Andrew Potter
Division of Biometrics I
FDA CDER
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INTRODUCTION TO MMRM AND A REGULATORY VIEW OF THE MMRM – USES AND LIMITATIONS

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- How do we want to assess treatment effects of a new drug when the outcome is a clinical outcome assessment (COA)
  - Estimands
- How do we estimate a treatment effect that corresponds to our estimand?
  - MMRM with standard assumptions
- Regulatory Perspective

Clinical Outcomes in Depression Trials

- Goal: Does a new drug improve depressive symptoms over time?
  - Measured with a COA
- Measures:
  - Montgomery-Asberg Depression Rating Scale (MADRS)
  - Hamilton Depression Rating (HAM-D)
- Estimation: Mixed Model for Repeated Measures (MMRM)

Estimands Framework

- What scientific question to answer
- Before any consideration of statistical methods
- Five attributes (ICH E9R1)
  - Population
  - Endpoint
  - Treatment
  - Intercurrent Events that affect interpretation
  - Population Summary
- Different estimands yield different estimates

MMRM Estimand for Depression

- Population: patient with major depressive disorder
- Endpoint: change from baseline to week 4 in MADRS
- Treatment: drug X every three days + oral antidepressant (AD) vs placebo + oral AD
- Intercurrent Events: death, treatment discontinuation
  - Hypothetical strategy proposed
    - Is this a justifiable estimand strategy?
- Population Summary Measure: least square mean difference in MADRS between drug X and control

- MMRM was proposed as an estimator

More about intercurrent events in MMRM

- How does a patient's data contribute after an intercurrent event?
  - If excluded, observed patients' data are used to estimate means after the intercurrent event
    - MMRM estimates align with hypothetical estimand
    - Adjusts estimates using within patient correlation between visits
  - If included, the estimated mean may not reflect the estimand of interest
    - MMRM estimates may align more closely with a treatment policy estimand

What about death?

- In many psychiatric illnesses, suicides may be observed
  - Rare in major depressive disorder studies
    - May be more common in other diseases
  - Considered related to disease
  - Informative about the effect of treatment
  - Violates MMRM assumptions of ignorable missing data (MAR)
  - Solutions through the estimand framework?

