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Estimation with multiple intercurrent events and mixed estimand strategies

Ian White

Joint EFSPI & BBS virtual event

Addressing intercurrent events: Treatment policy and hypothetical strategies

15/12/2022

Smarter Studies
Global Impact
Better Health

Motivation

- In practice we have many types of intercurrent events
- We may address different intercurrent events differently

Intercurrent event = ICE

Example: trials of tuberculosis treatments

Particular example: STREAM 1

- Population: rifampicin-resistant tuberculosis (TB)
- Treatment: new shorter regimen (9 months) vs standard regimen (20 months)
  - non-inferiority trial: shorter regimen will be preferable if it is similarly effective
- Outcome: composite binary outcome (“favourable”)
  - alive & culture-negative at 132 weeks (i.e. no microbiological evidence of infection)
- Summary: risk difference
- Intercurrent events: see next

Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; 380: 1201–1213.

Example: trials of tuberculosis treatments

Intercurrent event	Handling in STREAM 1	Possible alternative
Minor treatment change	ignored (treatment policy)	✓
Major treatment change	unfavourable outcome (composite)	experimental to control: hypothetical other: treatment policy
Stop treatment	ignore in mITT analysis (treatment policy)	✓
TB-related death	unfavourable outcome (composite)	✓
Accidental / non-TB death	unfavourable outcome (composite)	hypothetical

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Pham TM et al. Rethinking intercurrent events in defining estimands for tuberculosis trials. *Clin Trials* 2022; 19: 522-533.

Plan

1. General thoughts
2. Two ICEs addressed by the treatment policy strategy
3. Two ICEs addressed by the hypothetical strategy
4. One ICE addressed by the treatment policy & one by the hypothetical strategy

Aim is to suggest some ways to do this – different ways certainly exist!

Ambitious & high-level

Focus on estimation, assuming estimand choice is given

The five strategies for handling intercurrent events

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	Restrict to a subgroup who wouldn't experience intercurrent event
While on treatment strategy	Restrict to possibly non-comparable groups

One intercurrent event addressed by treatment policy strategy

- Very simple with complete outcome data: analyse the observed outcome data
- Otherwise the big question is: does the intercurrent event predict both missingness of outcome and the outcome itself? – time-varying confounder
- Yes → we need to account for it in the analysis

With some outcome data observed after intercurrent event: impute sequentially, including intercurrent event in the imputation model (as in Thomas Drury's Dec 8th talk)	Without outcome data after intercurrent event: reference-based imputation (as in rbmi talk on Dec 8th)
• e.g. in TB trial with culture status $Y_1, Y_2, \ldots$ • impute Y_t from logistic regression on $Y_{t-1}, Y_{t-2}, I_t, \ldots$ • where I_t = indicator of the intercurrent event having occurred before time t	

Multiple intercurrent events: scope

We need to tailor our methods to

- What types of ICEs we have (e.g. two treatment policy + one hypothetical)
- In what order(s) the ICEs can occur
- Whether known/unknown confounders predict both ICEs and outcome

and to missing data issues (especially for treatment policy)

- Whether we have intermittent missing data, or a monotone (drop-out) pattern

- Whether we have loss to follow-up before ICEs
- Whether we have any follow-up after ICEs, or follow-up ends at an ICE

Multiple intercurrent events: estimation

Some challenges are

- Can we combine the methods corresponding to each ICE separately?
- Can we use a multi-stage multiple imputation (MI) approach, handling each ICE in turn?

Multiple intercurrent events: simple cases

Some cases are simple, e.g.

- ICE addressed by treatment policy strategy that doesn't predict missingness – genuinely ignore in analysis, so easy to combine with other ICEs
- ICE addressed by composite strategy – just handle it as part of the outcome definition
  - the only problem would arise if different components of the composite outcome were collected in different ways, giving different follow-up patterns
    - Pham TM, White IR, Kahan BC, et al. A comparison of methods for analyzing a binary composite endpoint with partially observed components in randomized controlled trials. *Stat Med* 2021; 40: 6634–6650.

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Multiple intercurrent events addressed by treatment policy strategy

