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A NEW TRIAL DESIGN FULLY INTEGRATING BIOMARKER INFORMATION FOR THE EVALUATION OF TREATMENT-EFFECT MECHANISMS IN PERSONALISED MEDICINE

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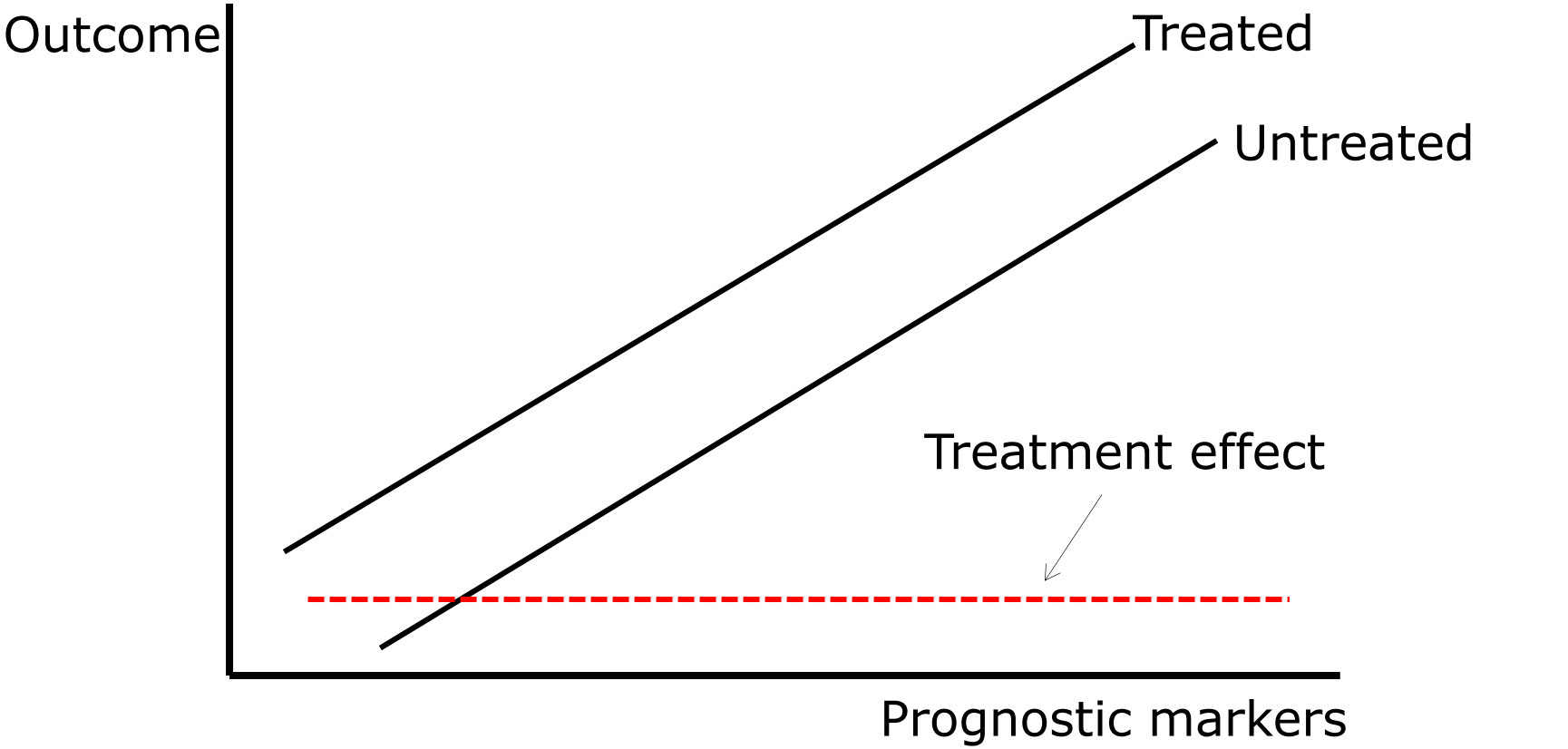
Personalised medicine and treatment effect heterogeneity

- Treatment effect heterogeneity, whereby a given treatment will be more efficacious for some patients than for others, is the underlying foundation of personalised medicine.
  - Stratified/predictive/targeted medicine
  - Genomic medicine
  - Pharmacogenomics

- If a treatment is effective, we are interested in knowing who is it (most) effective for, in advance of treatment allocation/decisions to treat.

