Sensitivity analysis for randomised trials with missing outcome data

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15 September 2011
UK Stata Users' Group

Motivation

- Analysis of data where the outcome is incomplete *always* requires untestable assumptions about the missing data – commonly that they are missing at random (MAR)
- Sensitivity analyses are essential
- Especially relevant to clinical trials
- Ideal approach is to express the untestable assumption as an assumption about the value of an unidentified parameter δ, and then explore sensitivity of results as δ is varied over a plausible range (Kenward et al., 2001)

Scope of the talk

Propose methods for sensitivity analysis to departures from MAR in randomised trials with

- a single outcome (i.e. not repeated measures)
- continuous / binary outcome
- adjustment for baseline covariates

I will use a **pattern-mixture model (PMM)** estimated by a **mean score** approach

Plan of the talk

1. Model & method
2. Implementation in `rctmiss`, demonstrated in two trials
3. Fine-tuning to make `rctmiss` match standard analyses in special cases
4. Alternatives & extensions

This is work with James Carpenter (LSHTM) and Nick Horton (Smith College, USA)

Analysis model

If we had complete data...

- Analysis model: $g(\mathrm{E}[y_i|\mathbf{x}_i]) = \beta'_A \mathbf{x}_i$
- y is outcome
- $g(.)$ is link function (typically identity or logit)
- $\mathbf{x}$ is a covariate vector including 1's, randomised group r and baseline covariates – we're interested in the component of β_A corresponding to r
- Estimate the analysis model using estimating equations

$$\sum_i \mathbf{x}_i \{y_i - g^{-1}(\beta'_A \mathbf{x}_i)\} = 0$$

Incomplete data:

- Missing data occur in y only
- m_i indicates missingness of y_i

Mean score approach: imputation model

How do we solve the estimating equations $\sum_i \mathbf{x}_i\{y_i - g^{-1}(\beta'_A\mathbf{x}_i)\} = 0$ when y is incomplete?

- Mean score idea: replace score (estimating equation) with its expectation given the observed data.
- Since estimating equation is linear in y, we only have to replace the missing y_i with their expectation given the observed data.
  - i.e. we need $\mathrm{E}[y_i|\mathbf{x}_i, m_i = 1]$
- Model $\mathrm{E}[y_i|\mathbf{x}_i, m_i = 0]$ (pattern mixture approach)
- Assume $g(\mathrm{E}[y_i|\mathbf{x}_i, m_i = 1]) = g(\mathrm{E}[y_i|\mathbf{x}_i, m_i = 0]) + \Delta_i$
  - Δ_i is a user-specified departure from MAR: e.g. $\Delta_i = \delta_1$ if randomised to arm 1, δ_0 if randomised to arm 0.
  - $\Delta_i = 0$ for all i means the data are MAR; $\Delta \neq 0$ means the data are MNAR.
- Gives **imputation model** $g(\mathrm{E}[y_i|\mathbf{x}_i, m_i]) = \beta'_I\mathbf{x}_i + \Delta_{Ii}m_i$

Mean score approach: estimation

1. Estimate β_I in imputation model $g(\mathrm{E}[y_i|\mathbf{x}_i, m_i]) = \beta_I'\mathbf{x}_i + \Delta_i m_i$ by regressing y on x in complete cases ($m = 0$)
2. Form $y_i^* = \begin{cases} y_i & \text{if } m_i = 0 \\ g^{-1}(\beta_I \mathbf{x}_i + \Delta_i) & \text{if } m_i = 1 \end{cases}$
3. Solve $\sum_i \mathbf{x}_i(y_i^* - g^{-1}(\beta_A \mathbf{x})) = 0$ using `glm ystar x, family(...)` – allows fractional outcome for logistic regression

Mean score approach: variance

- Standard errors from `glm ystar x, family(...)` are too small – don't allow for imputation of the y_i^*
- We compute sandwich standard errors based on *both* estimating equations:

$$\begin{aligned} S_I(\beta_A, \beta_I) &= \sum_i (1 - m_i)\mathbf{x}_i \left\{ y_i - g^{-1}(\beta_I' \mathbf{x}_i) \right\} &= 0 \\ S_A(\beta_A, \beta_I) &= \sum_i \mathbf{x}_i \left\{ y_i^*(\beta_I) - g^{-1}(\beta_A' \mathbf{x}_i) \right\} &= 0 \end{aligned}$$