Example 1: two treatment policy ICEs

e.g. in TB trial, suppose we have

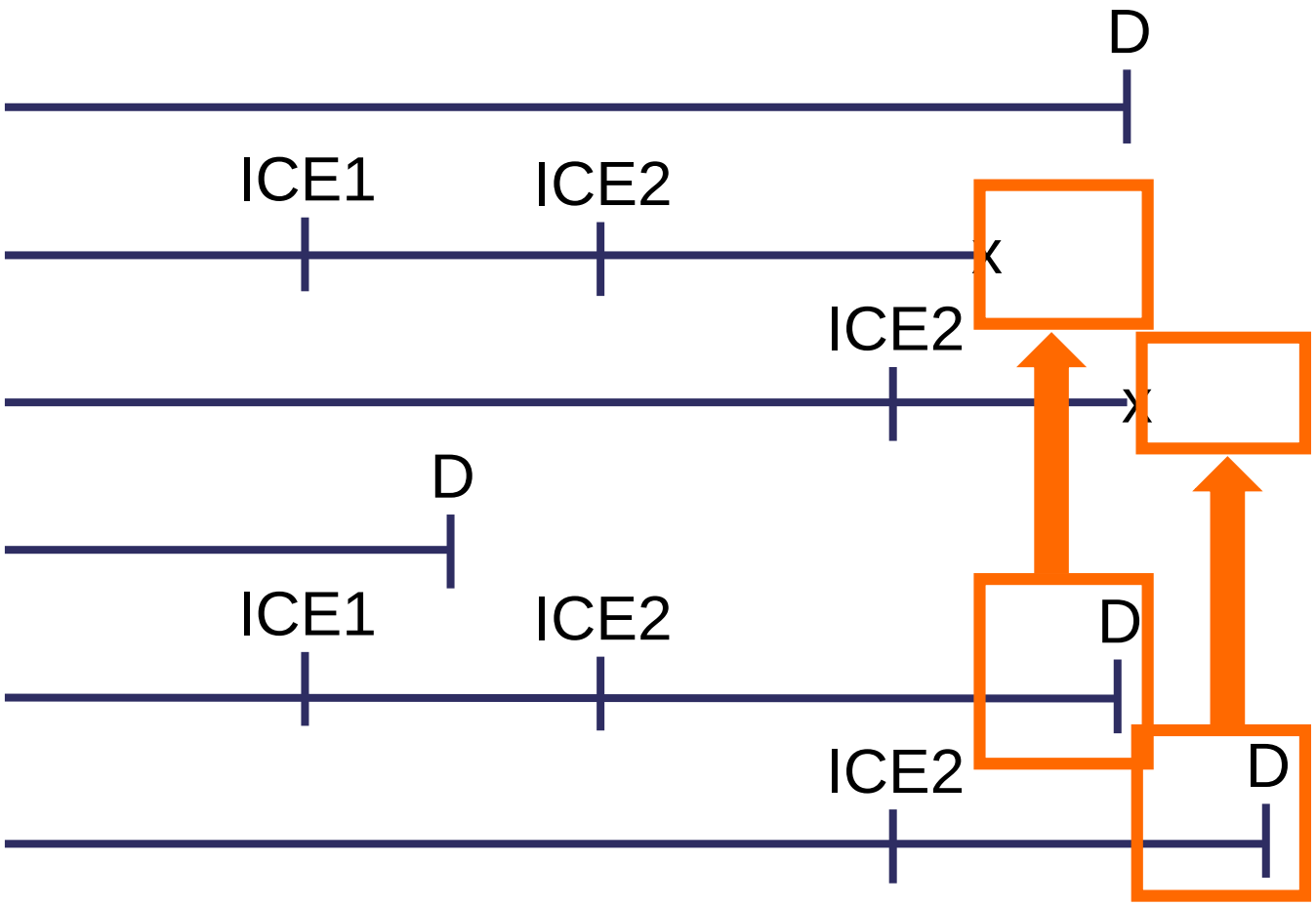
- ICE1 = minor treatment change
- ICE2 = treatment discontinuation
  - ICE1 cannot occur after ICE2

Initially suppose

- No loss to follow-up before ICE2
- No intermittent missing data

Then we can adapt the sequential imputation approach:

Example 1: two treatment policy ICEs



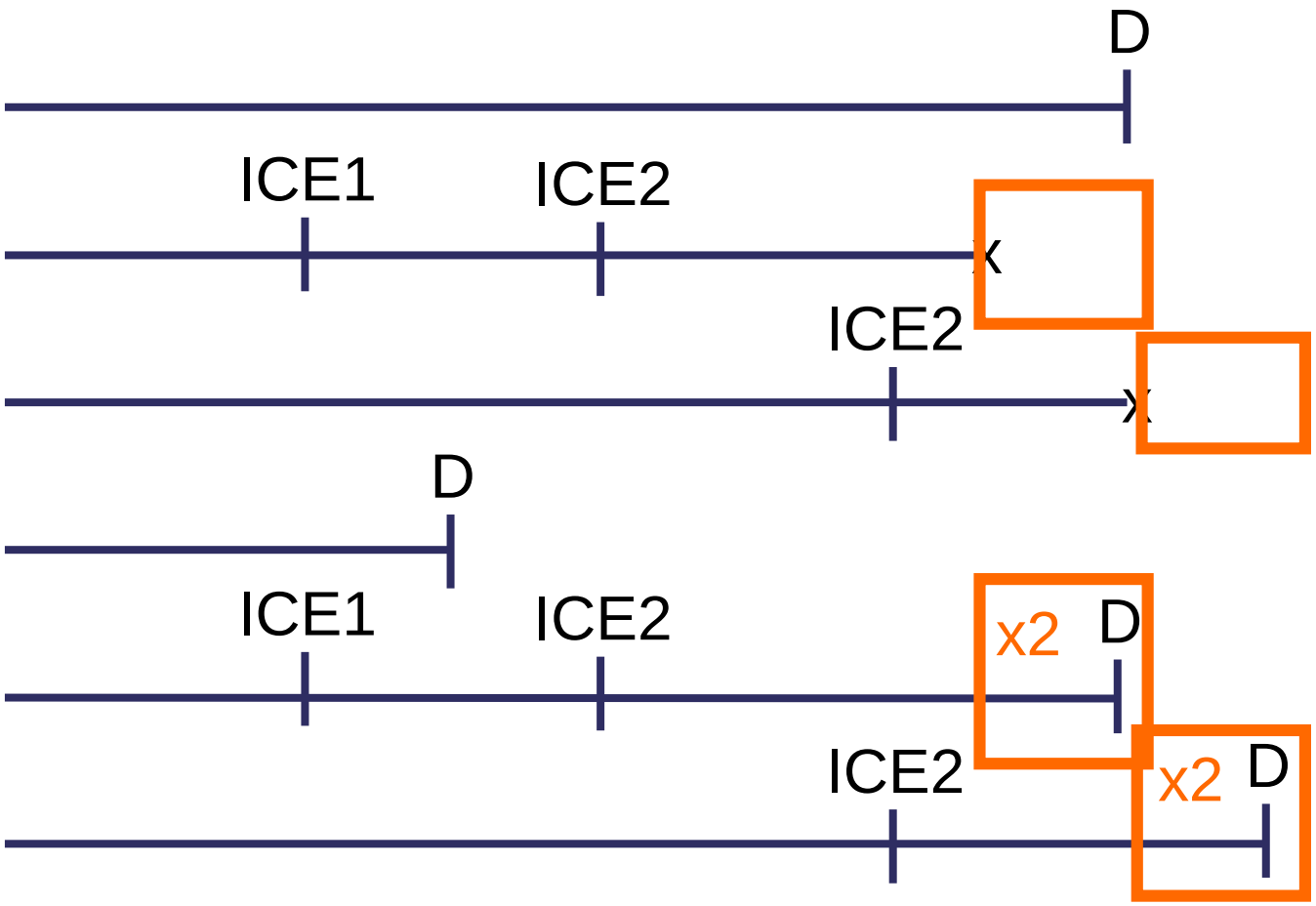
Sequential imputation approach: impute from left to right, modelling current outcome on

