Multiway Tipping Point Analyses in Longitudinal Clinical Trials with Missing Data

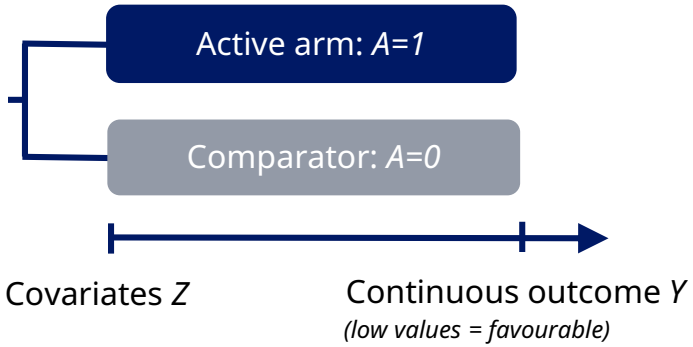
Anders Gorst-Rasmussen
agtr@novonordisk.com

Mads Jeppe Tarp-Johansen
mjtj@novonordisk.com

25 September 2020
2020 ASA Biopharmaceutical Section
Regulatory-Industry Statistics Workshop

Showing robustness to missing data assumptions

2-ARM PARALLEL GROUP RCT



PRIMARY ANALYSIS (ANCOVA-MI)

Impute Y_{MI}

Regress on A,Z

Apply Rubin's rule

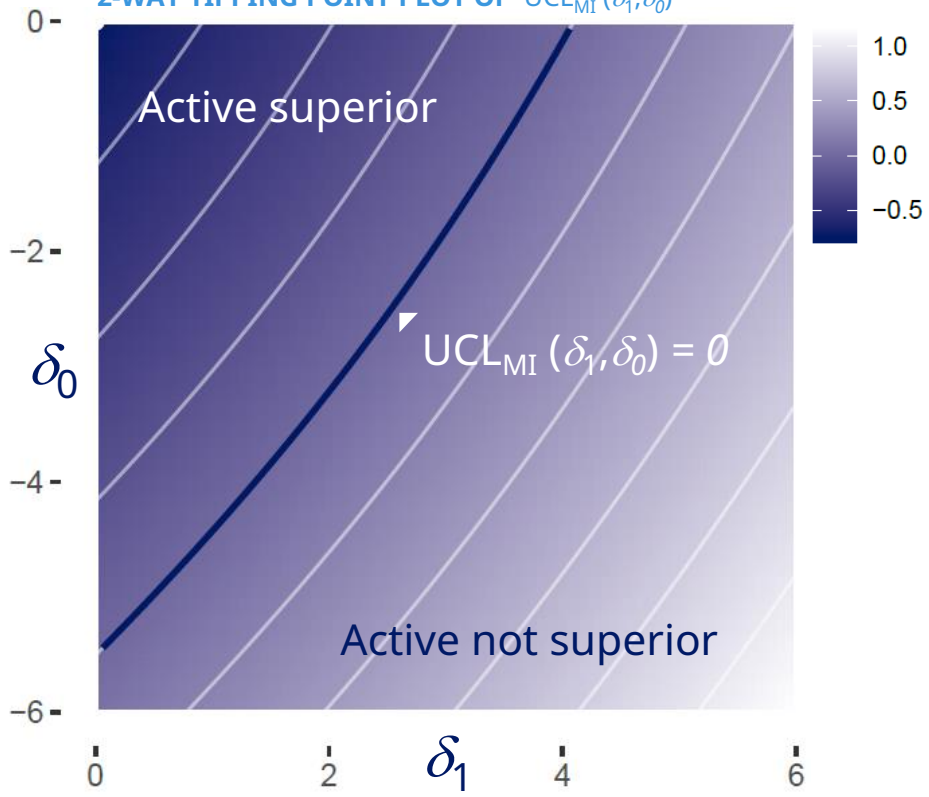
ETD_{MI} $[LCL_{MI}$; $UCL_{MI}]_{95\%\ CI}$

2-WAY TIPPING POINT SENSITIVITY ANALYSIS

Y_{MI} if observed
$Y_{MI} + \delta_0$ if missing and $A = 0$
$Y_{MI} + \delta_1$ if missing and $A = 1$

Regress on A,Z Rubin's rule

2-WAY TIPPING POINT PLOT OF UCL_{MI} (δ_1,δ_0)



Re-estimating regression models and re-applying Rubin's rule in a 2D grid is a chore! **Can we tip faster?**

With little missing data, the information-to-ink ratio in a 2-way tipping point plot is small. **Can we tip smarter?**

Why stop at arm-specific penalisation – how about going subject-specific? **Can we tip more generally?**

Can we tip faster?