- Variance $= B^{-1} C B^{-T}$ where
  - B involves derivatives of $(S_A(\beta), S_I(\beta))$ with respect to (β_A, β_I)
  - C involves sums of squares of score terms
  - both can be computed using `matrix opaccum`

Strategy for sensitivity analysis

- Recall Δ is the difference in $g(\mathrm{E}[y_i|\mathbf{x}_i, m_i])$ between $m_i = 1$ and $m_i = 0$
- If the main analysis assumed MAR ($\Delta = 0$), we propose
  1. sensitivity analysis assuming $\Delta_i = \delta$ for all individuals
  2. sensitivity analysis assuming $\Delta_i = \delta$ for all in intervention arm; $\Delta_i = 0$ for all in control arm
  3. sensitivity analysis assuming $\Delta_i = \delta$ for all in control arm; $\Delta_i = 0$ for all in intervention arm

  over a range of δ that is plausible in the scientific context.

QUATRO trial

- European multicentre RCT to evaluate the effectiveness of adherence therapy in improving quality of life for people with schizophrenia (Gray et al., 2006)
- Primary outcome: quality of life measured by the SF-36 MCS scale at baseline and 52-week follow up
- Basic results:

	Intervention	Control
Total randomised	204	205
Missing outcome	14%	6%
Mean of observed outcomes	40.2	41.3
SD of observed outcomes	12.0	11.5

- Quantitative outcome: Δ is $\{$mean unobserved outcome - mean observed outcome$\}$ adjusted for $\mathbf{x}$

QUATRO: MAR analysis

```
. xi: reg sf_mcs alloc sf_mcsba i.centreid

      Source |       SS       df       MS              Number of obs =     349
-------------+------------------------------           F(  5,   343) =   22.26
       Model |  11573.4109     5  2314.68217            Prob > F      =  0.0000
    Residual |  35672.4054   343  104.001182            R-squared     =  0.2450
-------------+------------------------------           Adj R-squared =  0.2340
       Total |  47245.8162   348   135.76384            Root MSE      =  10.198

------------------------------------------------------------------------------
      sf_mcs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       alloc |  -.3993286   1.098267    -0.36   0.716    -2.559515    1.760858
    sf_mcsba |   .4588515   .0482864     9.50   0.000     .3638767    .5538263
_Icentreid_2 |  -2.263799   1.664294    -1.36   0.175    -5.537306    1.009708
_Icentreid_3 |  -4.345429   1.602894    -2.71   0.007    -7.498169   -1.19269
_Icentreid_5 |  -.2169148   1.530906    -0.14   0.887    -3.228061    2.794231
       _cons |   24.76862    2.41699    10.25   0.000     20.01463    29.52261
------------------------------------------------------------------------------
```