- previous outcomes and
- current status on ICEs

Note: could also achieve this by IPCW (inverse probability of censoring weighting)

D=disease event, x=lost to follow-up;
ICE1 = minor treatment change, ICE2 = treatment discontinuation

Example 1: two treatment policy ICEs



Sequential imputation approach: impute from left to right, modelling current outcome on

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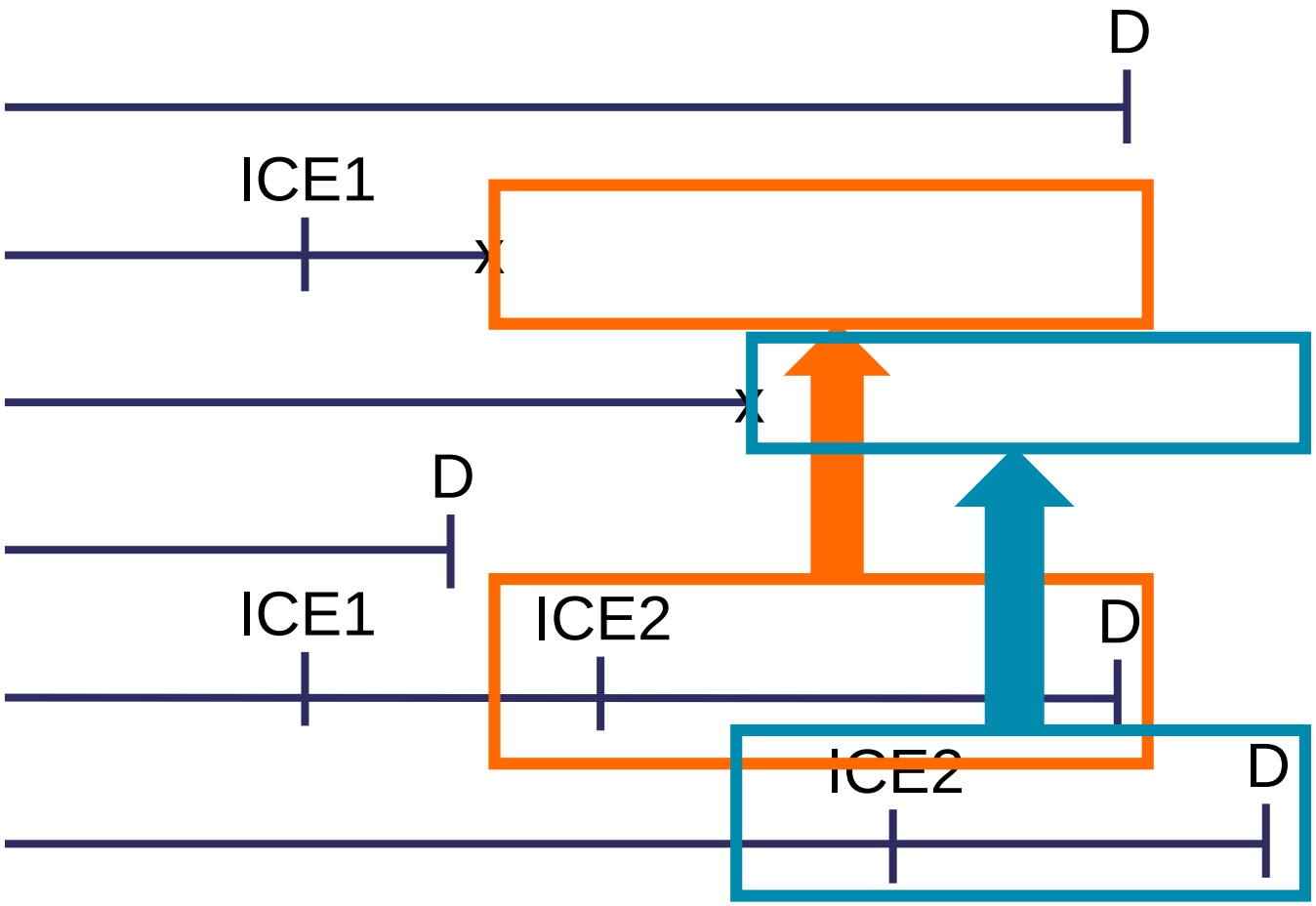
D=disease event, x=lost to follow-up;
ICE1 = minor treatment change, ICE2 = treatment discontinuation

