day	128	5	3.9%
	400 mg/day	118	9	7.6%
8	Placebo	161	0	0.0%
	100 mg/day	70	2	2.9%
	200 mg/day	117	0	0.0%
	400 mg/day	112	2	1.8%

Imputation Models

- We need to specify a model for the distribution of missing VAS scores given the observed data. Specifically, we need to model

$$f(\overline{V}_{C,mis}|X, Z, \bar{R}_9, \overline{A}_C, \overline{M}_C, \overline{V}_{C,obs})$$

- Under the assumption of missing at random,this equals

$$f(\overline{V}_{C,mis}|X, Z, \bar{R}_9, \overline{A}_C, \overline{V}_{C,obs})$$

- For each visit t $(t < C)$, a model for

$$f(V_t|\overline{V}_t, X, Z, R_t = 0, R_{t+1}, \ldots, R_8, \overline{A}_t)$$

- In particular, we assume

$$f(V_t|\overline{V}_t, X, Z, R_t = 0, R_{t+1}, \ldots, R_8, \overline{A}_C) = f(V_t|V_{t-1}, X, R_t = 0, R_{t+1}, RM_t)$$

and the conditional distribution of $V_t/100$ given $V_{t-1}, X, R_t = 0, R_{t+1}, RM_t$ follows a Beta regression model with logit of the mean, for $1 \leq t \leq 8$,

$$\gamma_{0,t} + \gamma_{1,t} I(X = 1) + \gamma_{2,t} I(X = 2) + \gamma_{3,t} I(X = 3) + \gamma_{4,t} V_{t-1} + \gamma_{5,t} RM_t +$$
$$\gamma_{6,t} I(R_{t+1} = 1) + \gamma_{7,t} I(R_{t+1} = 2) + \gamma_{8,t} I(R_{t+1} = 3)$$

and for $t = 8$,

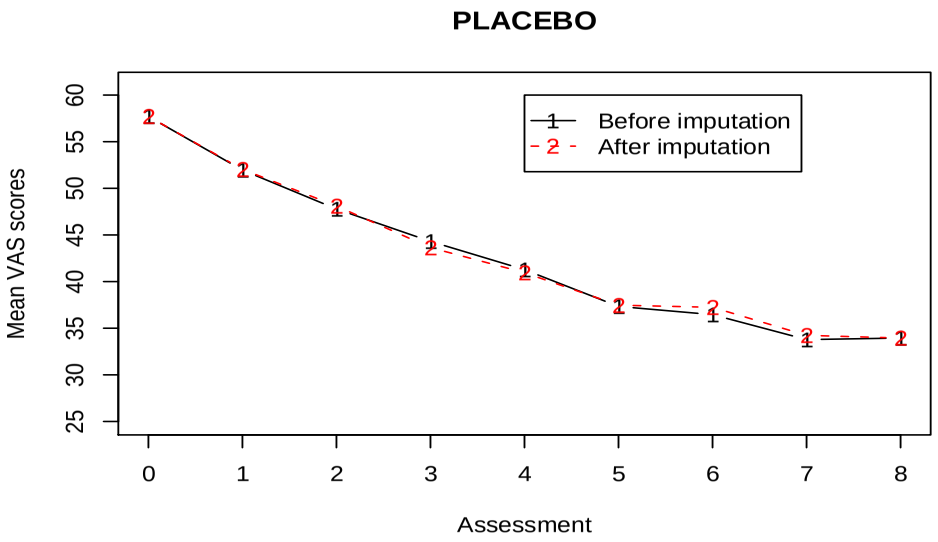
$$\gamma_{0,8} + \gamma_{1,8} I(X = 1) + \gamma_{2,8} I(X = 2) + \gamma_{3,8} I(X = 3) + \gamma_{4,8} V_7 + \gamma_{5,8} RM_8$$

