An estimand perspective on the Mixed Model Repeated Measures (MMRM) for the analysis of longitudinal PRO data in clinical trials

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Innovative science to capture the patient voice

Introduction

- Patient-reported outcomes (PRO) endpoints are commonly included as secondary endpoints in oncology clinical trials to evaluate quality of life (QoL)
- This presentation has a focus on the example of a 2-arm (active vs control) phase 3 clinical trial in a late-phase solid-tumour oncology setting, considering *"change from baseline in QoL"* as a secondary endpoint, where the primary endpoint is PFS or OS.

The aim of this presentation is to examine the research questions that the commonly used MMRM model **can** and **cannot** answer

Clinical trial objectives are often defined in broad terms

Example objective in protocols, publications etc

"Change from baseline in QoL"

Timeframe

1. At a specific timepoint?
2. Over time, by timepoint X?

Non-exhaustive list of possible questions – including several unreasonable ones

Death	Discontinuation of randomized treatment	Receipt of other treatments
1. While alive? 2. Regardless of death? 3. If patients had not died? 4. In survivors?	1. While on randomized treatment? 2. Regardless of treatment discontinuation? 3. If patients had not stopped randomized treatment?	1. Before switching to other antineoplastic treatments? 2. Regardless of treatment received? 3. If patients had not switched to other therapies?

These events have been named Intercurrent Events (ICEs) and the potential questions correspond to some of the strategies proposed in the ICH E9(R1) Addendum

MMRM is often used to answer the “change from baseline in QoL” question

- Mixed Model Repeated Measures (MMRM) is a common approach for analyzing continuous PRO scores measured repeatedly, as it accounts for the correlations of the measures taken from the same patient.
- It has been recommended by SISAQoL (2020): *“Although the linear mixed model (time as continuous), pattern mixture model, and joint longitudinal model satisfy the set criteria,* ***the linear mixed model (time as discrete) was recommended because less assumptions were needed to be made a priori*** *(eg, regarding the relationship between time and outcome variable)”.*

Note: not all patients provide data up to timepoint X

A common specification of an MMRM model

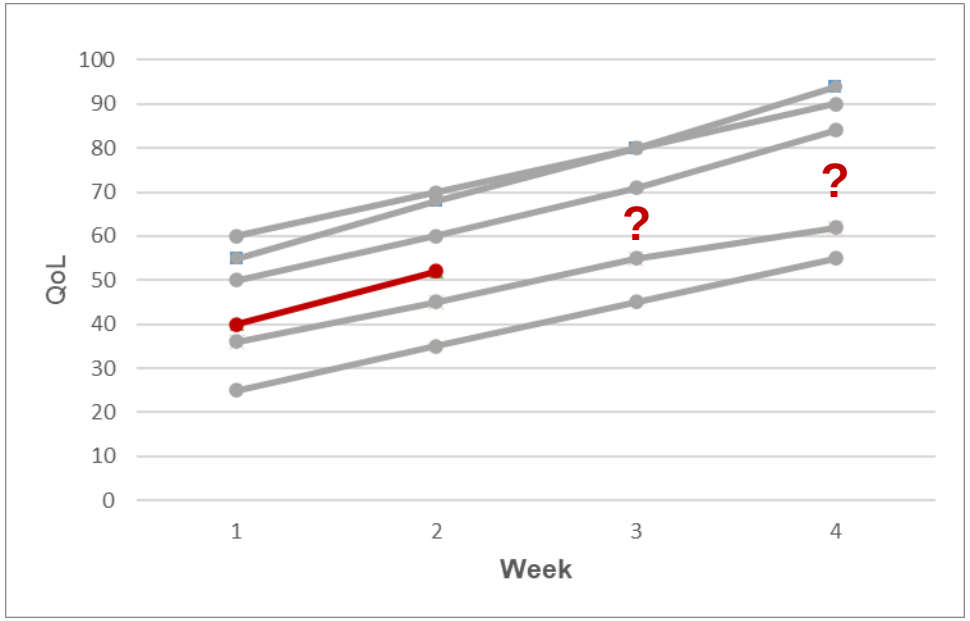
- **Response variable**: Change from baseline **to timepoint X**
- **Covariates**: Treatment, Visit, Treatment*Visit, Baseline PRO score, Baseline PRO score*Visit, stratification factors
- **Covariance structure**: unstructured (ideally)
- Visit is typically considered a categorical variable
- Treatment effect presented: Difference in adjusted mean change from baseline (AKA LSMeans) between active vs control:
  - at timepoint X and/or
  - over time, up to timepoint X

