MRC Clinical Trials Unit

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Aligning analysis with the estimand

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Aim

- I'll focus on the intercurrent event attribute of the estimand

But the population-level summary attribute of the estimand is also very important

- e.g. if the estimand is a marginal mean difference or risk difference
  - estimation can use a covariate-adjusted regression model (to gain power)
  - then use the regression results to estimate the estimand
    - e.g. Morris TP *et al*. Planning a method for covariate adjustment in individually randomised trials: a practical guide. *Trials* 2022; 23: 328.

Recap: The five strategies for addressing intercurrent events in defining an estimand

Strategy	Meaning
Treatment policy strategy	Outcomes after intercurrent event are still relevant
Composite strategy	Intercurrent event is an outcome event
Hypothetical strategy	Consider outcomes if intercurrent event hadn’t happened
Principal Stratum strategy	Restict to a subgroup who wouldn’t experience intercurrent event
While on treatment strategy	Restrict to possibly non-comparable groups

Outline

1. Treatment policy strategy: missing data issue, reference-based imputation
2. Composite strategy: easy
3. Hypothetical strategy: “exclude” approach (MI/IPCW); “model” approach (IV/RPSFTM)
4. Principal stratum strategy: only with simple ICEs
5. While on treatment strategy: while alive
6. Hybrid approaches

Estimation for treatment policy strategy

Treatment policy strategy

- If you have complete outcome data, this is very simple: analyse the observed data
  - recall: treatment policy strategy means that the outcome remains meaningful after an intercurrent event
- The problem is that you may have incomplete outcome data
  - but we have standard ways to handle missing data ☺
- In particular, intercurrent events like treatment discontinuation make missing data more likely and make outcomes worse
  - here our standard ways may not be reasonable ☹

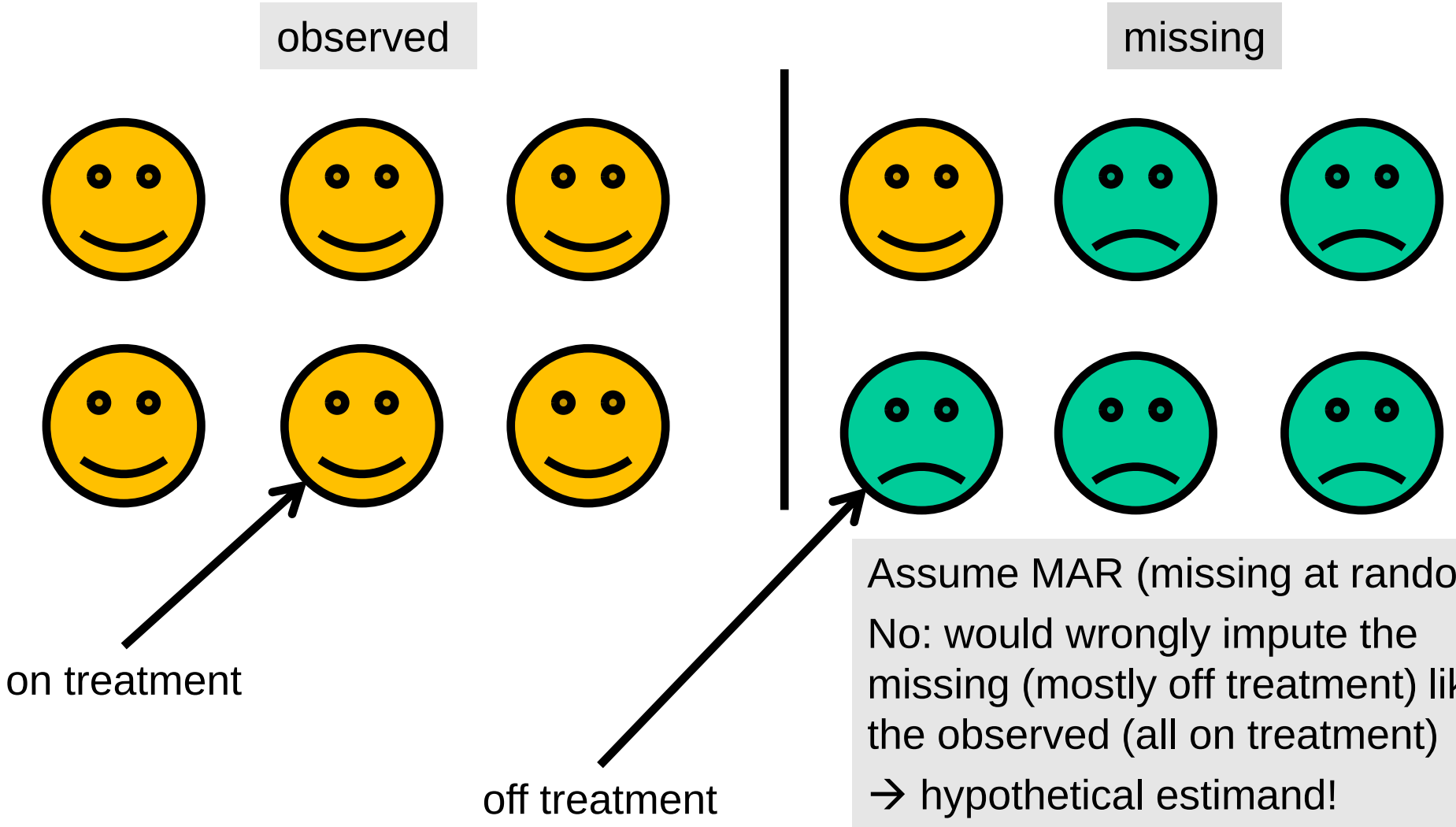
- Consider 2 flavours of the problem:
  1. no data after treatment discontinuation
  2. some data after treatment discontinuation

  Preferred! PeRSEVERE project shows how: https://ukcrc-ctu.org.uk/page-persevere/

Why is this a problem?
Because standard approaches to missing data assume data are missing at random, and this is unlikely to be true unless we take treatment discontinuation into account

No data after treatment discontinuation

Treatment policy strategy



Assume MAR (missing at random)?