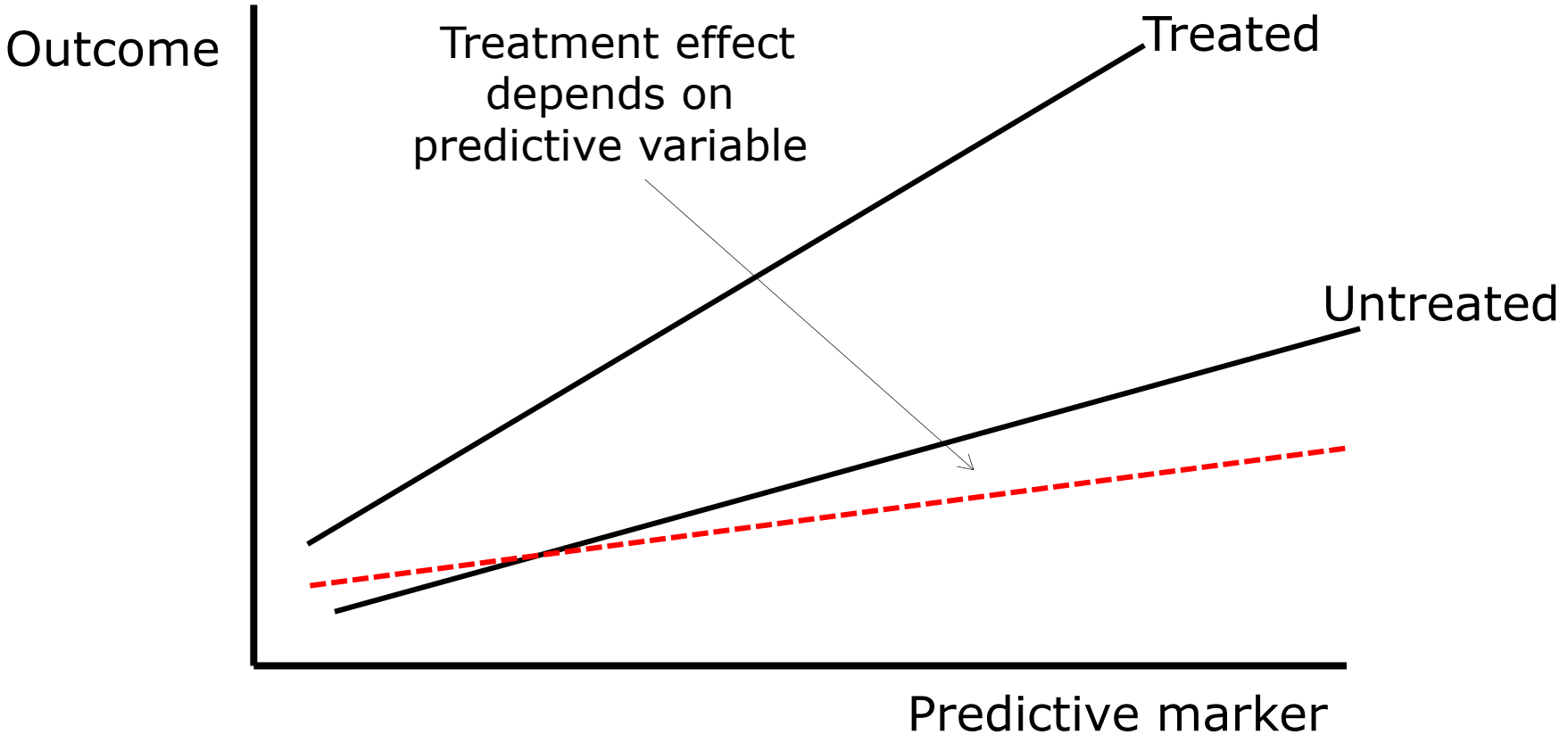
- We need access to pre-treatment characteristics that predict treatment-effect heterogeneity
  - **Not just predict outcome/response to treatment**

Prognostic markers (risk factors)



A '**prognostic biomarker**' is a biological measurement made before treatment to indicate long-term outcome for patients either untreated or receiving standard treatment. (Simon 2010).