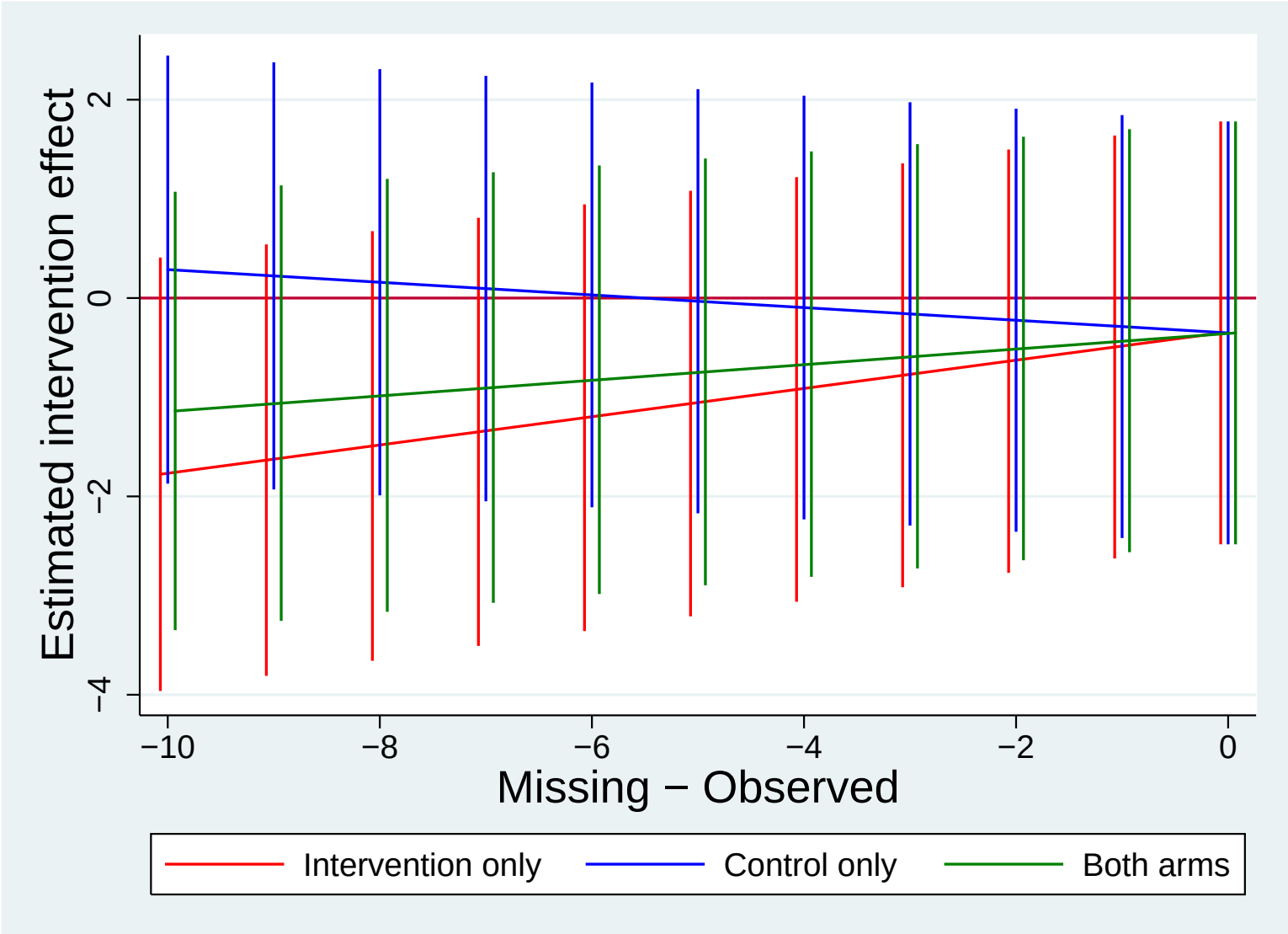
QUATRO: one sensitivity analysis

```
. xi: rctmiss, pmmdelta(-10): reg sf_mcs alloc sf_mcsba i.centreid

Using 349 observed outcomes and 37 unobserved outcomes
Results allowing for MNAR
PMM delta: -10
------------------------------------------------------------------------------
      sf_mcs |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       alloc |   -1.22321   1.138477    -1.07   0.283    -3.454584     1.008164
    sf_mcsba |   .4577975   .0501139     9.14   0.000     .3595761     .5560189
_Icentreid_2 |  -1.724996   1.742822    -0.99   0.322    -5.140865     1.690873
_Icentreid_3 |  -3.243663   1.665751    -1.95   0.052    -6.508476     .0211496
_Icentreid_5 |   .8303046   1.596404     0.52   0.603     -2.29859       3.9592
       _cons |   23.56718   2.520281     9.35   0.000     18.62752     28.50684
------------------------------------------------------------------------------
```

QUATRO: full sensitivity analysis

```
. xi: rctmiss, sens(alloc) pmmdelta(-10/0): reg sf_mcs alloc
> sf_mcsba i.centreid

Using 349 observed outcomes and 37 unobserved outcomes
Results allowing for MNAR
Performing sensitivity analyses..........
Drawing graph...
```