No: would wrongly impute the missing (mostly off treatment) like the observed (all on treatment)

→ hypothetical estimand!

No data after treatment discontinuation

Treatment policy strategy

- This means we have to find a MNAR procedure
- “Reference-based imputation” says that we should
  - identify a reference group whose outcomes may inform the outcomes of off-treatment patients
  - construct the distribution of the missing data by combining information on fully observed individuals in that treatment group with information from the reference group
- I’ll describe this for continuous outcomes but the idea applies for other outcome types

Reference-based imputation for continuous outcomes

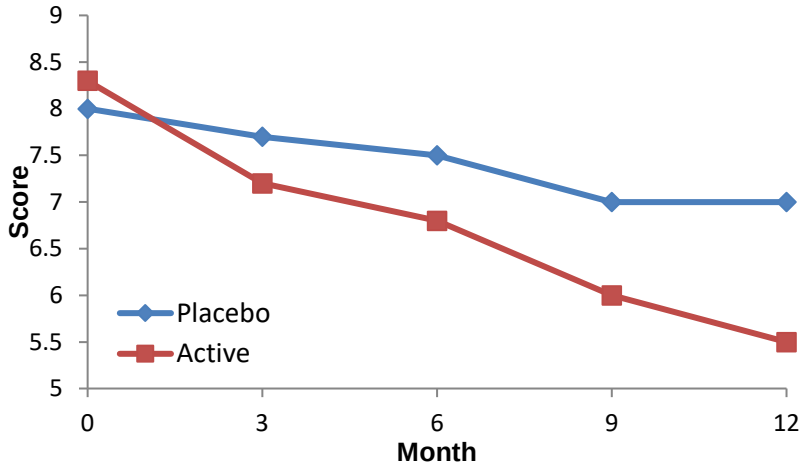
Treatment policy strategy

Carpenter et al. *J Biopharm Stat* 2013; 23: 1352–71.

1. For each treatment arm, fit a multivariate normal linear model
2. For each treatment arm, draw a mean vector and variance-covariance matrix from the posterior

Step 1 & 2: Estimate & draw means & variances

Treatment policy strategy



Reference-based imputation for continuous outcomes

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1. For each treatment arm, fit a multivariate normal linear model
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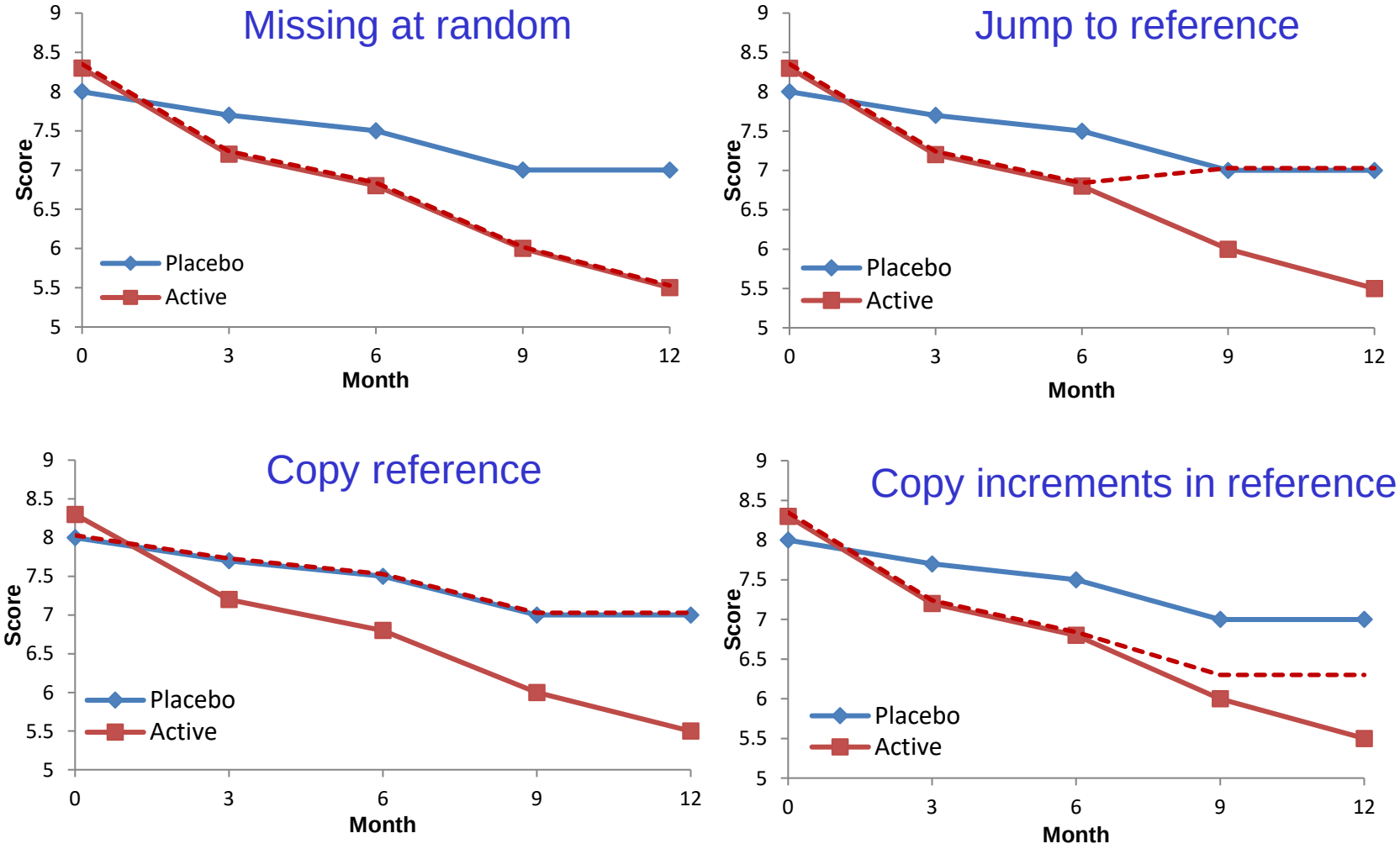
3. For each patient who discontinued treatment, form joint distribution of pre- and post-discontinuation data from reference (various flavours)