Predictive marker



A '**predictive biomarker**' is a biological measurement made before treatment to identify which patient is likely or unlikely to benefit from a particular treatment. (Simon 2010).

Biomarker stratified design

1. Stratify patients according to predictive marker status, and randomize to treatments within each marker stratum.

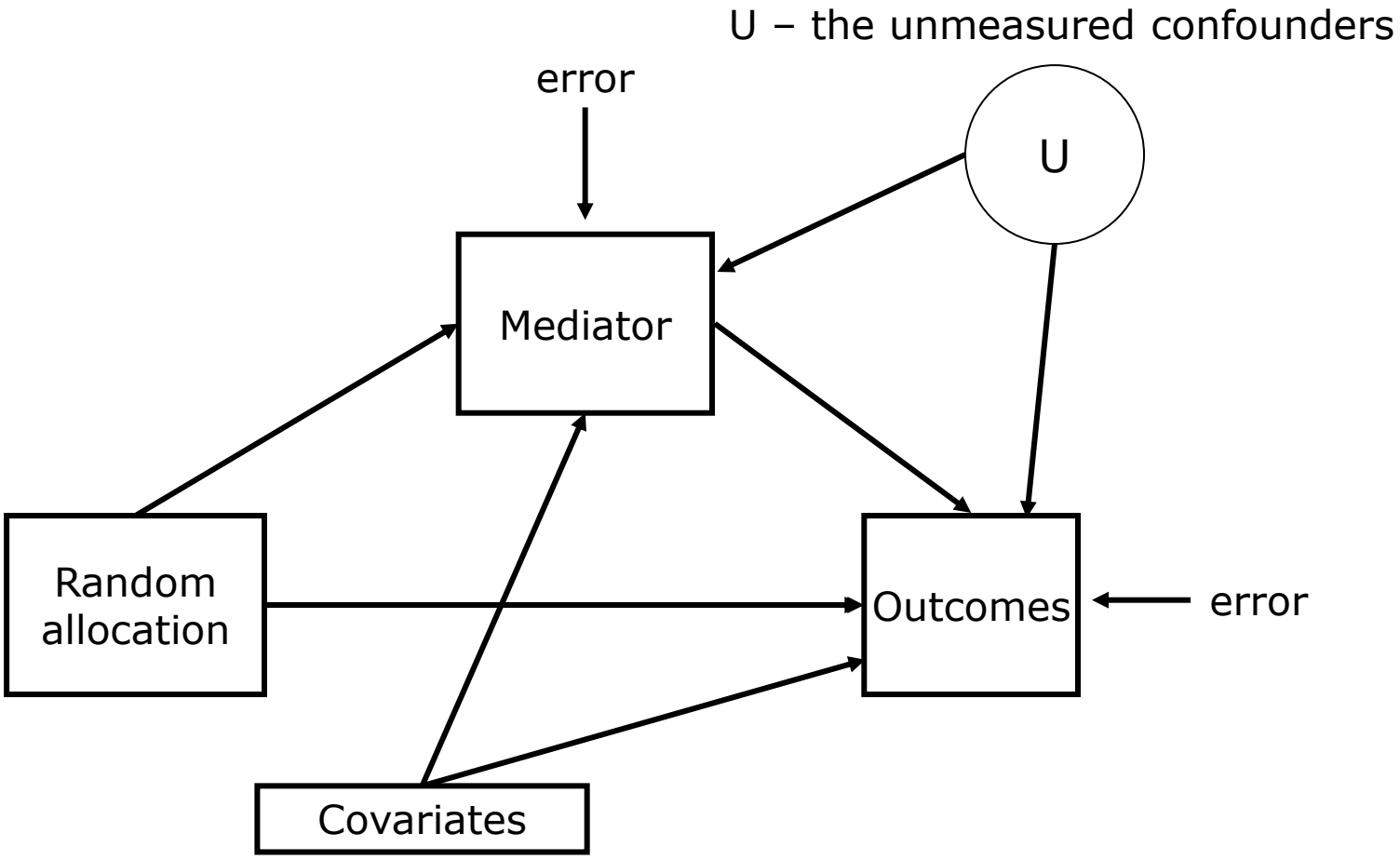
2. Two parallel randomized clinical trials are conducted to compare the treatments within each marker stratum.

