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Handling unplanned disruptions in randomised trials using missing data methods: a four-step strategy

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Outline

- Background and motivating example: the ASCOT trial

- Four step-strategy for handling unplanned disruptions:
  1. Clarifying the treatment estimand of interest
  2. Establish what data are missing for the chosen estimand
  3. Primary analysis under the most plausible assumptions
  4. Sensitivity analysis under alternative plausible assumptions

- Discussion/alternative approaches

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BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic

Background

- Covid-19 presents a variety of challenges for the conduct and analysis of ongoing trials

- Subject to participant/investigator safety data collection continue for as long as possible → remotely (FDA/EMA/MHRA)

- Protocol deviations inevitable resulting in:

  (i) increased missing data & for non-standard reasons

  (ii) participants providing data during Covid-19 when their outcomes are influenced by it

The ASCOT trial

Adjunctive Steroid Combination in Ocular Trauma

- Surgery only
- Surgery + adjunctive triamcinolone acetonide

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The ASCOT trial

Adjunctive Steroid Combination in Ocular Trauma

Surgery only	Surgery + adjunctive triamcinolone acetonide
3 months: ETDRS (0-100)	3 months: ETDRS (0-100)
6 months: ETDRS (0-100)	6months: ETDRS (0-100)

ETDRS:

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The ASCOT trial - timelines

Ocular Trauma

Recruitment began October 2014

Recruitment end March 2020 (n=300)

Last participant follow-up end Sep 2020

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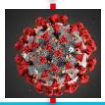
The ASCOT trial - timelines

Ocular Trauma

Recruitment began October 2014

11th March 2020
Pandemic (WHO)

24th March 2020
UK Lockdown



Recruitment end March 2020 (n=300)

Last participant follow-up end Sep 2020

10% participants in follow-up experiencing unplanned disruptions:

- Disruptions to standard care
- Loss to follow-up (participant behaviour changes)
- Covid-19 infection

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Estimands & ICH E9 addendum

- In any trial to ensure answer question of interest important to precisely define the treatment estimand

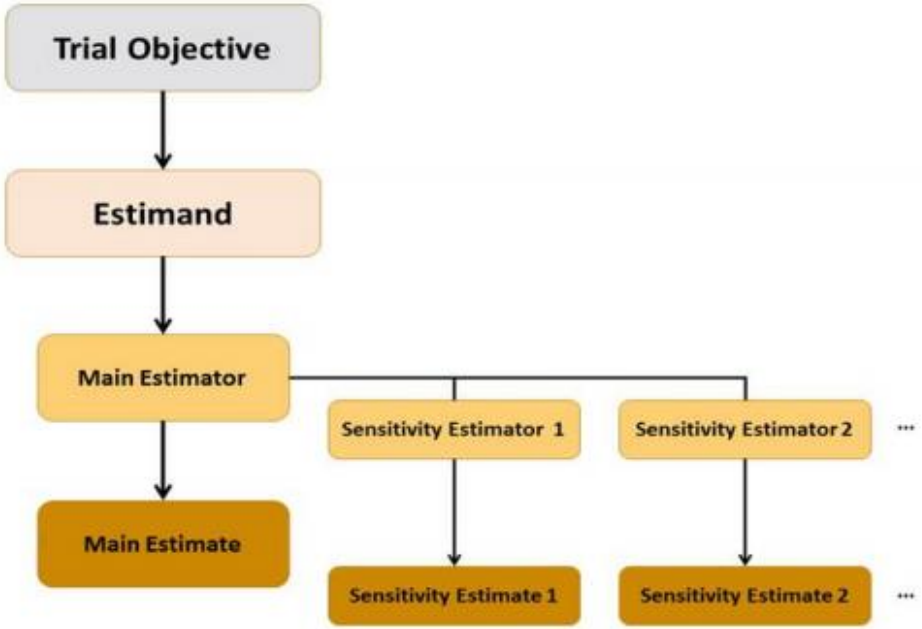

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

Estimands & ICH E9

- ICH E9(R1) addendum describes 5 key attributes of an estimand:

  A) The population

  B) The treatment condition

  C) The variables (or endpoint)

  D) How to account for intercurrent events

  E) The population level summary for the variable

Estimands & ICH E9

- ICH E9(R1) addendum describes 5 key attributes of an estimand:
  - A) The population – *Adults with full thickness, open-globe ocular trauma undergoing pars plana vitrectomy*
  - B) The treatment condition – *Triamcinolone Acetonide (4mg/0.1ml IVTA and 40mg/1ml subtenons) given during surgery*
  - C) The variables (or endpoint) – *ETDRS at 6 months*
  - D) How to account for intercurrent events – *Post-randomisation intraoperative events/subsequent eye procedures handled using a treatment policy approach*
  - E) The population level summary for the variable – *mean treatment group difference in ETDRS at 6 months*