Step 3: Mean (dashed line) for active arm who discontinue treatment after 6 months

Treatment policy strategy



reference=placebo

Reference-based imputation for continuous outcomes

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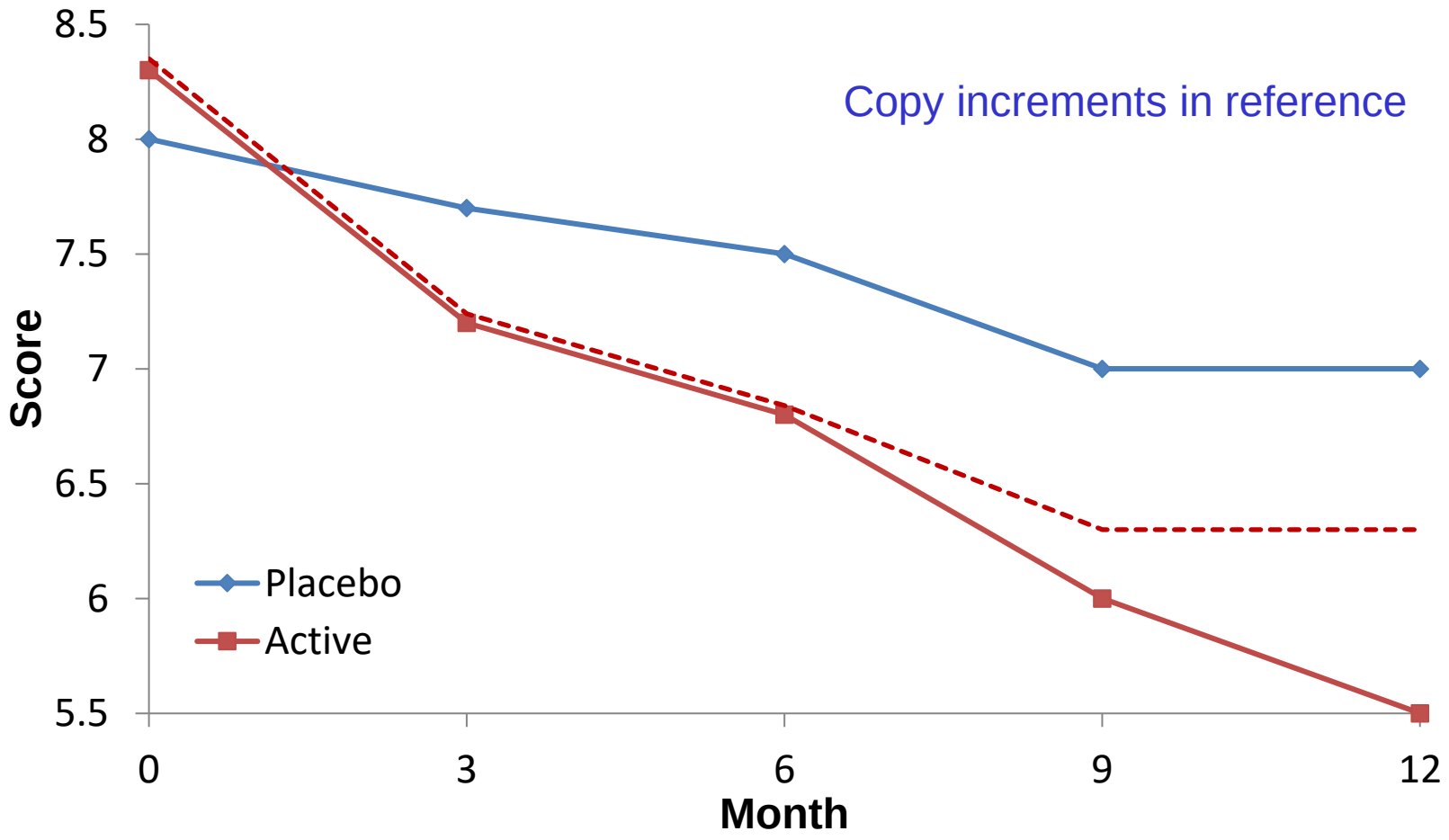
3. For each patient who discontinued treatment, form joint distribution of pre- and post-discontinuation data from reference (various flavours)
4. For each patient who discontinued treatment, impute post-discontinuation data from their conditional distribution given observed data