3. We assess the predictive value of the marker by formally testing whether the treatment effect is the same in each of the marker strata; that is, we assess the marker–treatment interaction.

- These tells us whether the intention-to-treat effect differs in each strata:
  - Treatment effect moderation;
  - Subgroup analysis.

- Says nothing about WHY there might be differences…

Efficacy and mechanisms evaluation: estimating valid effects in trials



Stratified medicine: we need more information to make progress

- Genetic and phenotypic markers
- Clinical history
- Past environmental exposures, lifestyle, etc.

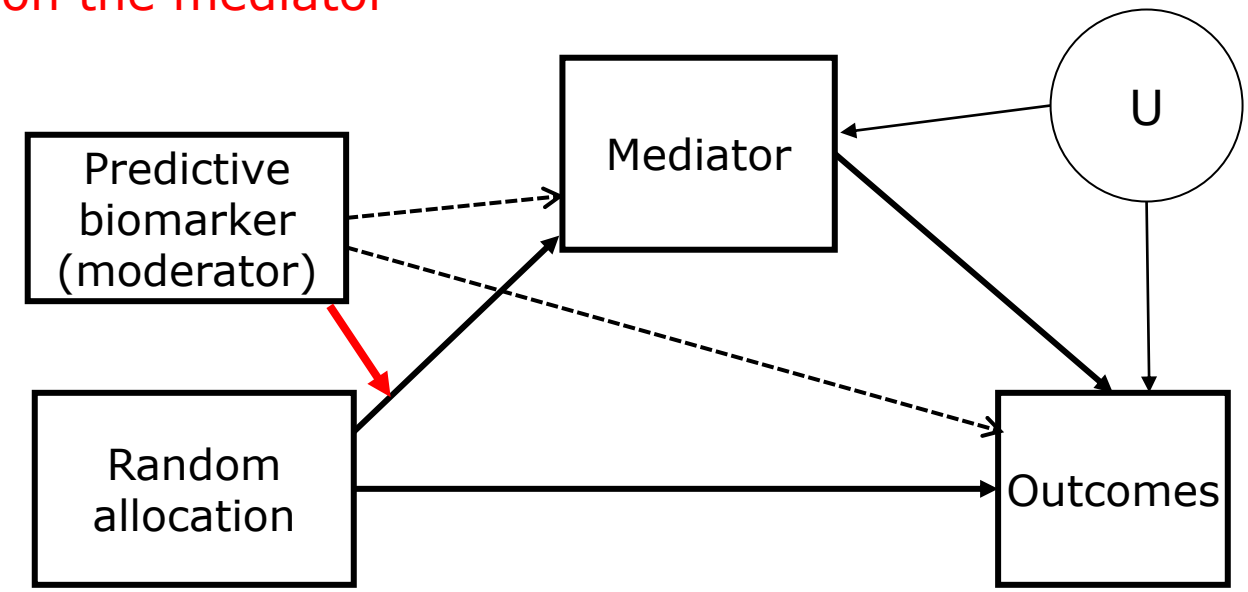
- Advantage of genetic markers is that they are essentially randomised and, in particular, (in a conventional RCT) independent of treatment allocation. And, of course, they are not influenced by treatment.

- Can we use **markers** (prognostic and predictive markers, e.g. biological or biomarkers, social and psychological markers) as this extra information?
  - How we do this depends on the assumptions we make about relationships between markers and outcomes.