Example 1: extensions

If we also have…	We could…	Comment
Intermittent missing data?	Impute it **first** under MAR, ignoring ICEs	Assumes ICE status unimportant given previous & subsequent outcomes – OK?
Loss to follow-up before ICE2?	Use only observed ICE history in imputation model	Wrongly assumes no ICEs after loss to follow-up
No follow-up after ICE2?	Use only observed ICE1 history in imputation model	Wrongly assumes outcomes are similar before & after ICE2 (treatment discontinuation)

Possible ways to handle these?

Example 1 + LTFU before ICE2

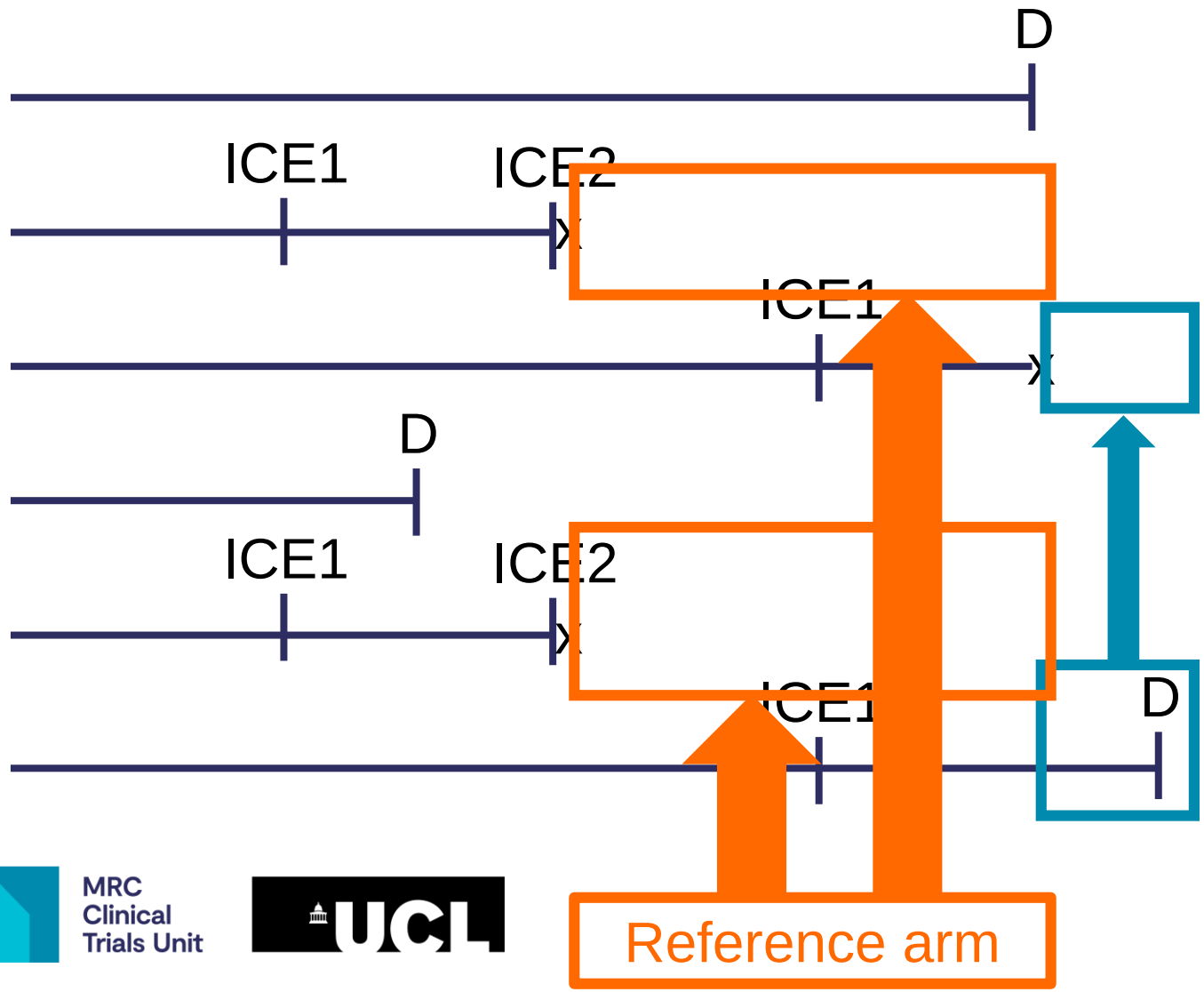


Visually it's still clear what we need to do

But how to do it in practice?