Estimands & ICH E9

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  - D) How to account for intercurrent events – *Post-randomisation intraoperative events/subsequent eye procedures handled using a treatment policy approach*
  - E) The population level summary for the variable – *mean treatment group difference in ETDRS at 6 months*

Estimands & ICH E9

- Intercurrent (post-randomisation) events are events affecting the interpretation or existence of trial outcomes

- Potential strategies for handling intercurrent events:
  - Treatment policy
  - Hypothetical
  - Composite variable
  - While on treatment
  - Principal stratum

Step 1: Clarify the treatment estimand

- If the pandemic introduces unplanned intercurrent events clarification on how to account for these is required

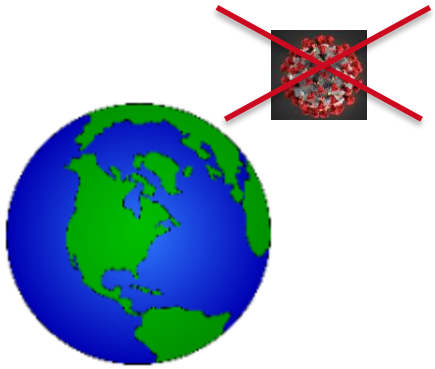
- Pandemic may *directly* affect participant outcomes:
  e.g. Infection with Covid-19

- Pandemic may *indirectly* affect participant outcomes:
  e.g. Standard care/treatment disruptions
  Participant behaviour changes

Step 1: Clarify the treatment estimand

- The treatment effect in a ‘pandemic-free world’

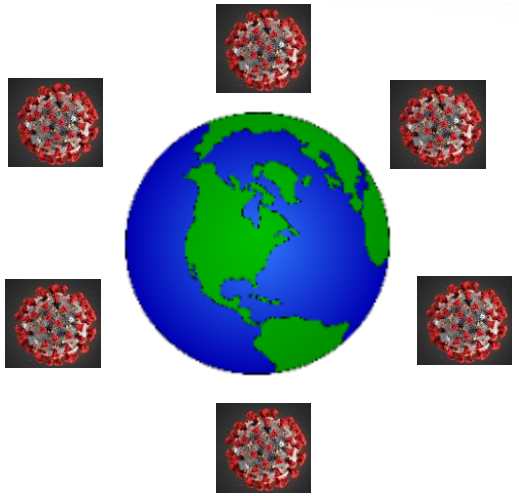
- Interest lies in the treatment effect we would have seen had the pandemic not happened



- A hypothetical strategy can be used to deal with unplanned intercurrent events

Step 1: Clarify the treatment estimand

- The treatment effect in a 'world including a pandemic'



- Treatment effect that occurs including the pandemic
- The effects of the pandemic (e.g. infection of trial participants, treatment interruptions,…) are directly relevant to the estimand
- A treatment policy approach can be used to deal with unplanned intercurrent events

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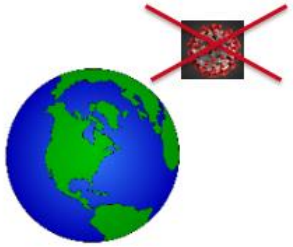
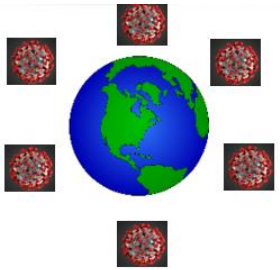
Step 1: Clarify the treatment estimand

‘pandemic-free world’



vs.

‘world including a pandemic’



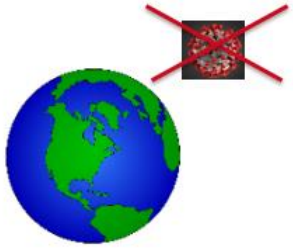
- Most appropriate estimand will be trial specific
- Value of each estimand may depend on the degree of overlap/severity of pandemic impact
- More than one estimand of interest may be of interest: supplementary analysis address alternative estimand(s)

Step 2: Establish what data are missing for the chosen estimand

- Missing data = data required to estimate the estimand of interest but are unavailable
- Data may be physically missing (not collected)
- Some observed data may be treated as missing* in the analysis if not relevant for the estimand
- *Alternative modelling options may be used

Step 2: Establish what data are missing for the chosen estimand

‘pandemic-free world’