QUATRO: full sensitivity analysis

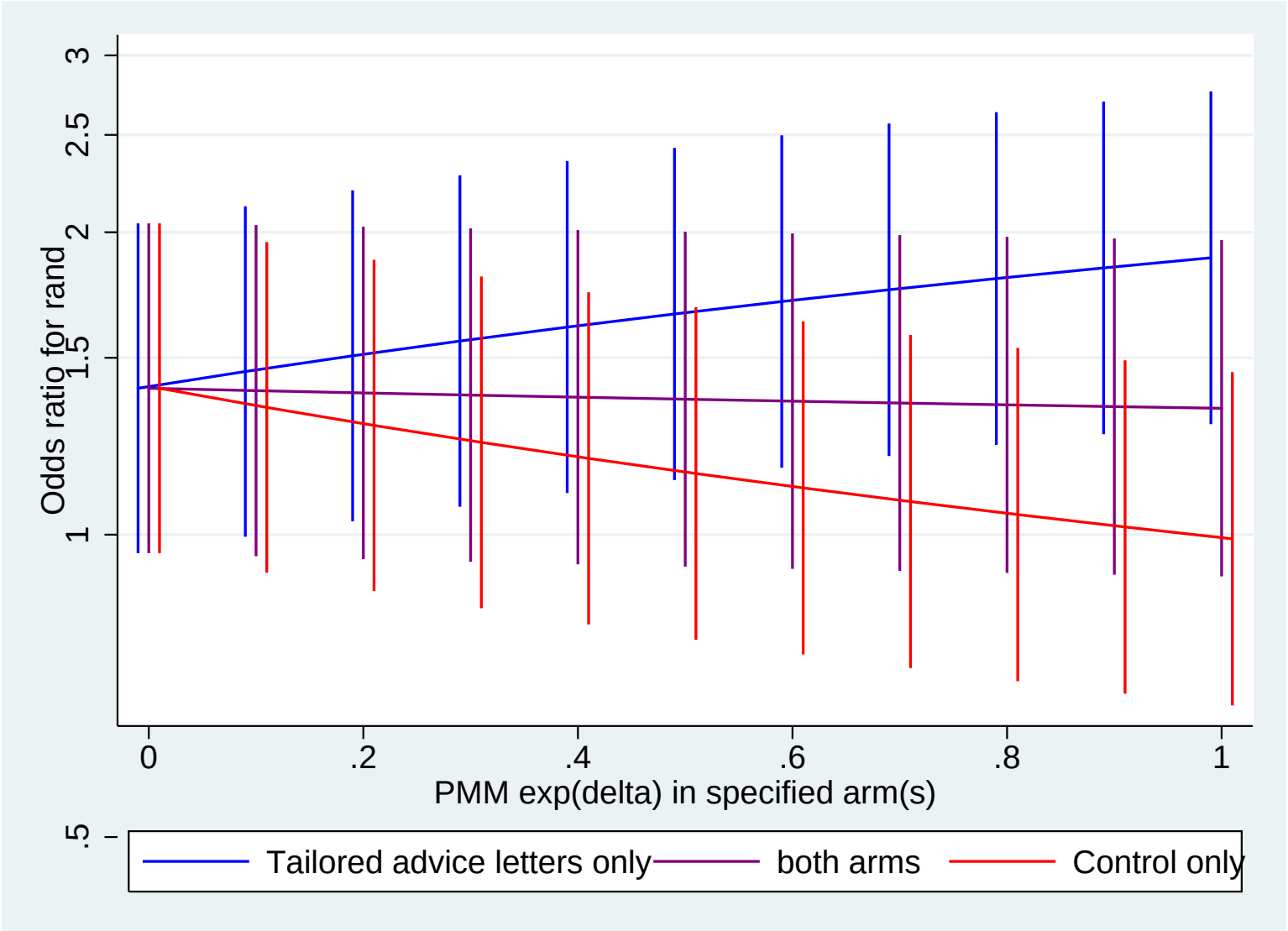


Incomplete binary outcome in smoking cessation trials

- Outcome is binary (have you quit?) and it is common to impute missing values as failures (still smoking).
- Δ is the log odds ratio between outcome y and missingness m, adjusted for $\mathbf{x}$
- Convenient to use the Informative missingness odds ratio $\text{IMOR} = \exp(\Delta)$
- "Missing=smoking" corresponds to $\text{IMOR} = 0$ for everyone
- We can do a sensitivity analysis over $0 \leq \text{IMOR} \leq 1$:
  `rctmiss, pmmdelta(0(0.1)1, log base(0))`
  `sens(rand): logistic quit rand`
- Sutton & Gilbert (2007):

	Intervn.	Control
Quit	73	51
Not quit	390	364
Missing	136	150

Smoking cessation trial: sensitivity analysis



Agreement with MAR and "missing=failure"