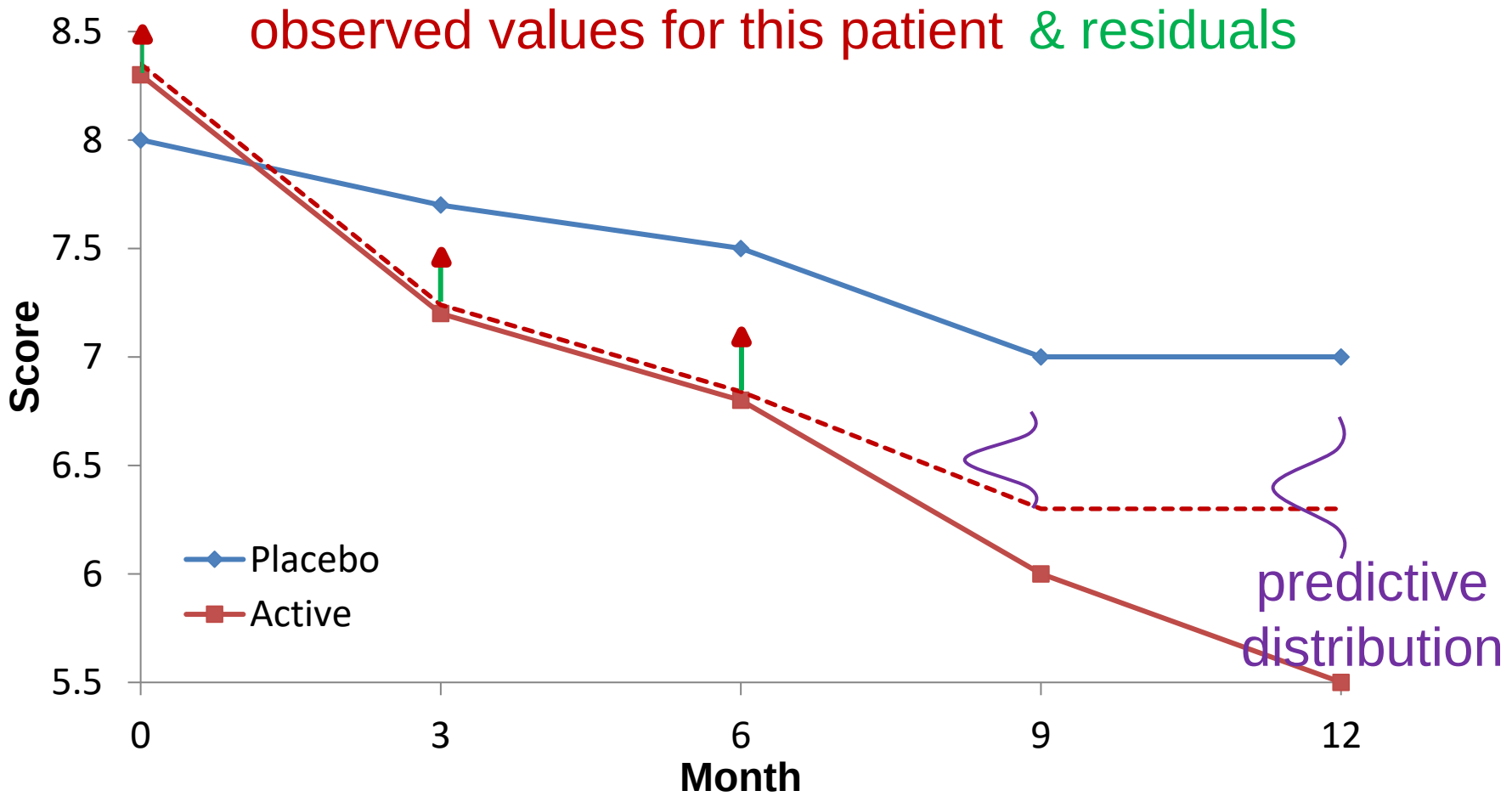
Step 4: impute post-discontinuation data

Treatment policy strategy



Step 4: impute post-discontinuation data

Treatment policy strategy



Reference-based imputation for continuous outcomes

Treatment policy strategy

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1. For each treatment arm, fit a multivariate normal linear model
2. For each treatment arm, draw a mean vector and variance-covariance matrix from the posterior
3. For each patient who discontinued treatment, form joint distribution of pre- and post-discontinuation data from reference (various flavours)
4. For each patient who discontinued treatment, impute post-discontinuation data from their conditional distribution given observed data
5. Repeat steps 2-4 m times (m imputed data sets)
6. Fit the model of interest to each imputed dataset, and combine the parameter estimates using Rubin's rules

Assumptions underlying reference-based imputation

Treatment policy strategy

The RBI methods turn out to correspond to assumptions about the effect of the treatment after it is discontinued

- Jump to reference: treatment has no effect after it is discontinued
- Copy reference: treatment has decaying effect after it is discontinued
- Copy increments in reference: treatment has maintained effect after it is discontinued

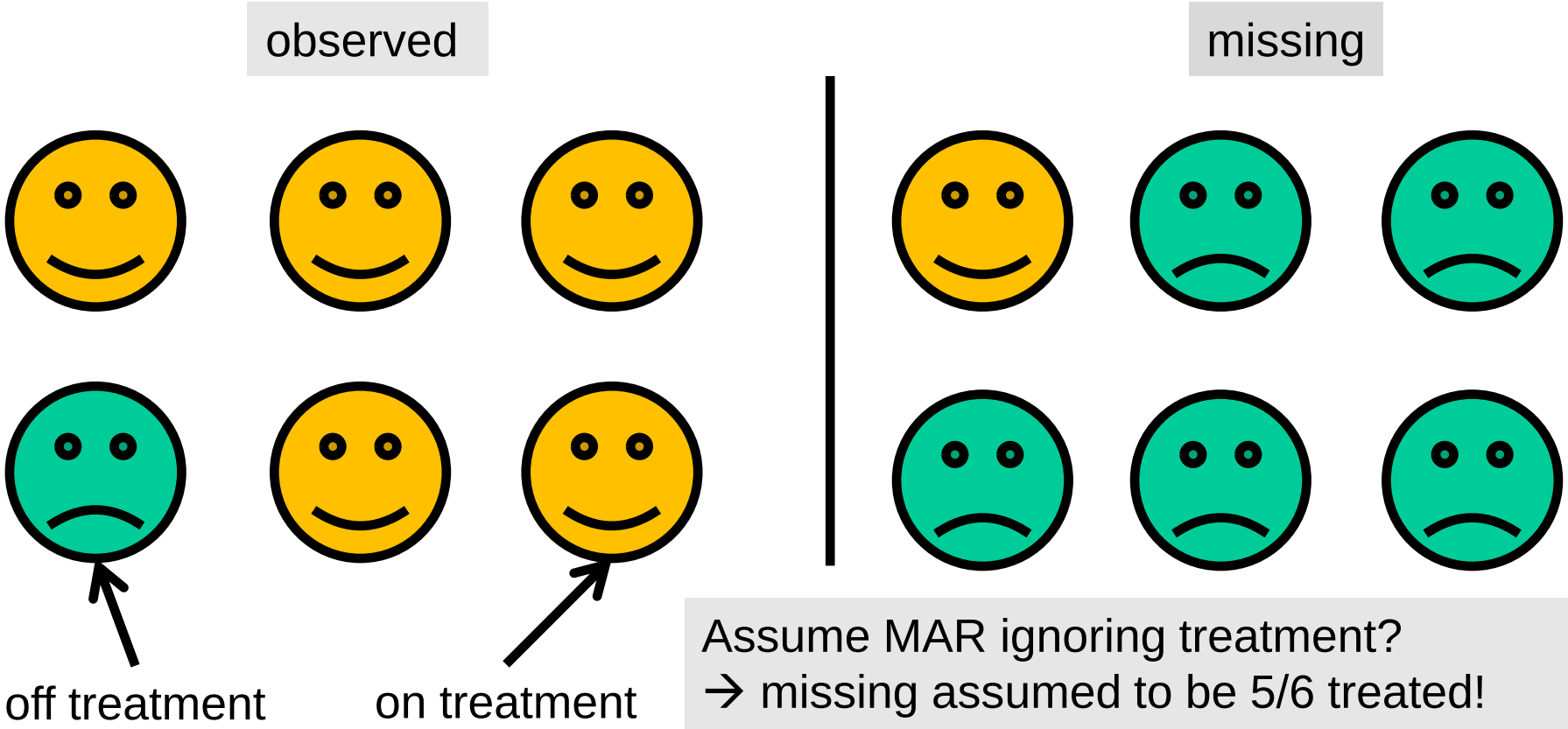
White, Joseph, Best. *J Biopharm Stat* 2020;30:334-350