Stratification and mechanisms evaluation

Predictive effect only acts on the mediator

U – unmeasured confounders

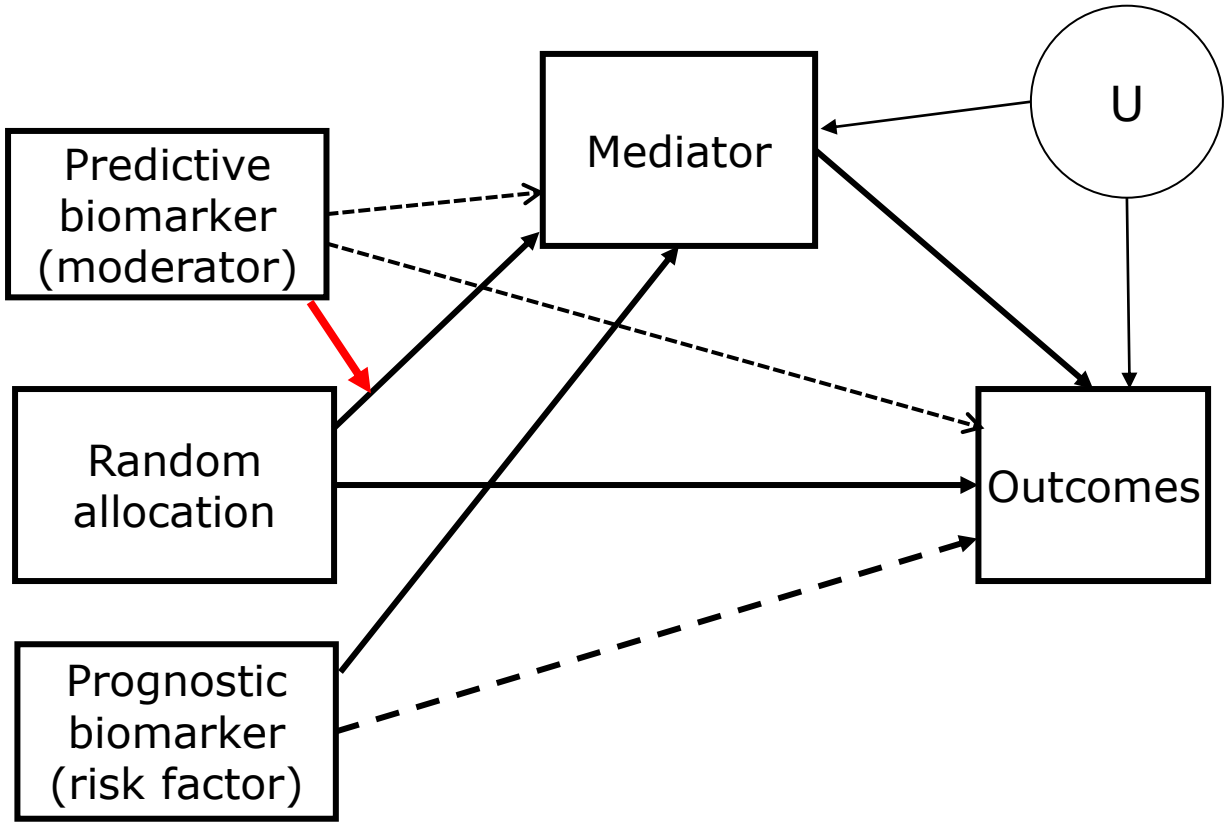


- Are we correct in assuming that there is no moderating effect on the other pathways?
- Dependent on prior knowledge of the biology/biochemistry of the system.

Combining prognostic and predictive markers for mechanisms evaluation

Predictive effect only acts on the mediator

U – unmeasured confounders



Analysis method: instrumental variables and structural mean models

- The interaction between predictive marker and randomisation is an instrumental variable.

- An instrumental variable regression in *Stata*:

ivregress 2sls *Y Z X* (*M* = *X*Z*), first**

- This is a two-stage least-squares procedure which simultaneously estimates:
  - the effect of *Z*, *X* and *X***Z* on *M* (the first-stage regression),
  - the effect of *Z*, *X* and first stage prediction of *M* on *Y* (the second stage).

- In the linear case, this is equivalent to a structural mean model (see the causal inference literature).