1. Sequential imputation: need to impute ICEs as well as outcomes **tricky**
2. Block imputation: impute the whole future **not in software**
3. IPCW approach: construct weights given history up to LTFU **best?**

Example 1 + no follow-up after ICE2 (treatment discontinuation)



Visually it's again clear what we need to do

But how to do it in practice?

Possible two-stage MI:

1. Impute after LTFU (not after ICE2) using sequential imputation (+ICE1 history)
2. Impute after ICE2 using reference-based imputation

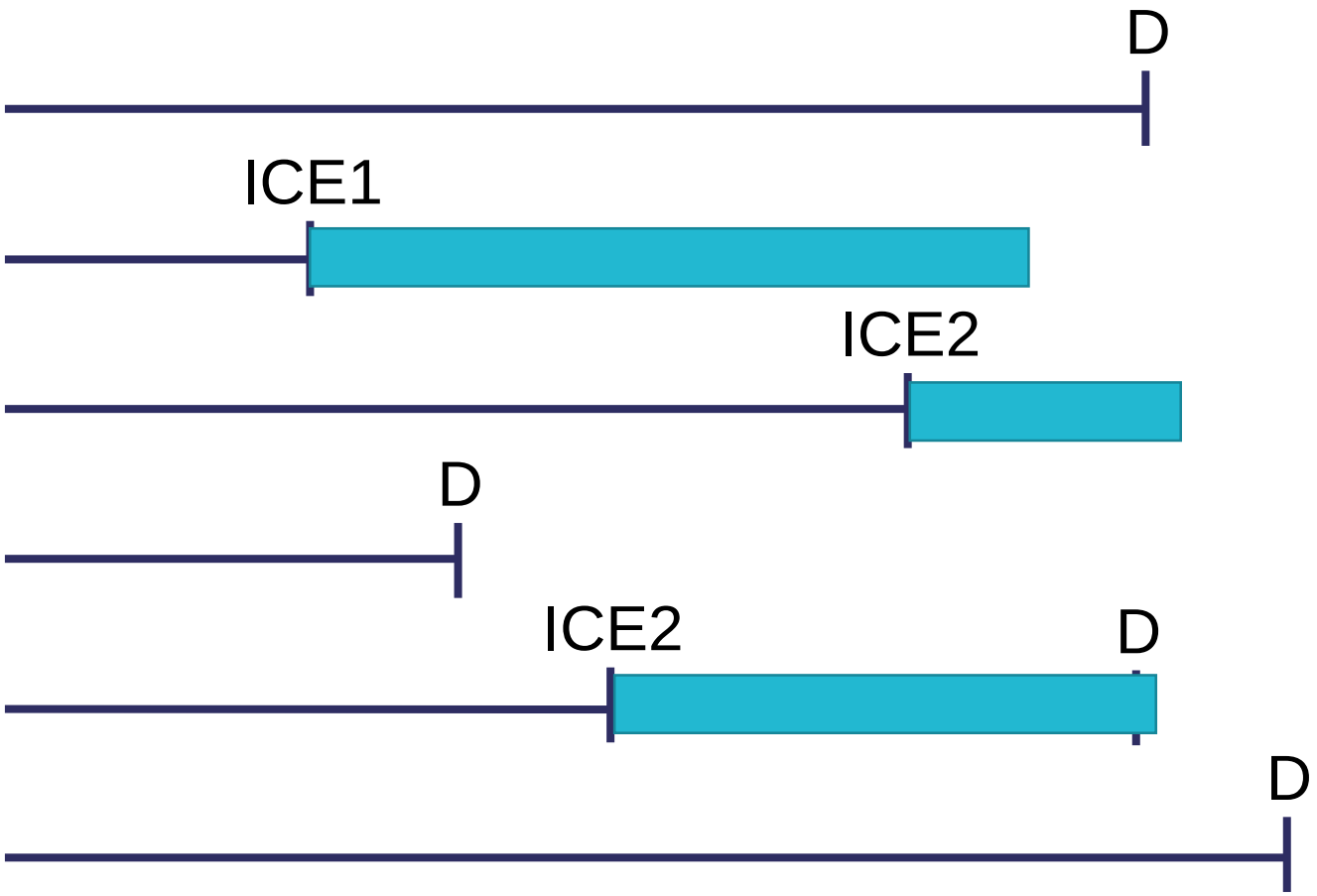
Does order matter?