- Only data that was unaffected by the pandemic are required for the analysis
- Affected data may be set missing

- May also be missing data from:
  - participants whose outcomes were not directly/indirectly clinically impacted by the pandemic, but are unobserved
  - ‘usual’ missingness from pre- and/or-post-pandemic times

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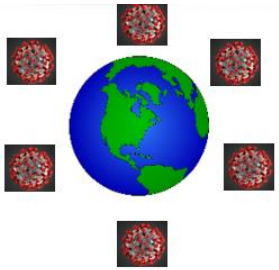
Step 2: Establish what data are missing for the chosen estimand

‘world including a pandemic’



- All participant data,
  pre-
  during-
  & post- pandemic is required for analysis

Step 3: perform primary analysis

- Perform primary analysis under the most plausible missing data assumptions (trial/estimand specific)

- Three general classes of missing data assumptions:
  - **Missing-completely-at-random (MCAR):**
    The probability that data are missing does not depend on the values of the unobserved or observed data
  - **Missing-at-random (MAR):**
    The probability that data are missing may depend on the values of the observed data, but does not depend on the values of the unobserved data
  - **Missing-not-at-random (MNAR):**
    The probability that data are missing depends on the values of the unobserved data

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Step 3: perform primary analysis

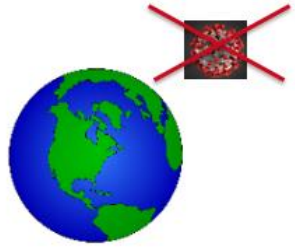
- Participants directly/indirectly clinically affected by a pandemic:

MAR— conditional on randomised treatment arm and all observed variables expected to be associated with *both* outcome and being missing (i.e. being directly or indirectly affected)

- Predictors of both missingness and outcome could include:
  - baseline characteristics (e.g. in ASCOT baseline vision, sex, comorbidity)
  - earlier observed data under pre-pandemic times (e.g. 3 month vision)

during−/post-pandemic times provided not affected by pandemic events.

‘pandemic-free world’



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Step 3: perform primary analysis

- Participants lost to follow-up during pandemic:

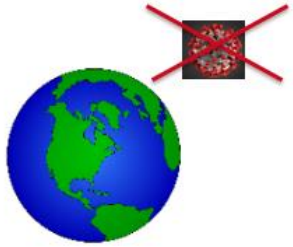
MAR— conditional on randomised treatment arm and all observed variables expected to be associated with *both* outcome and being missing (being lost to follow-up during pandemic)

- Participants lost to follow-up during non pandemic times

MAR— conditional on randomised treatment arm and all observed variables expected to be associated with *both* outcome and being missing (i.e. being lost to follow-up during non-pandemic times)

- Relative to non-pandemic time may be different factors expected to be associated with both outcome being lost to follow-up during pandemic e.g. Age in ASCOT

‘pandemic-free world’



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Step 3: perform primary analysis

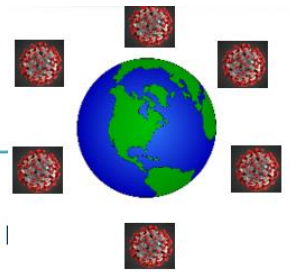
- Participants directly affected by a pandemic:

  MAR, including an indicator of direct pandemic impact e.g. Covid-19 infection status, and all observed data expected to be associated with both trial outcome and missingness (e.g. treatment, risk factors for being impacted by Covid-19 and the vision outcome such as age or diabetes)

- Or if no/little observed data from directly impacted participants:

  MNAR e.g. - worst case: jump-to-reference
  - outcome X% worse than predicted under MAR

'world including a pandemic'



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Step 3: perform primary analysis

- Participants indirectly affected by a pandemic

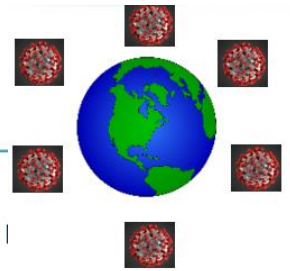
MAR, including an indicator of pandemic time period e.g. during/pre-/post-, and all observed data expected to be associated with both trial outcome and missingness

If also directly impacted participants: + infection status

- Or if no/little observed data from directly impacted participants:

‘world including a pandemic’

MNAR



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Step 3: perform primary analysis

- Participants lost to follow-up during pandemic times:

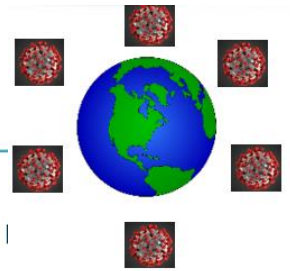
  MAR given observed data anticipated to be related to both outcome and missingness may be most relevant;

  If also includes observed data from directly/indirectly include infection status and/or pandemic time period

- Loss to follow-up during non –pandemic times:

MAR including an enlarged set of factors (to also handle participants with types (i), (ii) and/or (iii), e.g. also including diabetes, age, infection status, pandemic time point as relevant) may be suitable to handle loss to follow-up outside pandemic times.