The Biomarker Stratified-Efficacy and Mechanisms Evaluation (BS-EME) trial

- Taking the biomarker stratified design as described previously we supplement the baseline information (i.e. predictive marker*)* by:
  - measuring all previously-validated prognostic markers
  - baseline covariates (demographic information; clinical and treatment history; co-morbidity; social, psychological and cultural variables; etc.) thought to have prognostic value
  - baseline measurement of the putative mediator
  - baseline value for the final outcome measurement

- The rationale for all of these measurements is

  (a) to allow for as much confounding of the effects of the mediator on final outcome as is feasible,

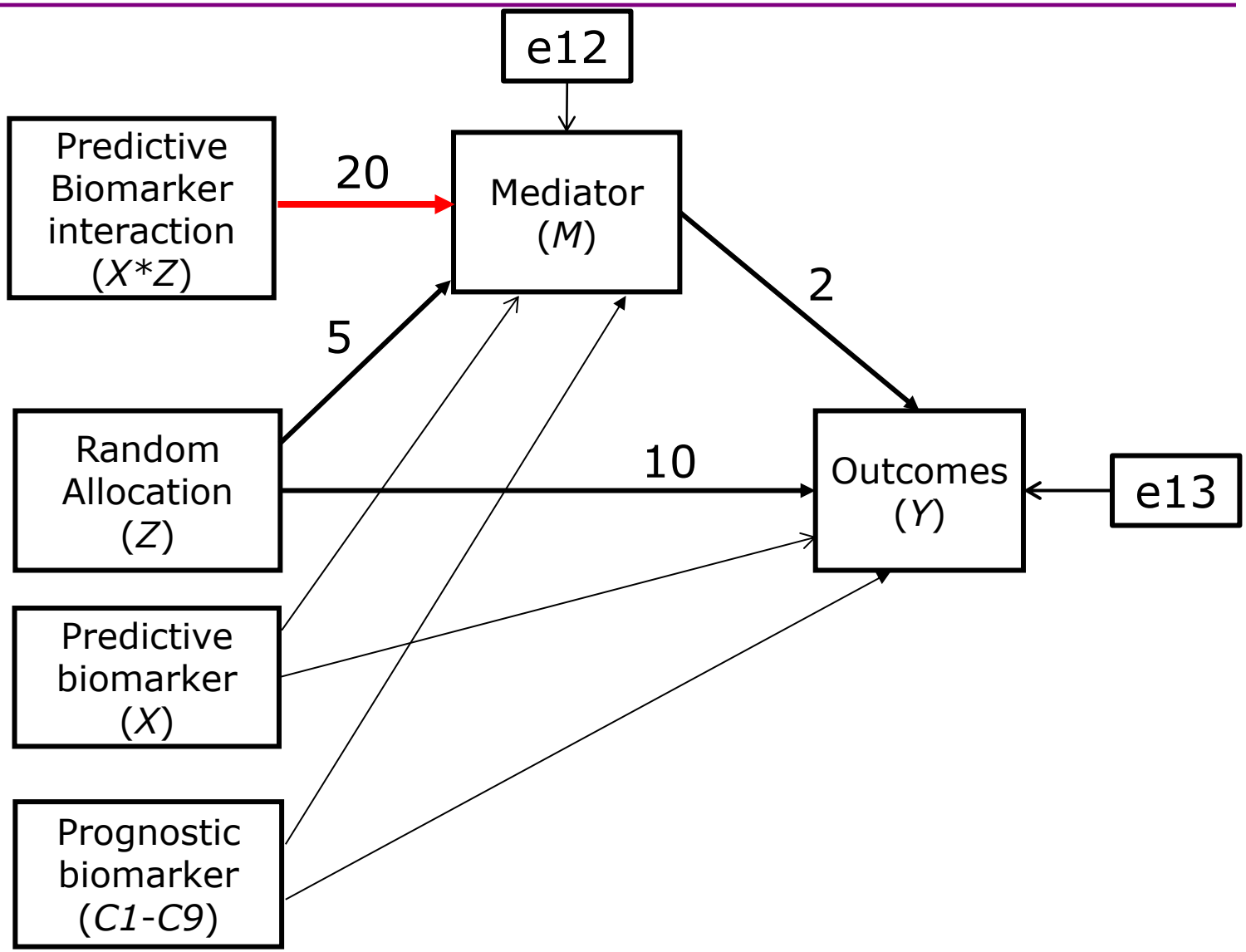
  (b) to assess sensitivity of the results to assumptions concerning residual hidden confounding and, perhaps more importantly,

  (c) increase the precision of the estimates of the important causal parameters.