Software:

- SAS: Five macros by James Roger at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data
- Stata: mimix by Cro et al. *Stata J* 2016; 16: 443–463.
- R: rbmi and RefBasedMI

Some data after treatment discontinuation

Treatment policy strategy



Assume MAR ignoring treatment?
→ missing assumed to be 5/6 treated!

We can fix this by assuming MAR conditional on treatment

Implement by multiple imputation

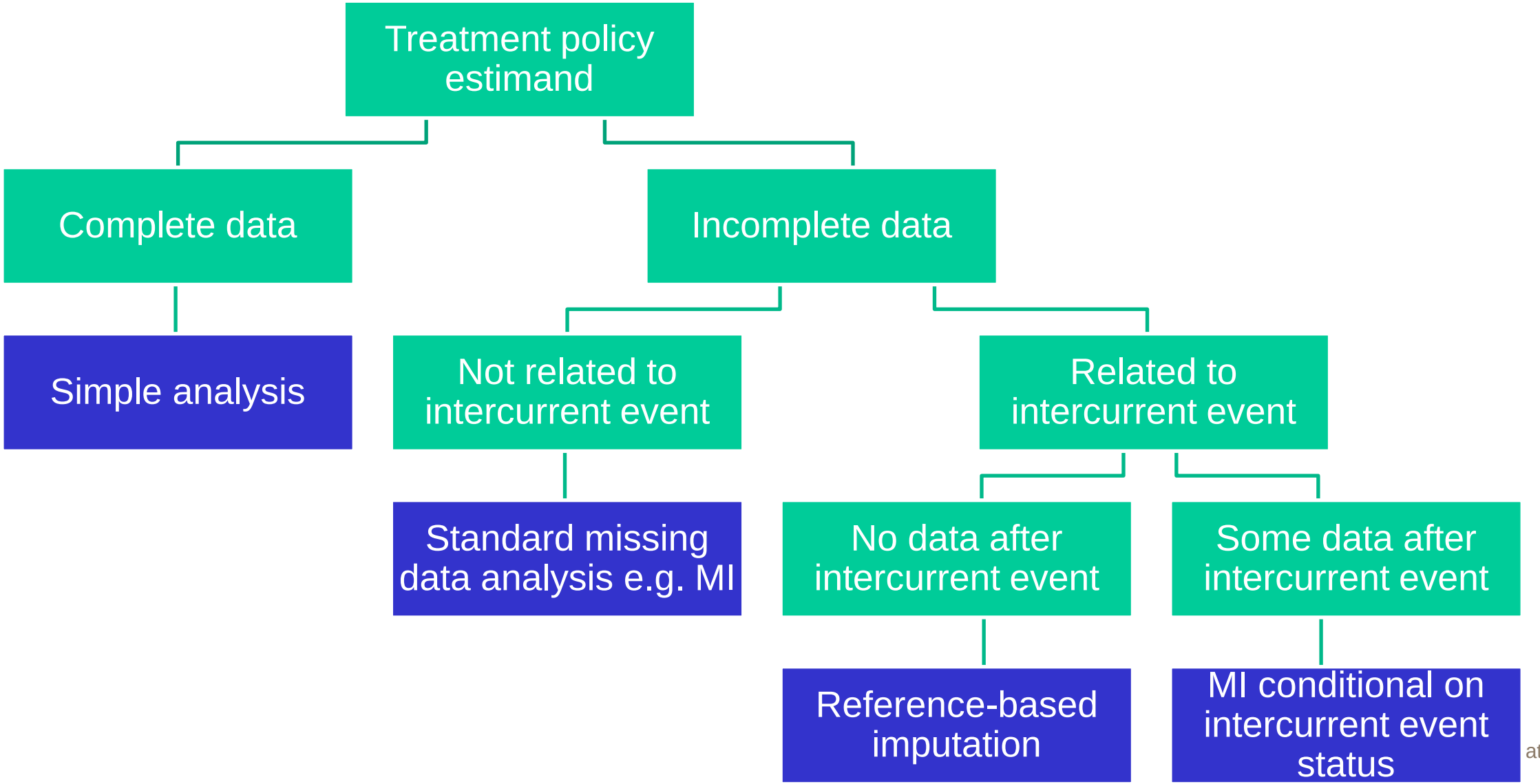
Some data after treatment discontinuation

Treatment policy strategy

- Possible approaches (Drury et al, in preparation):
  - Multiple imputation
    - work sequentially (impute each time point in turn)
    - allow on/off treatment status to affect mean outcome
    - and (optionally) the slope on previous outcomes
    - and (optionally) the time of previously stopping treatment
  - implemented in SAS proc MI but should work in other software
  - also macros by James Roger at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data
  - lots of other work ongoing

Summary for treatment-policy estimand

Treatment policy strategy



Estimation for composite strategy

- Easy!