Multiple intercurrent events addressed by hypothetical strategy

Multiple intercurrent events addressed by hypothetical strategy

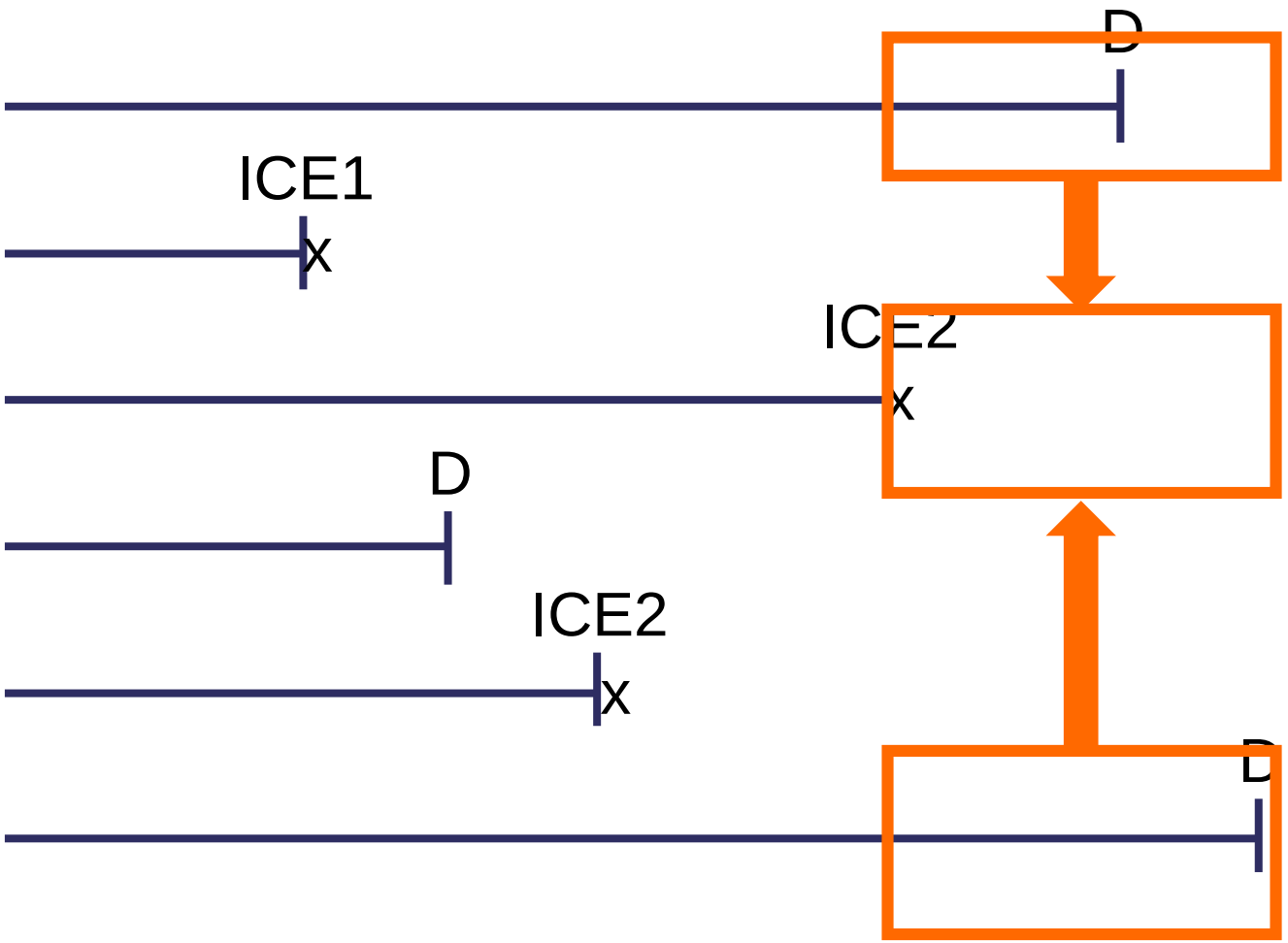
- e.g. in TB trial:
  - ICE1: treatment changes from experimental to standard
  - ICE2: non-TB death
- We *could* take a modelling approach
  - model effects of ICEs on outcome (allowing for selection)
  - then remove these effects
- I'm going to take a censoring approach
  - censor at ICEs then reduce selection bias

Example 2: two hypothetical ICEs



Step 1: censor at ICEs

Example 2: two hypothetical ICEs



Step 1: censor at ICEs

Again the picture is clear

Methods:

- Could impute, with time-varying confounders in the imputation model
- Better to use IPCW
  - model censoring (ICEs) given history
  - weight by inverse probability of remaining uncensored

Two hypothetical ICEs: IPCW method

- Censor at any ICE & use IPCW
- NB we don't *have* to deal with the different ICEs, because it's just censoring
- 2 options:
  - model the ICEs separately and multiply weights
  - model the composite ICE
- The difference is just in modelling assumptions
  - it may be easier to correctly model p(not ICE1 & not ICE2 | history) by modelling p(not ICE1 | history) * p(not ICE2 | history)
  - but beware of ties in ICE times
- Nick Latimer & Helen Bell Gorrod (U of Sheffield) are addressing this issue:

Multiple intercurrent events addressed by hypothetical strategy: Preliminary findings

- One large simulated data set, n=10,000
- Time-to-event outcome with 9% censoring
- ICE = treatment switch, with proportion = 19.5%
- 13% switch to treatment A, 6.5% to treatment B