A single simulated BS-EME trial

- Trial with 200 participants (100 treated, 100 controls).
- Quantitative outcome, *Y*.
- Binary predictive marker (*X*): Moderating effect of *X* on outcome solely through the mediator (*X* known to be an IV).
- Variants of *X* equally probable (50:50).
- Nine prognostic (genetic) uncorrelated binary markers *C1*-*C9* and all nine are confounders.

Simulated BS-EME trial



Simulated BS-EME trial

- Multiple regression models for the joint effects of treatment and the mediator on outcome:
  - No interactions (i.e. *X***Z*) in the analysis model.

Y as outcome		**Naïve model** (no adjustment)		**Full model** (adjusted for all confounders)	
Effect	**True**	**Estimate**	**s.e.**	**Estimate**	**s.e.**
Z	**+10**	**+3.16**	1.21	**+9.97**	1.04
M	**+2**	**+2.46**	0.05	**+2.00**	0.05

- On the left, assume no measure on any of *C1*-*C9*.
- On the right, have made adjustments for the effects of *C1*-*C9*.
- The results on the left are clearly biased. If we know all the confounders and if we make adjustments for them all then we can retrieve the correct treatment effects (the column on the right).

Simulated BS-EME trial

- Multiple regression models for the joint effects of treatment and the mediator on outcome:
  - Including a treatment by predictive marker interaction in the analysis model

Y as outcome		**Naïve model** (no adjustment)		**Full model** (adjusted for all confounders)	
Effect	**True**	**Estimate**	**s.e.**	**Estimate**	**s.e.**
Z	+10	+6.80	1.26	+9.97	1.08
M	+2	+2.63	0.05	+2.00	0.07
X*Z	**0**	**-12.41**	2.08	**+0.03**	2.07

- The results of the naïve analysis reveal a highly statistically significant interaction, which is an artefact of confounding.

- Only if we correctly allow for all of the known confounders (the column on the right) then we obtain a small and statistically non-significant effect.

Simulated BS-EME trial: instrumental variable estimators (interaction as the instrument)

M as outcome		**Naïve model** (no adjustment)		**Full model** (adjusted for all confounders)	
Effect	**True**	**Estimate**	**s.e.**	**Estimate**	**s.e.**
Z	**+5**	**+5.00**	1.28	**+5.02**	0.80
X*Z	**+20**	**+20.00**	2.83	**+20.00**	1.76
Y as outcome					
Z	**+10**	**+10.00**	2.07	**+9.97**	1.31
M	**+2**	**+2.00**	0.12	**+2.00**	0.07

Some conclusions from the simulations

- Larger sample sizes than 200 give the same results with respect to bias, but are obviously more precise.
- Varying the prevalence of the predictive marker to 90:10 increases the bias slightly.
- Standard approach is valid if but only if we measure all confounders and it is the most precise method.
  - But it seems unlikely to measure all prognostic markers.
- IV approach is unbiased but less precise – we don't get something for nothing.
- However, there is a considerable gain in precision with prognostic markers:
  - Measurement of prognostic markers not essential, but it makes the design more efficient (i.e. get away with a smaller trial) – perhaps the difference between a viable trial and one that's just not feasible.

Some conclusions on stratified medicine

1. Personalised (stratified) medicine and treatment-effect mechanisms evaluation are inextricably linked;

2. Stratification without corresponding mechanisms evaluation lacks credibility;

3. In the almost certain presence of mediator-outcome confounding, mechanisms evaluation is dependent on stratification for its validity;

4. Both stratification and treatment-effect mediation can be evaluated using a biomarker stratified trial design together with detailed baseline measurement of all known prognostic biomarkers and other prognostic covariates (BS-EME trial);

5. Direct and indirect (mediated) effects should be estimated through the use of instrumental variable methods together with adjustments for all known prognostic biomarkers (confounders) – the latter adjustments contributing to increased precision (as in a conventional analysis of treatment effects) rather than bias reduction.

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