- Any user starting out with `rctmiss` is likely to compare it with other commands
  - MAR analysis – e.g. `regress` and `logistic`
  - missing=failure analysis – `logistic`
- I think it's very desirable that they should agree exactly
- The point estimate is fine, but standard errors require some understanding of Stata's sandwich variance
- Stata uses $fB^{-1}CB^{-T}$ where $f = n/(n-p)$ for linear regression and $f = n/(n-1)$ for other GLMs
- But $n = n_{obs}$ for MAR and $n = n_{total}$ for missing=failure
- I came up with a formula for an effective sample size $n = n_{eff}$ in which individuals with missing outcome receive estimated weights between 0 & 1

Equivalence with missing=failure

```
. logistic quit_mf rand, robust

Logistic regression                             Number of obs   =       1164
------------------------------------------------------------------------------
             |               Robust
     quit_mf | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        rand |   1.398718   .2697208     1.74   0.082     .9584935    2.041131
       _cons |   .0992218   .0145731   -15.73   0.000     .0744026    .1323202
------------------------------------------------------------------------------

. rctmiss, pmmdelta(0, log): logistic quit rand
Using 878 observed outcomes and 286 unobserved outcomes
Effective sample size: 1164
------------------------------------------------------------------------------
        quit | Odds ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        rand |   1.398718   .2697208     1.74   0.082     .9584935    2.041131
       _cons |   .0992218   .0145731   -15.73   0.000     .0744026    .1323202
------------------------------------------------------------------------------
```

Equivalence with missing at random

```
. logistic quit rand, robust

Logistic regression                                     Number of obs   =        878
------------------------------------------------------------------------------
             |               Robust
        quit | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        rand |   1.335948   .2626823     1.47   0.141     .9087009    1.964075
       _cons |   .1401099   .0209606   -13.14   0.000     .1045028    .1878494
------------------------------------------------------------------------------

. rctmiss, pmmdelta(0): logistic quit rand
Using 878 observed outcomes and 286 unobserved outcomes
Effective sample size: 877.99993
------------------------------------------------------------------------------
        quit | Odds ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        rand |   1.335948   .2626823     1.47   0.141     .9087008    1.964075
       _cons |   .1401099   .0209606   -13.14   0.000     .1045028    .1878494
------------------------------------------------------------------------------
```

Stata command `rctmiss`

- `rctmiss, pmmdelta(`*exp*`)` *options*: *est_cmd*
- `rctmiss, pmmdelta(`*numlist*`) sens(`*varname*`)` *options*: *est_cmd*
- Available using `net from http://www.mrc-bsu.cam.ac.uk/IW_Stata/`
- **Imputes missing values in the covariates** using mean imputation / missing indicator (White and Thompson, 2005)
  - appropriate only when estimating effect of randomised treatment

Problems and extensions

- Easily extended to cluster-randomised trials: just do clustered sandwich variance
- Really need an extension to repeated measures:
  - probably need more Δ values – in principle one for each missing data pattern
  - difficulty is deciding how Δ should vary between individuals with early and late drop-out
  - especially hard for non-monotone missing data patterns
- Main practical problem is how to choose Δ – I've had some success here (Wallace et al., 2011)
- Alternatives include selection model + IPW (also in `rctmiss`) and MI

References

Gray, R., Leese, M., Bindman, J., Becker, T., Burti, L., David, A., Gournay, K., Kikkert, M., Koeter, M., Puschner, B., Schene, A., Thornicroft, G., and Tansella, M. (2006). Adherence therapy for people with schizophrenia: European multicentre randomised controlled trial. *British Journal of Psychiatry*, 189:508–514.

Kenward, M. G., Goetghebeur, E. J. T., and Molenberghs, G. (2001). Sensitivity analysis for incomplete categorical tables. *Statistical Modelling*, 1:31–48.

Wallace, P., Murray, E., McCambridge, J., Khadjesari, Z., White, I. R., Thompson, S. G., Kalaitzaki, E., Godfrey, C., and Linke, S. (2011). On-line randomized controlled trial of an Internet based interactive intervention for members of the general public with alcohol use disorders. *PLoS ONE*, 6:e14740.

White, I. R., Horton, N., Carpenter, J., and Pocock, S. J. (2011). Strategy for intention to treat analysis in randomised trials with missing outcome data. *British Medical Journal*, 342:d40.

White, I. R. and Thompson, S. G. (2005). Adjusting for partially missing baseline measurements in randomised trials. *Statistics in Medicine*, 24:993–1007.