Analysis	HR Cox (CI)
Truth	0.708
ITT	0.796 (0.76-0.83)
IPCW (treatments separate)	0.700 (0.67-0.73)
IPCW (treatments together)	0.699 (0.67-0.73)

Thanks to Nick Latimer & Helen Bell Gorrod (U of Sheffield)

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Intercurrent events addressed by treatment policy and hypothetical strategies

Intercurrent events addressed by treatment policy and hypothetical strategies

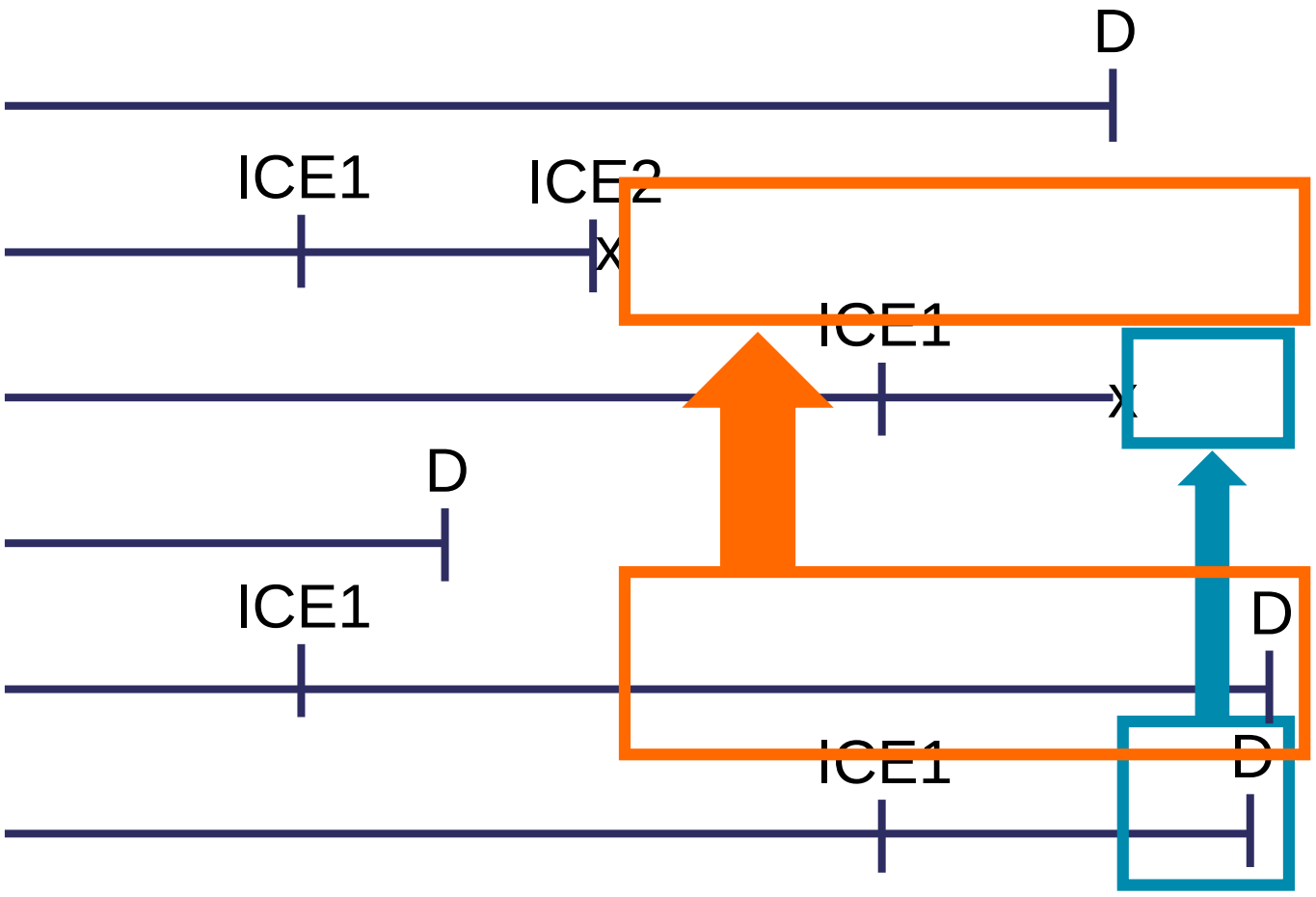
e.g. in TB trial:

- ICE1 = treatment change (treatment policy strategy)
- ICE2 = non-TB death (hypothetical strategy)

- Suppose no missing data before ICE1
- Assume ICE1 and ICE2 are both “tricky
  - ICE1 predicts outcome and missingness
  - time-varying confounders predict ICE2 and counterfactual outcome