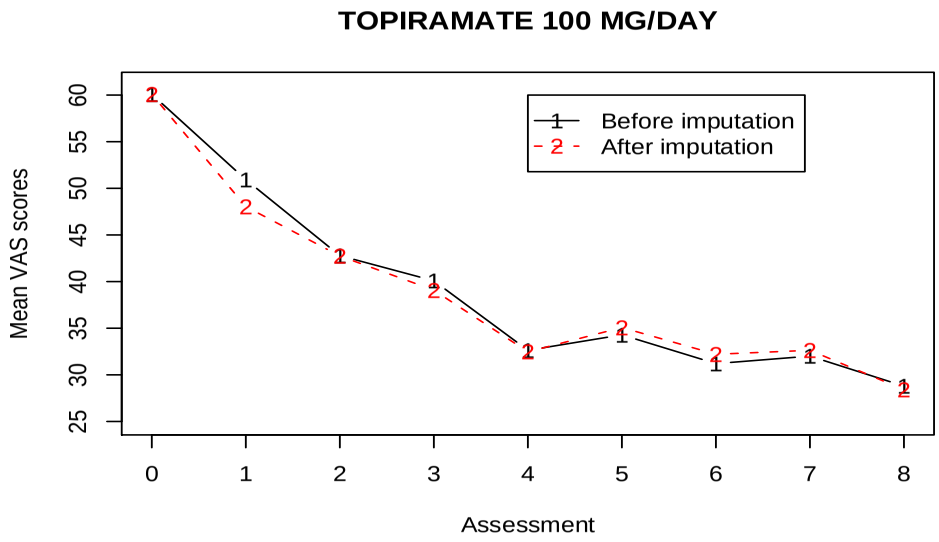
and visit-specific dispersion parameters $\gamma_{disp,t}$.

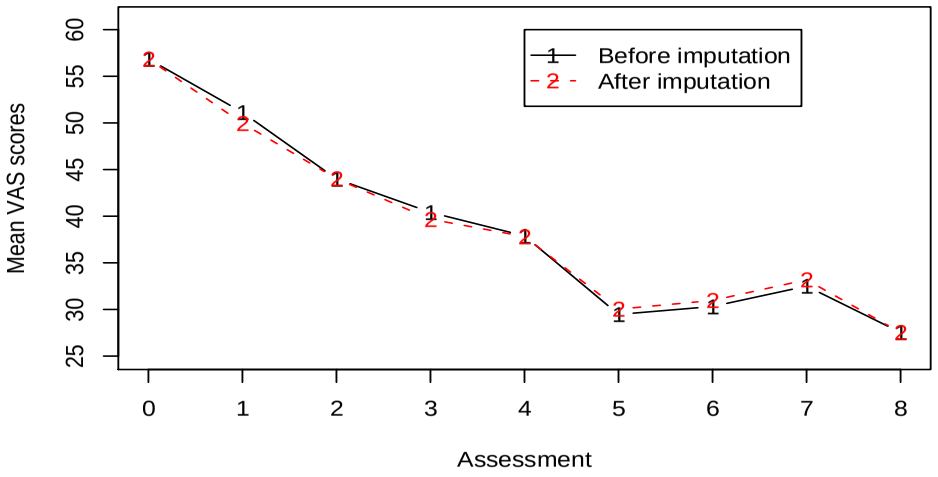
Imputation Algorithm

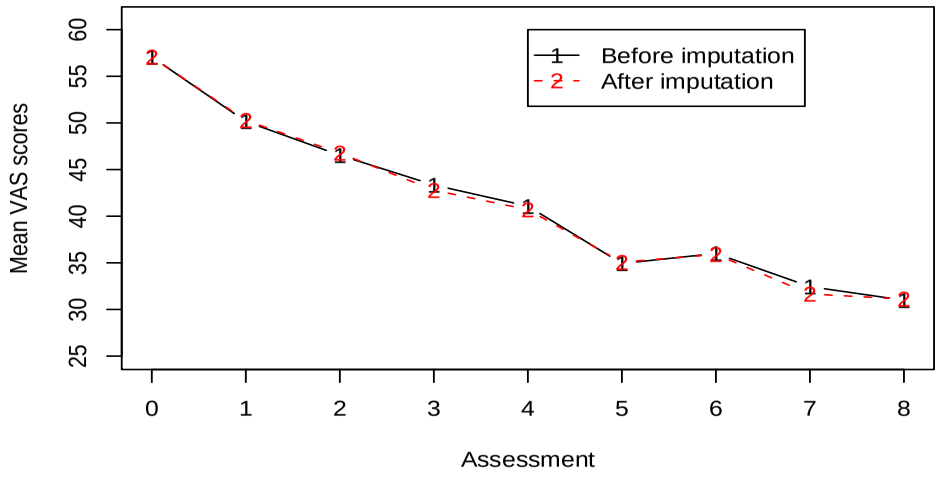
- Fully Bayesian MCMC to obtain posterior draws of the missing VAS scores.
- 5 complete datasets generated.