- (Although missing data issues in composite outcomes can still be tricky)
  - Pham et al. *Stat Med* 2021; 40: 6634–6650

Estimation for hypothetical strategy

Hypothetical strategy

Fundamentally there are 2 analytical approaches to estimate a hypothetical estimand "if the intercurrent event hadn't occurred":

- Exclude the observed data after the ICE (if any)
  - recreate the hypothetical data after the ICE e.g. by mixed model, MI or IPCW
  - recognise that this potentially causes selection bias
    - those with and without ICE may differ on baseline or time-varying covariates
  - adjust for these covariates – e.g. by multiple imputation or IPCW
    - "no unmeasured confounders" assumption
  - *selection bias also arises in reference-based imputation but is generally ignored*
- Model the effect of the ICE
  - work back to what would have been observed without the ICE
  - e.g. by assuming the effect of stopping treatment equals the [reversed] effect of randomised treatment

Estimation for hypothetical strategy: MI (“exclude”)

Hypothetical strategy

- Recall the problem of estimating the treatment policy estimand when there are no data after the intercurrent event
  - we’re estimating the treatment effect as if the intercurrent event didn’t occur
  - this is a hypothetical estimand!
- So we could simply exclude any data after the intercurrent event and analyse the remaining data by
  - multiple imputation: impute the missing data under MAR, which means assuming they behave like the observed on-treatment data
  - a mixed model: which does the same thing, but the imputation is implicit
- IPCW is a neat alternative …

Estimation for hypothetical strategy: IPCW (“exclude”)

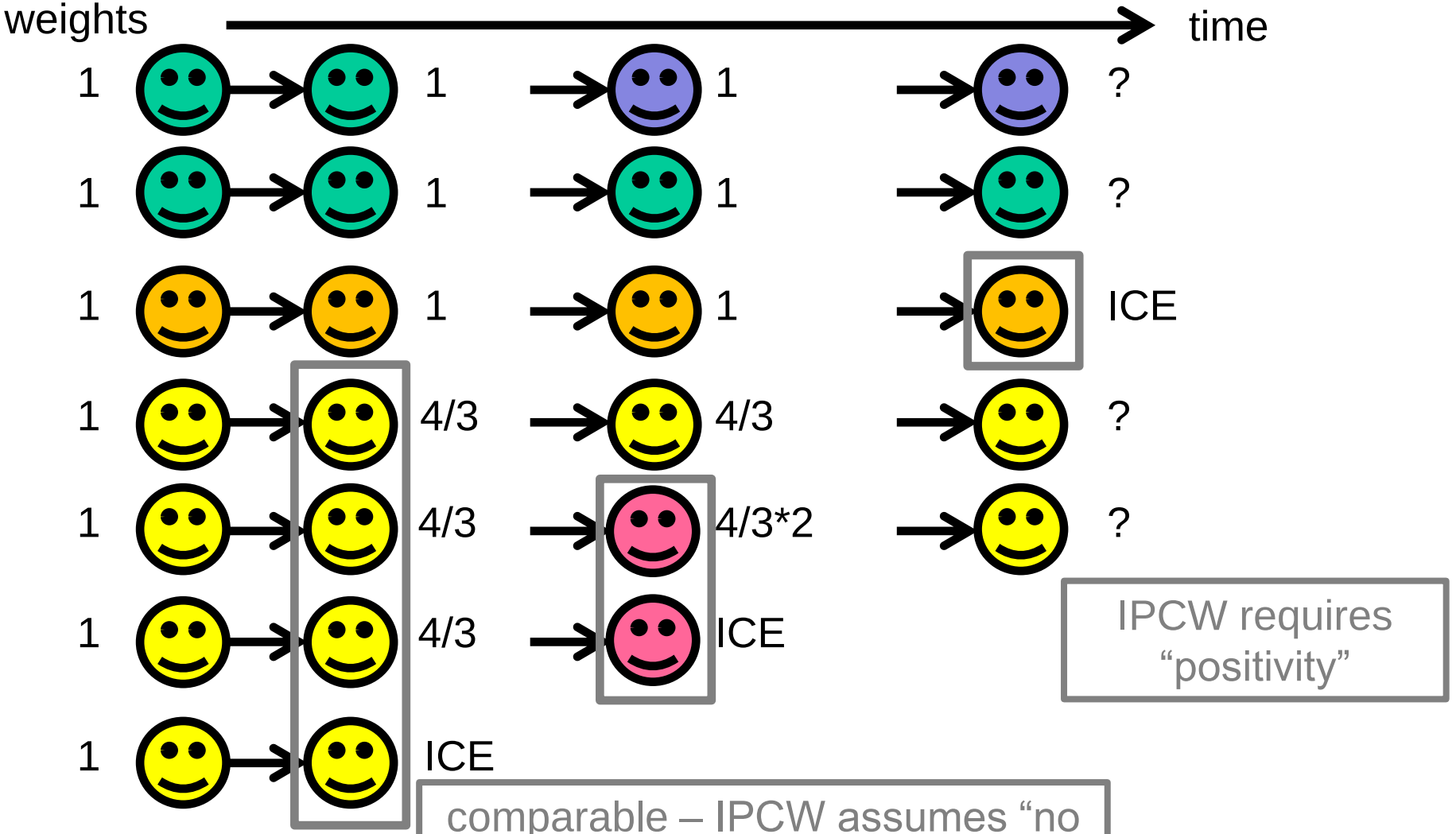
Hypothetical strategy

May apply very generally:

- IPCW = inverse probability of [not] censoring weighting
- For each type of intercurrent event handled by this strategy:
  - censor at this intercurrent event
  - model time to this intercurrent event using time-updated covariates
  - compute probability of remaining uncensored
  - use as time-dependent weights in analysis
  - e.g. Dodd et al, *Trials* 2017:18;498.
- Design implication – record all time-updated covariates that are prognostic *and* predict switching