'world including a pandemic'



Step 3: perform primary analysis

- MAR analysis options (not exhaustive):
  - complete case (incorporating variables associated with outcome/missing)
  - mixed model for repeated measures
  - multiple imputation

- MNAR analysis options (not exhaustive):
  - selection models
  - pattern mixture models: controlled multiple imputation

Controlled MI

- Data is imputed from a pattern mixture model multiple times - each analysed with the analysis model of interest- results combined Rubins' rules
- The analyst has direct 'control' over the imputation distribution
- The parameters of the MAR distribution can be shifted using a numerical offset term, delta (delta based multiple imputation)
- Reference-based imputation draws imputed values with some reference to the observed data in other groups of the trial, typically in other treatment arms

Controlled MI

- Different distributions for the missing data of different groups of individuals can be used for data imputation

  e.g. MAR (loss to follow-up) and MNAR (Covid-19 infected)

- An accessible tutorial with worked examples and Stata code, incl. where different assumptions are incorporated in one analysis

DOI: 10.1002/sim.8569

TUTORIAL IN BIOSTATISTICS

Statistics in Medicine WILEY

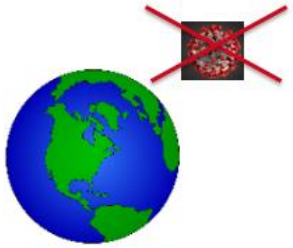
Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: A practical guide

Suzie Cro[1] | Tim P. Morris[2,3] | Michael G. Kenward[4] | James R. Carpenter[2,3]

Step 4: sensitivity analysis

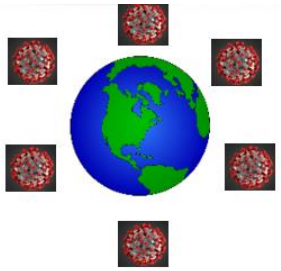
- Sensitivity analysis should address the same question –hence estimand- as the primary analysis
- Sensitivity analyses under alternative plausible MNAR assumptions most likely required
- The MAR distribution may be used as a departure point: shifting the parameter values of the distribution in a contextually relevant manner

Step 4: sensitivity analysis



‘pandemic-free world’

In the absence of a pandemic participants with missing data could have had worse/or better outcomes than those observed in the trial

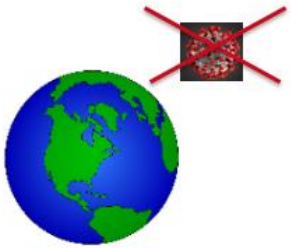


‘world including a pandemic’

Those affected by the pandemic —or also those that decide not to attend follow-up visits (in person or remotely) — could have had poorer outcomes than those observed in pandemic time

Or, depending on the trial context, it may be healthier participants who stay at home — since they feel they don’t have an essential need for clinical follow-up.

Summary



Step 1

Clarify the treatment estimand of interest with respect to the occurrence of the pandemic

Step 2

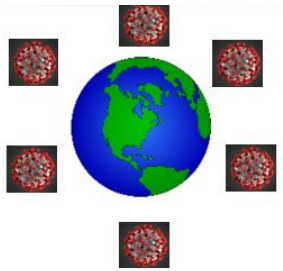
Establish what data is missing for the chosen estimand

Step 3

Perform primary analysis under the most plausible missing data assumptions

Step 4

Perform sensitivity analysis under alternative plausible assumptions



Discussion

- Clarification of estimand:
  - How to establish primary estimand of interest?
  - How degree of overlap influences ‘world including a pandemic estimand’ and its value?
  - What degree of overlap renders ‘pandemic free world estimand’ unsuitable?
  - Other estimands with respect to the pandemic and their value e.g. treatment effect during a pandemic

Discussion

- Using missing data methods:

  Careful thought/justification required for any assumption

  How to justify a MNAR assumption if most relevant e.g. for clinically affected data for the world including a pandemic estimand?

Discussion

- Alternative modelling approaches (vs. missing data methods) to estimate the treatment effect in a ‘pandemic free world’
  - e.g. Instrumental variable methods/ treatment switching methods
  - Other causal model
  - Assumptions required & communication of these to results reviewers