Yes! Utilising the simple form of ANCOVA-MI, we can evaluate the full 2-way tipping point surface essentially at the cost of 1 MI analysis + 2 regressions + some sums

$$\mathrm{UCL}(\delta_1,\delta_0) = \underbrace{\mathrm{ETD}_{\mathrm{MI}}(\delta_1,\delta_0)} + 1.96 \cdot \underbrace{V_{\mathrm{MI}}(\delta_1,\delta_0)}^{1/2}$$

Linear term in δ_1,δ_0

- Coefficients from primary ANCOVA-MI and linear regressions of arm-specific missingness indicators on *A,Z*

Quadratic term in δ_1,δ_0

- Coefficients from (co)variance expressions with residuals from previous regressions

HIGH-LEVEL ALGORITHM FOR FAST 2-WAY TIPPING POINT

1. Do primary MI analysis with *M* imputations
2. Calculate average residual across *M* ANCOVAs from 1
3. Regress arm-specific missingness indicators on *A,Z* and save residuals
4. Pre-calculate V_{MI} coefficients
5. Calculate $\mathrm{UCL}(\delta_1,\delta_0)$ in *D* x *D* grid

Can we tip smarter?

Yes! Do the two 1-way tipping point analyses, draw a line between the points. If everything "south-east" of that line is clinically implausible then conclusions are robust to missing data

$UCL_{MI}(\delta_1, \delta_0)$ is a convex function

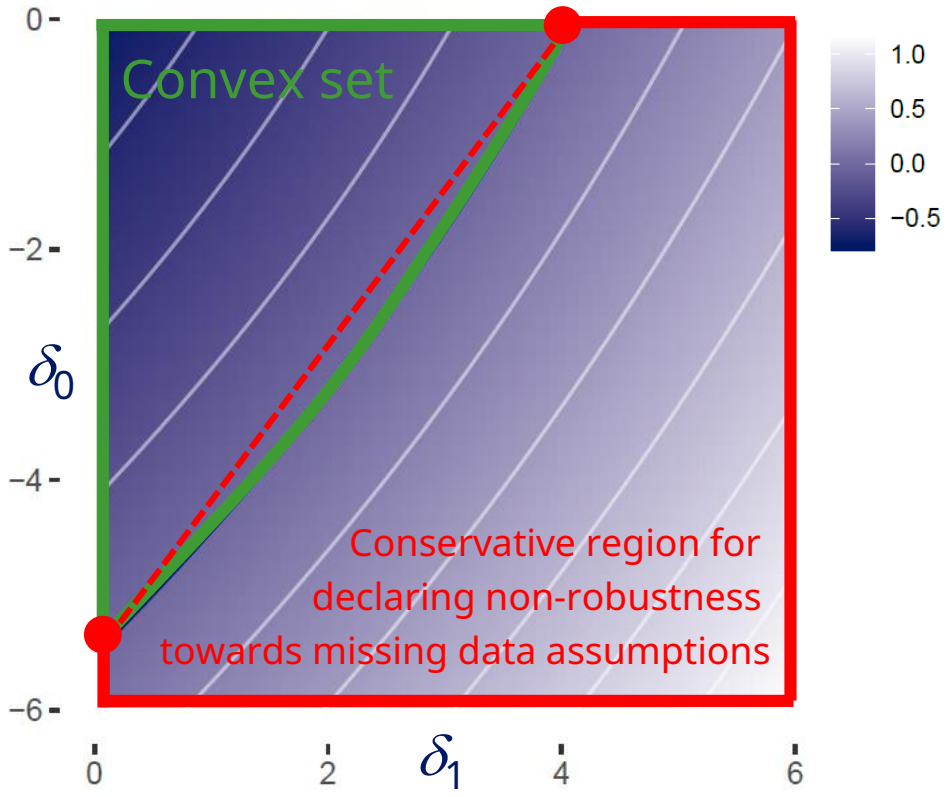
- It's the sum of a linear function and the square root of a positive definite quadratic form