- 2 approaches
- Both start by censoring at ICE2

Treatment policy (ICE1) and hypothetical (ICE2) strategies: approach 1



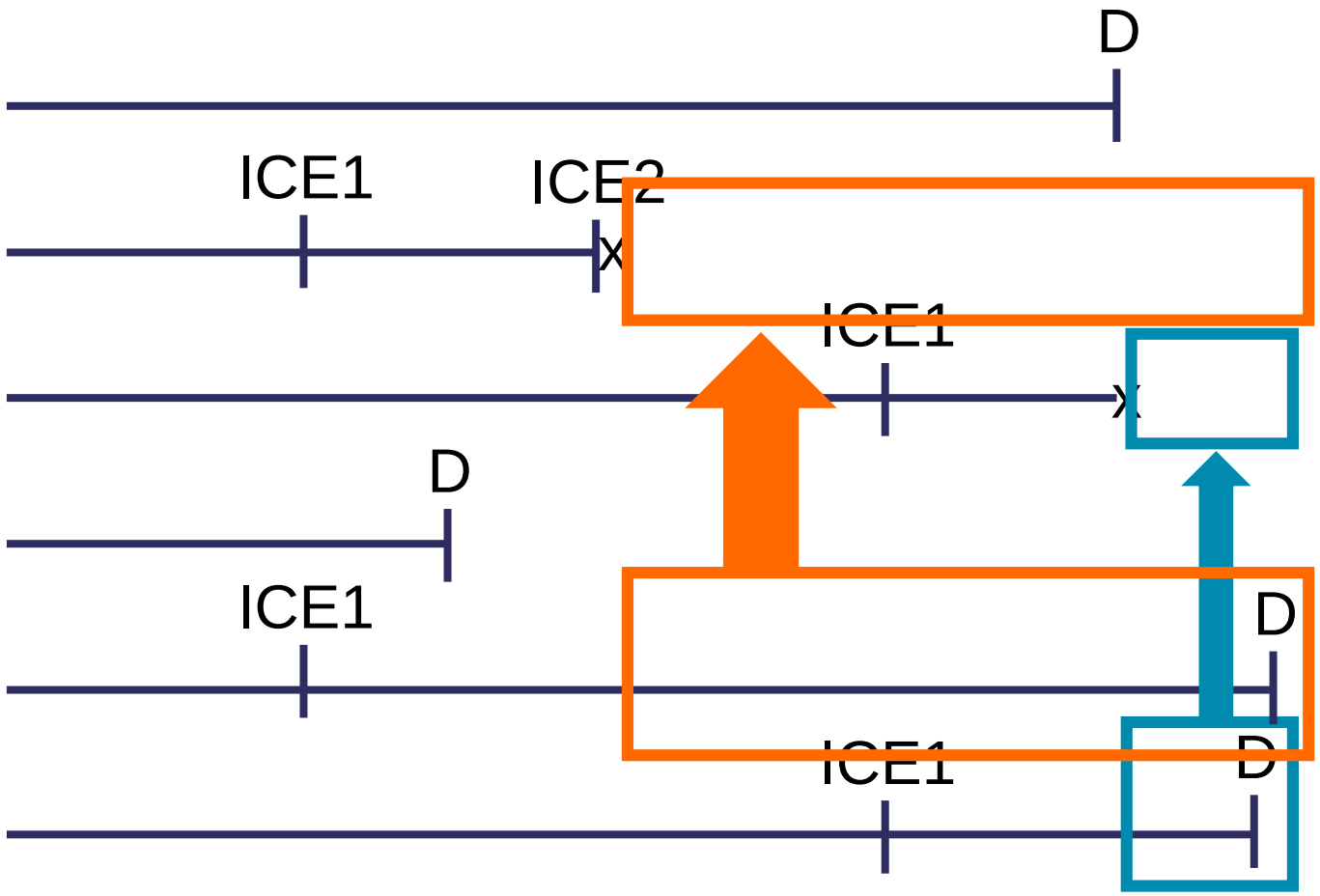
We've censored at ICE2

Possible two-stage procedure:

1. Impute after LTFU (not after ICE2) using sequential imputation (+ICE1 history)
2. Allow for selection to ICE2 by IPCW (in each imputed dataset) or MI

Could use reference-based imputation and/or address intermittent missing data

Treatment policy (ICE1) and hypothetical (ICE2) strategies: approach 2



We've censored at ICE2

Possible IPCW procedure:

1. Use IPCW for LTFU (not after ICE2) (censoring model includes ICE1 history)
2. Use IPCW for ICE2 (censoring model includes time-varying confounders)

Intermittent missing: could start with MAR imputation.

Reference-based: ???

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Concluding thoughts

IPCW vs MI

- IPCW methods for hypothetical estimands generally try to take account of a multitude of time-varying confounders
- MI methods for treatment policy estimands generally only take account of one time-varying confounder: treatment discontinuation
- Why the difference? They are tackling similar problems

How can we know what is correct?

- This is complex and methods are various
- We need a way to explain clearly what concepts we are allowing for and what each method allows for
- How do we convince ourselves? Others?

- Part of this should be a large simulation study to explore the options carefully
- Need to generate ICEs that are associated with
  - outcome
  - missingness
  - each other
- Probably a high incidence of ICEs in order to tease strategies apart

Acknowledgements

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Helen Bell Gorrod (Sheffield)

We have a new online MSc:
Statistics for Clinical Trials
https://www.ucl.ac.uk/clinical-trials-and-methodology/study

Conclusions

- All the estimands can be estimated
- Treatment policy and hypothetical estimands require untestable assumptions
- Estimation methods can be combined, but care is needed
- Two-stage estimation methods may be needed
- IPCW seems a promising combined approach

- It’s often easier to state a method than to state the assumptions it makes
- I’ve only sketched some approaches