However, the MMRM, *in its most common form*, can only answer a limited subset of the research questions posed in previous slide

Considerations around time defined as continuous or categorical will not be covered here

Coens et al 2020. SISAQoL recommendations.

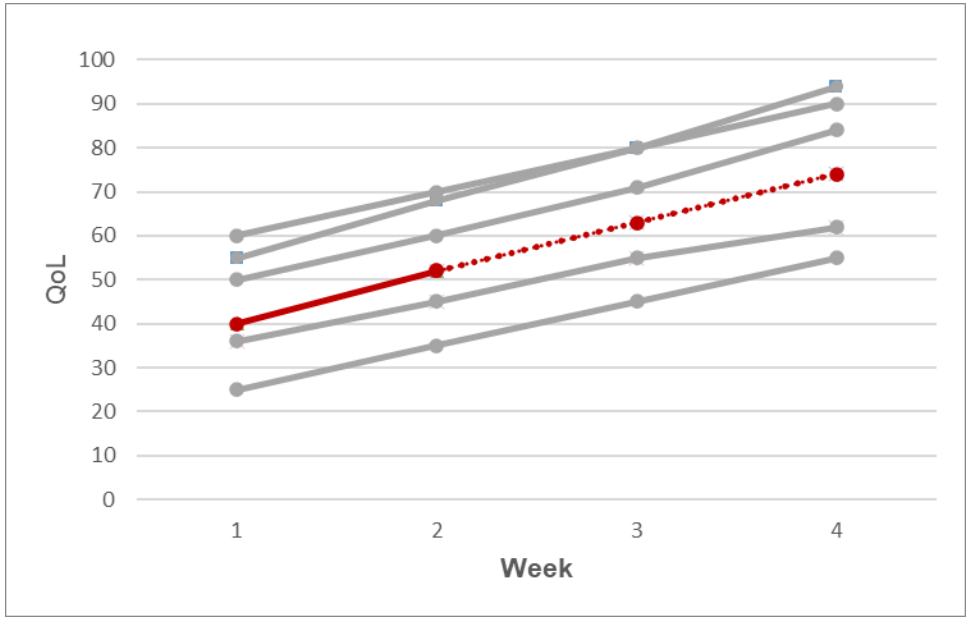
MMRM makes the assumption that the missing data are missing at random (MAR)



Red solid line
Observations of subject that has an ICE at week 2

Grey solid line
observations of subjects in the same treatment arm who have similar baseline characteristics

Red dashed line
Inferred values under MAR



Under MAR, the MMRM model estimates the mean treatment effect assuming that "*. . . after withdrawal, subjects* ***would have continued*** *just like their peers in the same arm who have the same covariates and same observed data (so far)".*

Hypothetical language ☺

Quote by James Roger. https://www.psiweb.org/docs/default-source/resources/psi-subgroups/scientific/2015/estimands-28-09-2015/jamesroger.pdf?sfvrsn=bba3d0db_2
Graph inspired by presentation by Jiawei Wei "On the role of hypothetical estimand in clinical trials and its estimation" (PSI One-day meeting: sMissing data in clinical trials – Past, present and future, 4th May 2021)

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A couple of common Oncology clinical trial designs

Setting

- Randomized, two-arm clinical trial comparing treatment A to treatment B
- PRO assessments are collected at baseline and every X weeks
- Two scenarios are possible for planned PRO data collection:
  - **Scenario 1**: until *treatment* discontinuation
  - **Scenario 2**: until *study* discontinuation, i.e. after disease progression and treatment discontinuation