MMRM – Statistical Details

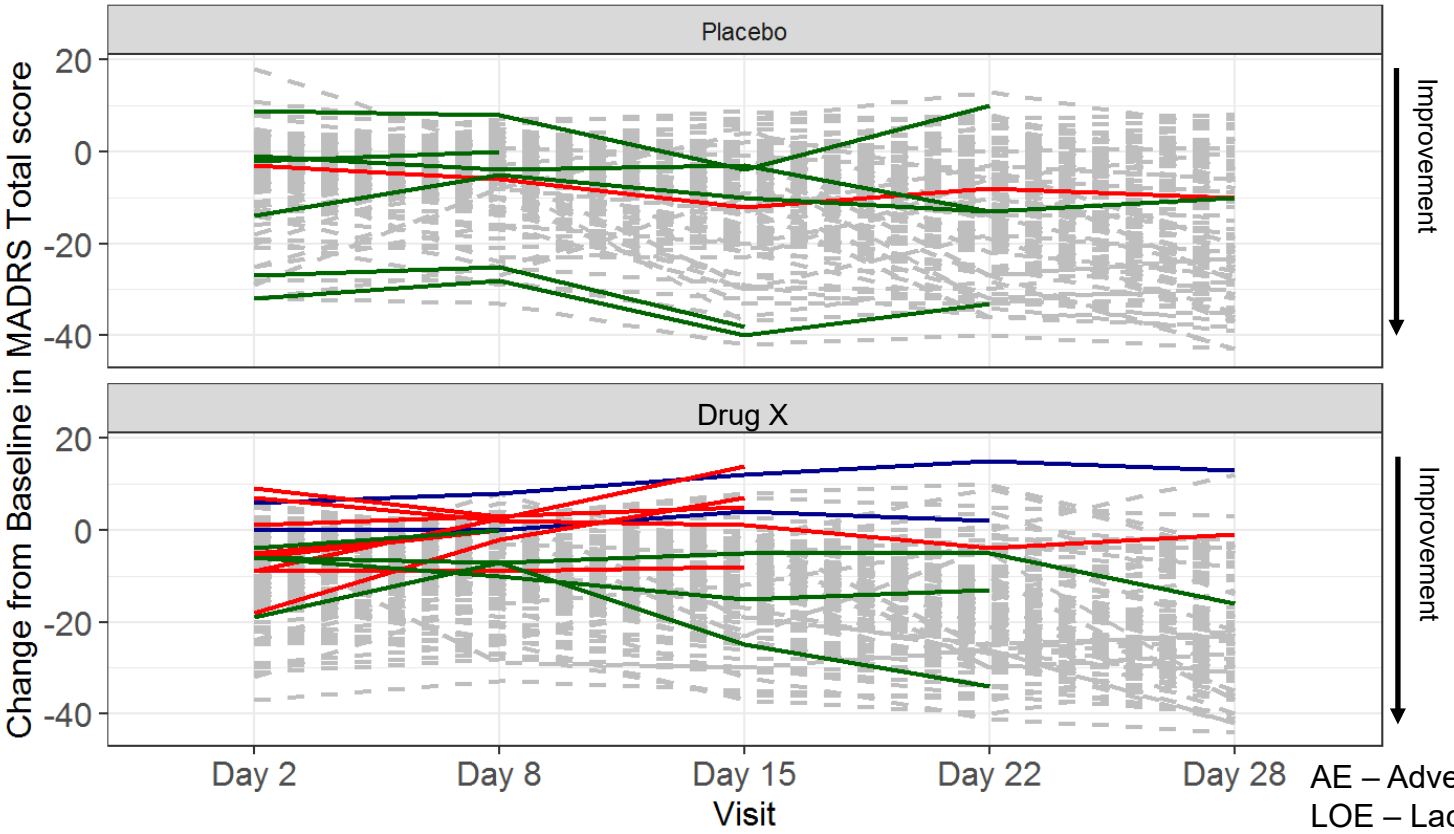
Key Assumptions

- Normally distributed data
- Within subject data is correlated
- Missing data is missing at random (MAR)
  - Missing observations are related to the observed observations
  - Missing data is ignorable
- Any intercurrent events that lead to missing data are equivalent to MAR assumption for missing data

Mathematical Details

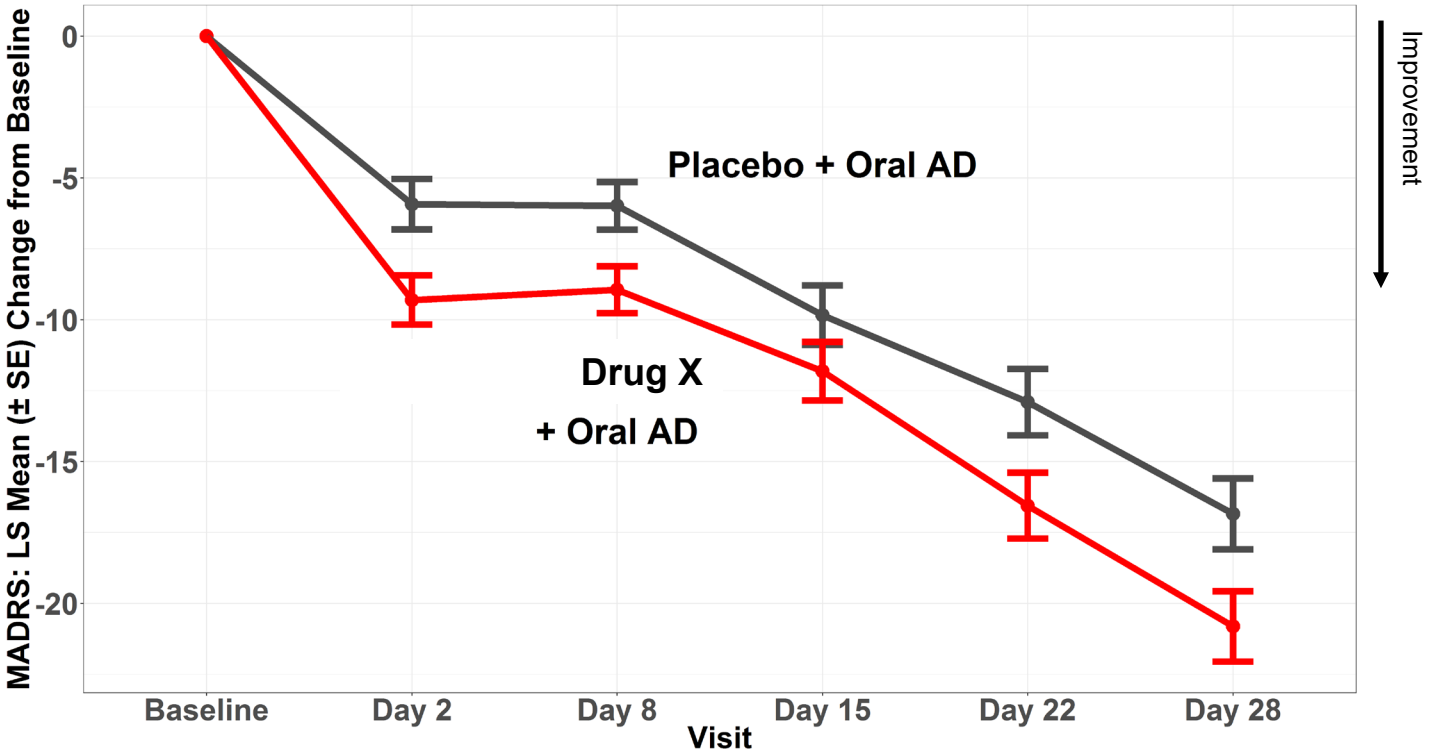
- Models within subject correlation by:
  - Covariance pattern model
    - Unstructured or structured covariance matrix
  - Mixed model with random subject
- Model group means at multiple visits
- Visits linked through within subject correlation
- Adjust for baseline differences
- Estimate group differences after estimation
- What about missing data?

Subject MADRS Scores over Time



AE – Adverse event
LOE – Lack of efficacy
Else – All other reasons

Treatment Arm Average
MADRS Scores over Time – Output from MMRM



Other diseases

- Schizophrenia
  - Study dropout or treatment may be informative about the outcome
- Oncology
  - Treatment arms may have differing death rates caused by the drug's impact on overall survival

Is MMRM Useful?

- It depends!
  - Varies by disease
  - Death may make interpretation challenging
  - Needs to be **justified** for an estimand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