Example of IPCW (one trial arm)

Hypothetical strategy



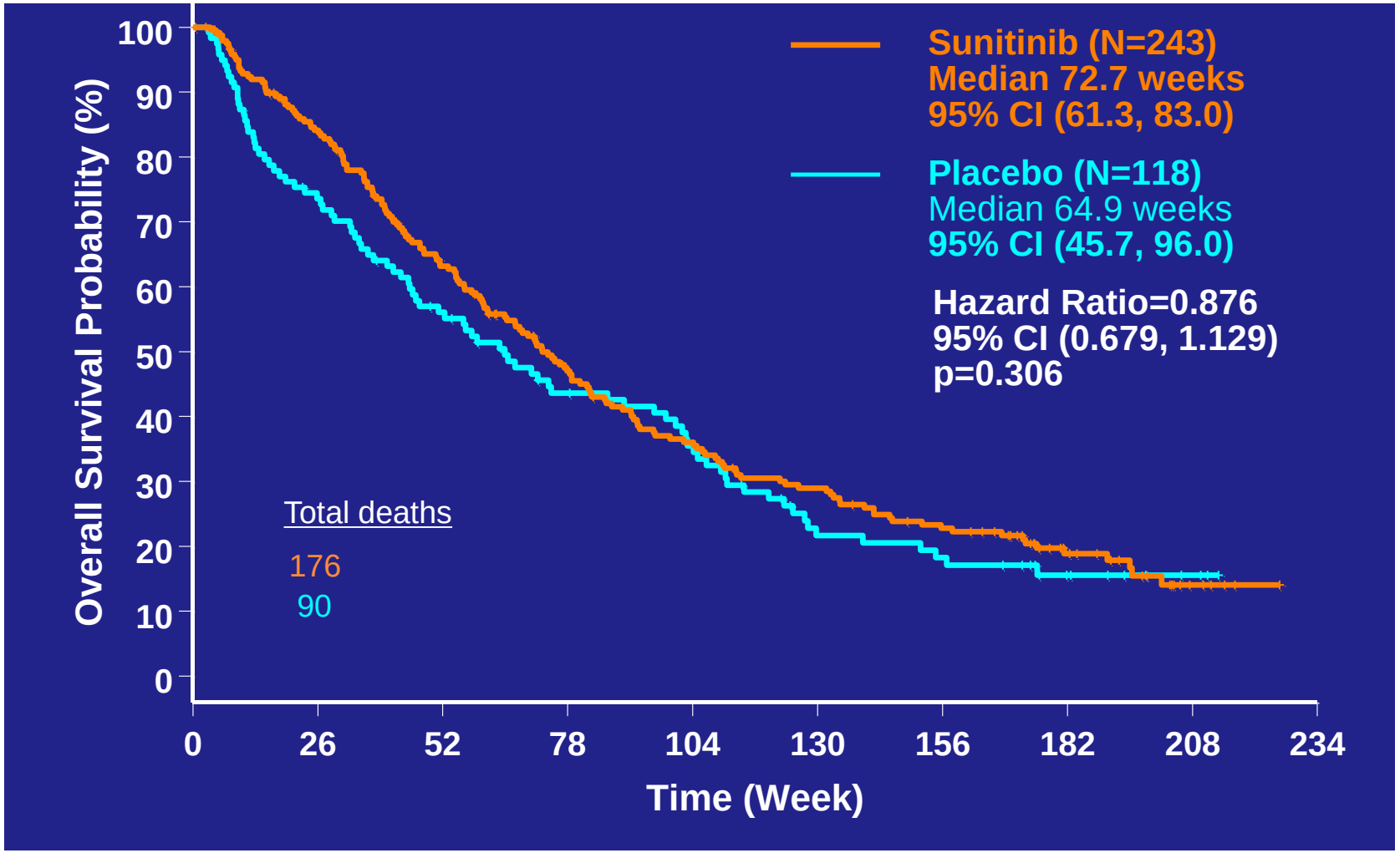
Estimation for hypothetical strategy: instrumental variable estimation (“model”)

Hypothetical strategy

- IPCW makes no unmeasured confounders assumption and requires positivity
- Instrumental variable (IV) estimation avoids both, but
  - makes the different assumption of common treatment effect: same treatment effect whether randomised or switched
  - handles limited ICEs: non-adherence or switch to treatment of another trial arm
- Basic idea is
  - model relates observed outcomes to potential untreated outcomes
  - potential untreated outcomes must balance across randomised groups
  - model parameter is estimated to achieve balance
- Model depends on outcome type
  - quantitative outcome: standard econometric methods e.g. Stata `ivreg`
  - survival data: rank-preserving structural failure time model (RPSFTM)