If a standard MMRM is used, the following strategies are implicitly used

	Scenario 1 PRO data beyond txt discontinuation ***not*** collected			**Scenario 2** PRO data beyond txt discontinuation **collected *and* used**		
ICE	**Data available after ICE**	**MMRM assumes patients with unobserved data after the ICE will follow the same trajectory as patients that are still…**	**Inferred Strategy**	**Data available after ICE**		**Inferred strategy**
Treatment discontinuation	No	On randomized treatment, i.e. "**as if patients were still on treatment**"	Hypothetical	Yes	If PRO data collected beyond treatment discontinuation are used in the MMRM model, i.e. treatment effect "**regardless of adherence to treatment**"	Treatment policy **– is it?**
Start of new therapy	No	On randomized treatment, i.e. "**as if patients were still on randomized treatment and have not received a new therapy**"	Hypothetical	Yes	If PRO data collected after treatment switching are used in the MMRM model, i.e. treatment effect "**regardless of treatment discontinuation and/or treatment switching**"	Treatment policy **– is it?**
Death	No	Alive, i.e. "**as if death had not occurred and patient had continued to participate in the study**"	Hypothetical	No	Alive, i.e. "**as if death had not occurred and patient had continued to participate in the study**"	Hypothetical

Not only may it not have happened; it may even be impossible (James Roger)

James Roger. https://www.psiweb.org/docs/default-source/resources/psi-subgroups/scientific/2015/estimands-28-09-2015/jamesroger.pdf?sfvrsn=bba3d0db_2

Including post-txt disc PRO data in a standard MMRM does *not* serve a treatment policy approach

1- Apparently

- The (presumably) poorer post-progression/off-treatment values will be used by the model to predict more pessimistic trajectories for similar patients that have missing data (although planned to be collected, these will probably occur at some point)
- IQWiG likes it

2- The reality#

- MMRM will use all observed data to infer unobserved data
- MAR assumes that off-txt unobserved patients are like all of the observed patients, conditional upon other patient characteristics and previous responses
- Observed data are primarily on-txt, e.g. if 90% observed data are on-txt, we would be implicitly *imputing the unobserved data as being 90% on-txt*
- Essentially, the issue is that such a model is **not making distinction between on- and off-txt assessments**, therefore we cannot claim it is estimating a treatment effect "regardless of txt status"

3- How do we do treatment policy then?#

A variation of the MMRM model with an introduction of **time-dependent off-treatment covariate** could be employed if **treatment policy** is desired#:

Treatment/visit/off-trt interactions
Combine estimates by observed on-/off-trt proportions and adjust variance

Schematic and explanation as in presentation by James Bell "The practicalities of treatment policy estimation" (PSI One-day meeting: Missing data in clinical trials – Past, present and future, 5th May 2021)

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Key take-away messages

MMRM CAN

- MMRM, in its most commonly applied form, applies a **hypothetical** strategy for any ICE after which data are unobserved, e.g. *"Change from baseline in QoL as if patient is still taking randomized treatment"*
- If post-ICE data are collected, and an on- and off-ICE indicator is included, then **treatment policy** (for that ICE) is possible

MMRM CANNOT

- Answer questions like – "*Change from baseline in QoL…*"
  - While on (randomized) treatment
  - Before progression
  - While alive
  - In survivors
  - In patients that would tolerate txt
  - Where death is a "bad" outcome
- When such questions are of interest, analysts should seek analytical solutions beyond the standard MMRM framework

While-on-treatment

Principal stratum

Composite

*For some proposed solutions, watch **Oral presentation 106.3 Choosing appropriate estimators for estimands in PRO endpoints***
*For estimand considerations on Time-to-event endpoints, watch **Oral brief B202.5 Estimand Considerations for Time-to-Event Analysis of Patient-Reported-Outcomes***

Thank you for listening

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