	1	2	3	4	5	6	7	8
$intercept$	-1.41 (-1.65, -1.15)	-1.51 (-1.72, -1.32)	-1.73 (-1.92, -1.54)	-1.86 (-2.07, -1.67)	-1.84 (-2.03, -1.64)	-2.07 (-2.27, -1.89)	-2.16 (-2.38, -1.95)	-2.05 (-2.24, -1.89)
$I(Z = 2)$	-0.15 (-0.36, 0.08)	-0.15 (-0.36, 0.05)	-0.12 (-0.35, 0.11)	-0.25 (-0.53, -0.03)	0.02 (-0.24, 0.27)	-0.20 (-0.44, 0.01)	0.05 (-0.20, 0.31)	-0.35 (-0.63, -0.03)
$I(Z = 3)$	-0.04 (-0.22, 0.17)	-0.15 (-0.31, 0.05)	-0.09 (-0.30, 0.13)	-0.07 (-0.27, 0.10)	-0.38 (-0.57, -0.20)	-0.16 (-0.36, 0.05)	0.10 (-0.11, 0.33)	-0.27 (-0.48, -0.05)
$I(Z = 4)$	-0.06 (-0.24, 0.12)	0.01 (-0.15, 0.17)	-0.06 (-0.24,0.12)	0.01 (-0.17, 0.17)	-0.17 (-0.35, 0.03)	0.01 (-0.18, 0.22)	-0.05 (-0.27, 0.19)	-0.10 (-0.32, 0.10)
V_{t-1}	2.39 (2.00, 2.73)	2.58 (2.28, 2.89)	2.93 (2.67, 3.18)	3.15 (2.80, 3.48)	3.13 (2.79, 3.47)	4.05 (3.70, 4.46)	3.82 (3.44, 4.19)	3.86 (3.53, 4.20)
RM_t	0.54 (0.31, 0.79)	0.17 (-0.09,0.47)	0.63 (0.31, 0.90)	0.40 (0.08, 0.71)	0.54 (0.15, 0.96)	0.07 (-0.36, 0.49)	0.86 (0.20, 1.47)	0.03 (-0.55, 0.61)
$I(R_{t+1} = 1)$	0.30 (-0.87, 1.48)	0.70 (0.31, 1.03)	0.36 (-0.13, 0.93)	0.31 (-0.05, 0.64)	0.24 (-0.13, 0.64)	0.37 (-0.06, 0.77)	0.31 (-0.24, 0.88)	-
$I(R_{t+1} = 2)$	-0.14 (-0.42, 0.12)	-0.14 (-0.52, 0.27)	0.07 (-0.25, 0.44)	0.03 (-0.32, 0.41)	0.05 (-0.38, 0.42)	0.53 (-0.17, 1.10)	-0.25 (-1.10, 0.52)	-
$I(R_{t+1} = 3)$	0.21 (-0.27, 0.70)	0.11 (-0.26, 0.50)	0.02 (-0.58, 0.74)	0.64 (0.18, 1.12)	0.81 (0.22, 1.40)	0.13 (-0.30, 0.54)	0.51 (-0.28, 1.36)	-
$\gamma_{disp,t}$	4.24 (3.83, 4.66)	3.86 (3.47, 4.30)	5.04 (4.48, 5.59)	4.36 (3.87, 4.88)	4.35 (3.83, 4.91)	5.23 (4.61, 5.91)	4.61 (3.99, 5.26)	5.05 (4.45, 5.72)


PLACEBO
Mean VAS scores
Assessment
Before imputation
After imputation


TOPIRAMATE 100 MG/DAY
Mean VAS scores
Assessment
Before imputation
After imputation


TOPIRAMATE 200 MG/DAY
Mean VAS scores
Assessment
Before imputation
After imputation


TOPIRAMATE 400 MG/DAY
Mean VAS scores
Assessment
Before imputation
After imputation