A trial of Sunitinib vs Placebo: overall survival

Hypothetical strategy

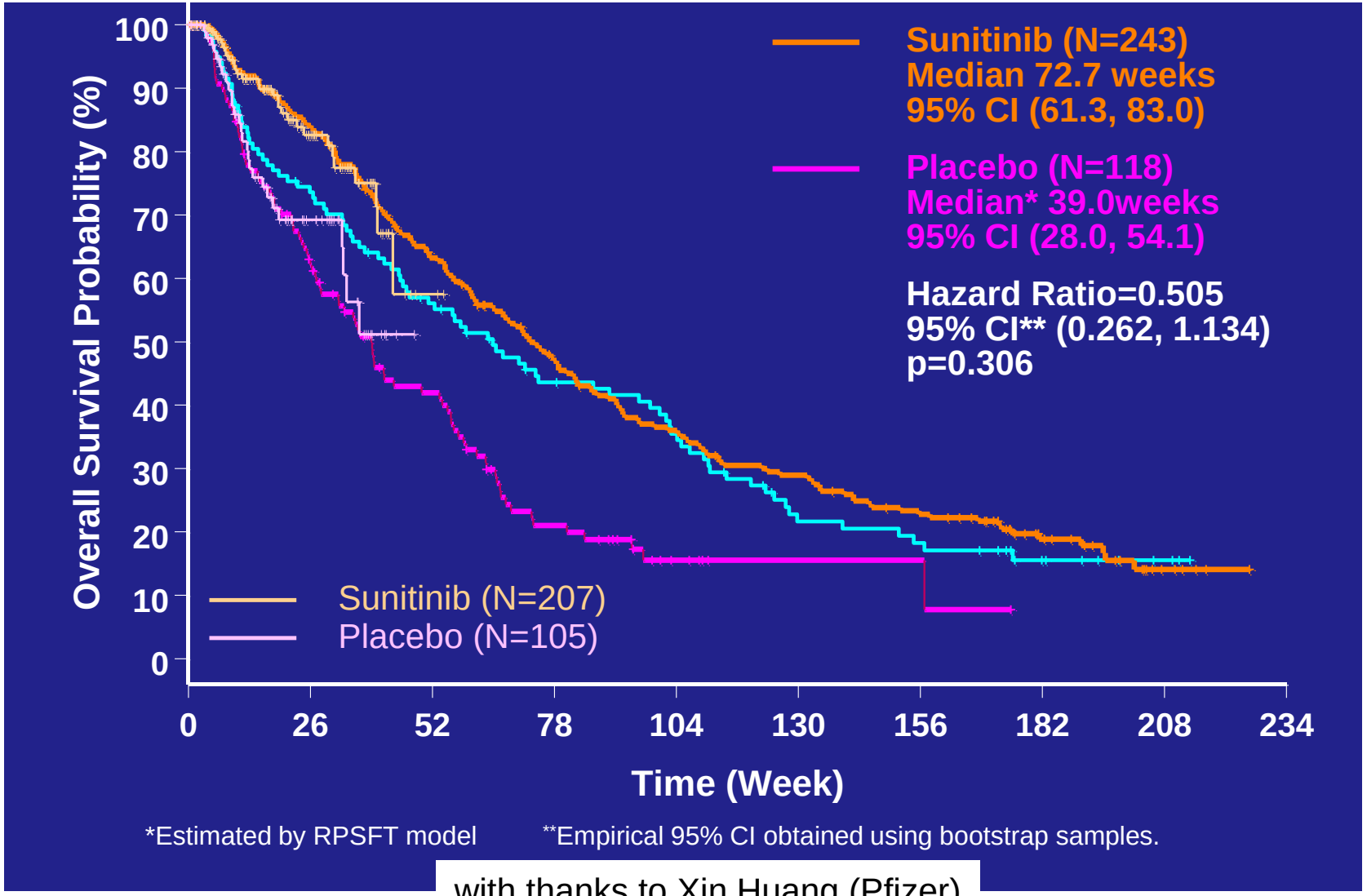


- In GIST (cancer)
- ICE: placebo arm patients may start sunitinib on disease progression
- Hypothetical estimand: because this switching wouldn't occur if drug weren't approved

with thanks to Xin Huang (Pfizer)

Sunitinib overall survival with RPSFTM

Hypothetical strategy



- P-value unchanged: no new evidence of treatment effect
- HR more extreme and CI wider: treatment effect un-diluted

with thanks to Xin Huang (Pfizer)

Estimation for principal stratum strategy

- Consider a specific ICE: not starting treatment
- In a double-blind trial, the subgroup of participants with the ICE should be comparable across treatment groups
  - "participants who will start treatment" is a valid principal stratum
  - an analysis that excludes participants who don't start treatment (modified ITT or per-protocol) validly estimates the treatment effect in this principal stratum
  - Brennan Kahan, work in progress
- In some other trials with all-or-nothing compliance (i.e. ICE only at start), we may estimate the complier average causal effect e.g. Dunn et al *BJPsych* 2003;183:323-331
- Computational approaches:
  - continuous outcome: instrumental variables regression [NB debatable whether hypothetical or PS]
  - binary outcome: see e.g. https://pure.hw.ac.uk/ws/portalfiles/portal/53307522/main_CACE_accepted.pdf
- Principal stratum estimands are hard to estimate with complex compliance

Estimation for while on treatment strategy

- I'm going to focus on data missing (truncated) due to death in trials in palliative care, where the outcome is symptoms / quality of life
  - almost the only setting I've met where this estimand makes sense
  - note that a treatment policy estimand does not make sense at all here
  - also called the "partly conditional" estimand: conditional on being alive
  - Kurland et al. *Stat Sci* 2009; 24: 211
- Single time point: simply compare the two treatment groups, restricted to those alive
  - NB these are not strictly comparable groups! must set this alongside a comparison of survival
- Multiple time points: avoid implicitly imputing data after death!
  - analyse time by time
  - if an overall analysis is needed (e.g. to fit a model where treatment effect is constant or proportional to time), achieve this by using "independence estimating equations", i.e. GEE with independence working correlation

A possible hybrid strategy

1. Define intercurrent events for which
   - treatment policy strategy is used (“included events”)
   - composite strategy is used (“component events”)
   - hypothetical strategy is used (“excluded events”)
2. Form composite
3. Censor at excluded events (but not at included events)
4. Multiply impute the missing data *except* those after excluded events
   - taking account of the included events: include event status in imputation model
   - use reference-based imputation if no observed data after event
5. Handle the missing data after excluded events by multiple imputation or IPCW
   - *not* taking account of the excluded events

Conclusions

- All the estimands can be estimated
  - but the principal stratum estimand should at present only be tackled in settings with simple ICEs (e.g. all-or-nothing compliance)
- Treatment policy and hypothetical estimand usually require untestable assumptions
  - treatment policy: around missing data
  - hypothetical:
    - around comparability of those with and without ICEs (if using MI/IPCW)
    - around common treatment effect / exclusion restriction (if using IV)
- ICH E9(R1) main message still applies:
  - clearly state estimand
  - clearly state assumptions needed to estimate it
- Questions?