So $\{(\delta_1, \delta_0) : UCL_{MI}(\delta_1, \delta_0) \leq 0\}$ is convex

- Convex functions have convex levels sets

So it's conservative to "tip at the line" between the two 1-way tipping points

- Lines between points in a convex set stay in that set



Can we tip more generally?

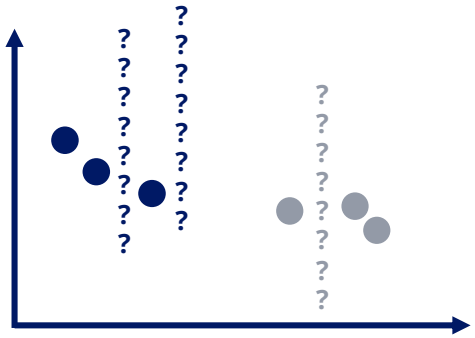
Yes! We can study UCL as a function of individual missing values – and investigate the most conservative configuration under (convex) clinically plausible constraints

$$UCL(\boldsymbol{w}) = ETD_{MI}(\boldsymbol{w}) + 1.96 \cdot V_{MI}(\boldsymbol{w})^{1/2}$$

Consider the upper confidence limit as a real-valued function of the individual, unknown missing values

$$\text{Maximize } UCL(\boldsymbol{w}) \text{ subject to } \boldsymbol{w} \in F$$

Given convex constraints F on missing values **w**, what's the globally most conservative configuration possible?



SOLUTION w_0 FOR $F = [a; b] \times \ldots \times [a; b]$ (BOX-CONSTRAINTS)

$$w_{0i} = \begin{cases} a \text{ if } A_i = 1 \\ b \text{ if } A_i = 0 \end{cases}$$

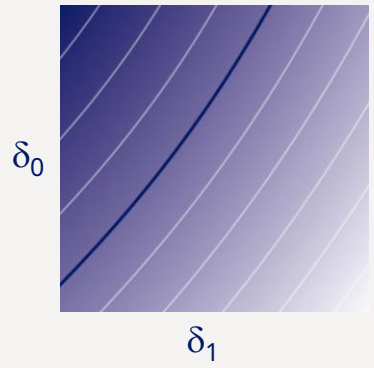
A SUFFICIENT CONDITION FOR ROBUSTNESS

1. Select a clinically plausible range $[a; b]$
2. Calculate $\boldsymbol{w}_0$ as per above
3. If $UCL(\boldsymbol{w}_0) < 0$ then no configuration in the clinically plausible range can tip the conclusion

Conclusion: 3 options to show robustness

All 3 options comprehensively explore the space of plausible missing data assumptions – but options 2 and 3 are simpler

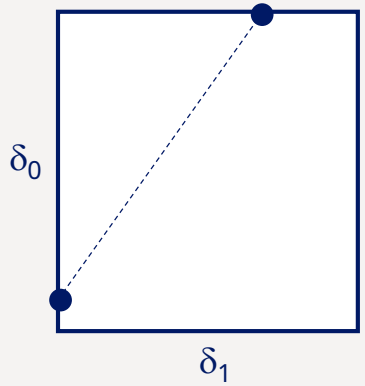
1



"We calculated and plotted the 2-way tipping point surface and level curve UCL=0 by [...long description ensues...]

Since values below the level curve UCL=0 are considered clinically implausible, conclusions are robust to missing data assumptions"

2



"We did two 1-way tipping point analyses and drew a line between results.

Since values below that line are considered clinically implausible, conclusions are robust to missing data assumptions"

3

"When tipping missing values to the extremes of the clinically plausible range by arm, we still observed UCL < 0

Hence no configuration in the clinical plausible range will have UCL ≥ 0, and so conclusions are robust to missing data assumptions"