Results

	Completers	LOCF	MAR
Placebo	33.95	42.71	38.71
	(29.73,38.17)	(39.17,46.26)	(32.43,44.99)
100 mg/day	28.42	35.35	30.66
	(21.99,34.84)	(30.47,40.23)	(24.06,37.25)
200 mg/day	27.53	37.61	30.13
	(22.89,32.17)	(34.03,41.20)	(25.09,35.17)
400 mg/day	31.11	39.42	33.58
	(26.78,35.44)	(36.14,42.70)	(28.58,38.58)
100 vs. Placebo	-5.53	-7.36	-8.05
	(-13.22,2.15)	(-13.40,-1.33)	(-17.21,1.10)
200 vs. Placebo	-6.47	-5.10	-8.58
	(-12.69,-0.14)	(-10.14,-0.06)	(-16.75,-0.41)
400 vs. Placebo	-5.10	-3.29	-5.13
	(-8.88,3.21)	(-8.12,1.54)	(-13.29,3.03)

$\tau_2^{(x)}$	$\widehat{\mu}_1$	$\widehat{\mu}_2$	$\widehat{\mu}_3$	$\widehat{\mu}_4$
0.00	38.71	30.66	30.13	33.58
0.10	38.72	30.69	30.16	33.62
0.20	38.74	30.73	30.20	33.66
0.30	38.75	30.76	30.23	33.69
0.40	38.76	30.80	30.26	33.73
0.50	38.78	30.84	30.30	33.77
0.60	38.79	30.88	30.34	33.81
0.70	38.80	30.93	30.38	33.85
0.80	38.82	30.97	30.42	33.90
0.90	38.83	31.02	30.46	33.94
1.00	38.85	31.06	30.51	33.99
1.10	38.86	31.11	30.56	34.04
1.20	38.88	31.17	30.60	34.09
1.30	38.90	31.22	30.65	34.14
1.40	38.91	31.27	30.70	34.19
1.50	38.93	31.33	30.76	34.25
1.60	38.95	31.39	30.81	34.30
1.70	38.96	31.45	30.87	34.36
1.80	38.98	31.52	30.93	34.42

$\tau_2^{(x)}$	$\widehat{\Delta}_2$	$\widehat{\Delta}_3$	$\widehat{\Delta}_4$
0.00	-8.05	**-8.58**	-5,13
0.10	-8.03	**-8.56**	-5.11
0.20	-8.01	**-8.54**	-5.08
0.30	-7.99	**-8.52**	-5.06
0.40	-7.96	**-8.50**	-5.03
0.50	-7.93	**-8.47**	-5.00
0.60	-7.91	**-8.45**	-4.98
0.70	-7.88	**-8.42**	-4.95
0.80	-7.85	**-8.40**	-4.92
0.90	-7.82	**-8.37**	-4.89
1.00	-7.78	**-8.34**	-4.86
1.10	-7.75	**-8.31**	-4.82
1.20	-7.71	**-8.28**	-4.79
1.30	-7.68	**-8.24**	-4.75
1.40	-7.64	-8.21	-4.72
1.50	-7.60	-8.17	-4.68
1.60	-7.55	-8.13	-4.64
1.70	-7.51	-8.09	-4.60
1.80	-7.47	-8.05	-4.56

Discussion

- Molenberghs *et al.* (2004) argue that a likelihood-based analysis using fully parametric models for the longitudinal outcomes (e.g., generalized linear mixed models) under the assumption of missing at random should be the primary tool for analyzing clinical trials with drop-out.
- Their view appears to be gaining traction with the FDA and pharmaceutical companies.

Counterpoint

Why?

- It is rare to have accurate scientific knowledge about the joint distribution of the full data outcomes.
- There is often better information about the factors and reasons that affect drop-out.
- Extrapolates outside the support of the observed data
- Need to integrate to marginalize for non-linear models.
- Cannot incorporate information on auxilliary factors that can be prognostic for drop-out and outcomes, without further modeling.
- Sensitivity analysis is more difficult.

Sensitivity Analysis

- MAR is untestable.
- Federal guidelines advocate sensitivity analysis.
- Sensitivity analyses should be smooth and coherent, in the sense that analysts should evaluate increasing perturbations away from a cornerstone assumption.
- The space of pertubations is not fully explorable, so analysts, can at best, consider very low-dimensional perturbations.

Take Home Points

- Inference in the presence of missing data is necessarily subjective.
- Minimize missing data and follow patients after treatment discontinuation.
- All ideas here extend to time-to-event data with informative censoring.
- We have an internal software package to implement sensitivity analysis for longitudinal and survival data.
- In collaboration with the Johns Hopkins Biostatistics Consulting Center, we offer consulting to help in the design and analysis of randomized and observational studies.

Daniel Scharfstein

For more information, email me at

dscharf@jhsph.edu

or call me at

410-955-2420