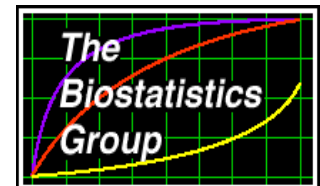

Designing Trials of Complex Interventions for Efficacy and Mechanisms Evaluation

Dr Richard Emsley*, Prof Jonathan Green, Prof Graham Dunn

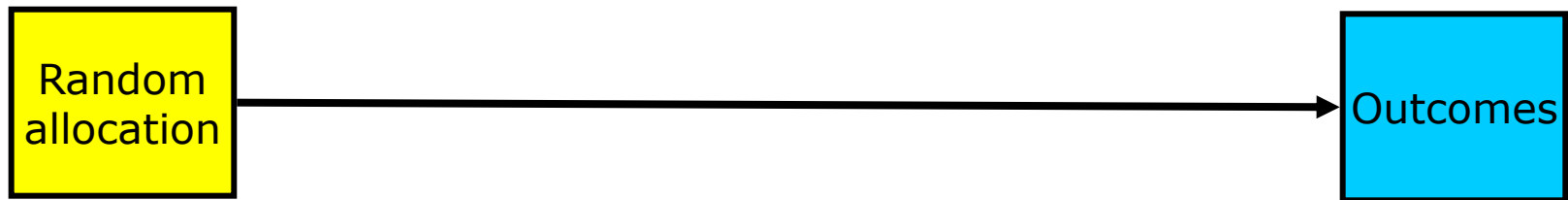
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School of Community Based Medicine,
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**MRC HTMR Conference, Bristol
Tuesday 4th October 2011**

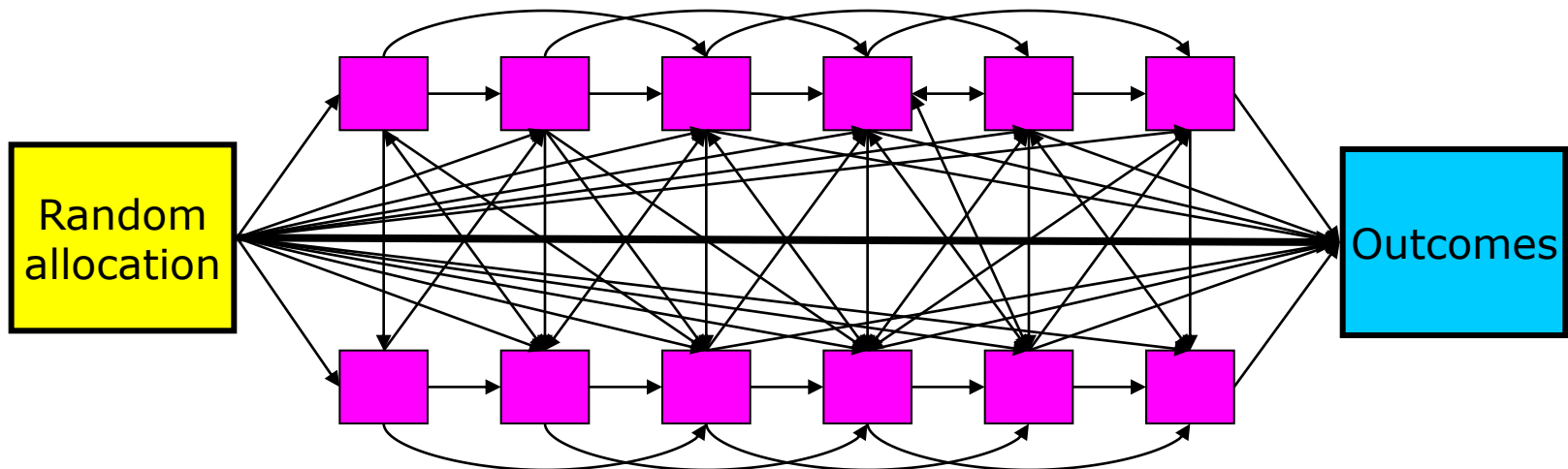


Learning More From Randomised Trials of Complex Interventions

- Intention to treat estimates this:

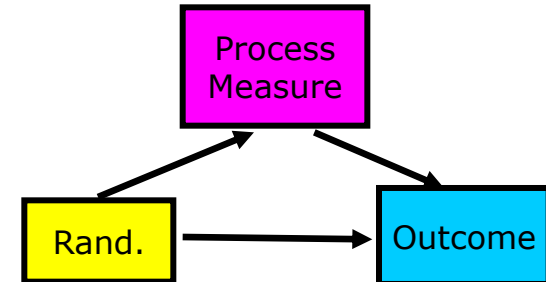


- In reality, the picture is more like this:



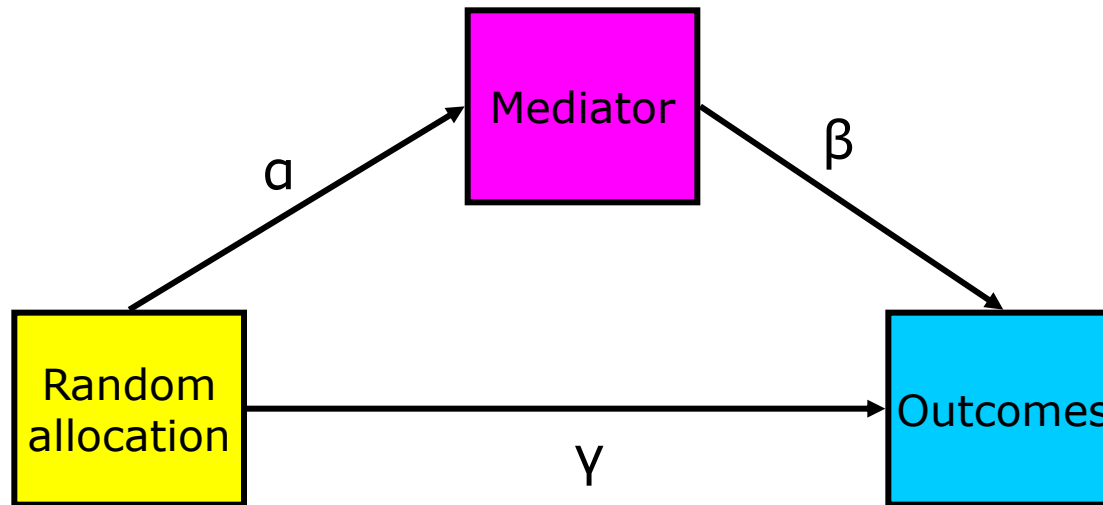
Process variables in complex interventions

- We want to measure the various aspects of the therapy (need scales) and test the underlying theory of the intervention.



- **Quality of the therapeutic relationship**
What is the strength of the therapeutic alliance, and how does this influence treatment effects?
- **Do people with psychosis jump to conclusions?**
Does psychotherapy reduce jumping to conclusions which in turn improves positive symptoms in psychosis?
- **Does higher synchronicity in play improve child outcomes?**
Does a parental training intervention for autism improve the parent-child synchronicity during interactions, which leads to improved child outcomes?

Simple mediation diagram



Total effect = direct effect (γ) + indirect effect ($\alpha*\beta$)

Motivation: the mediation industry

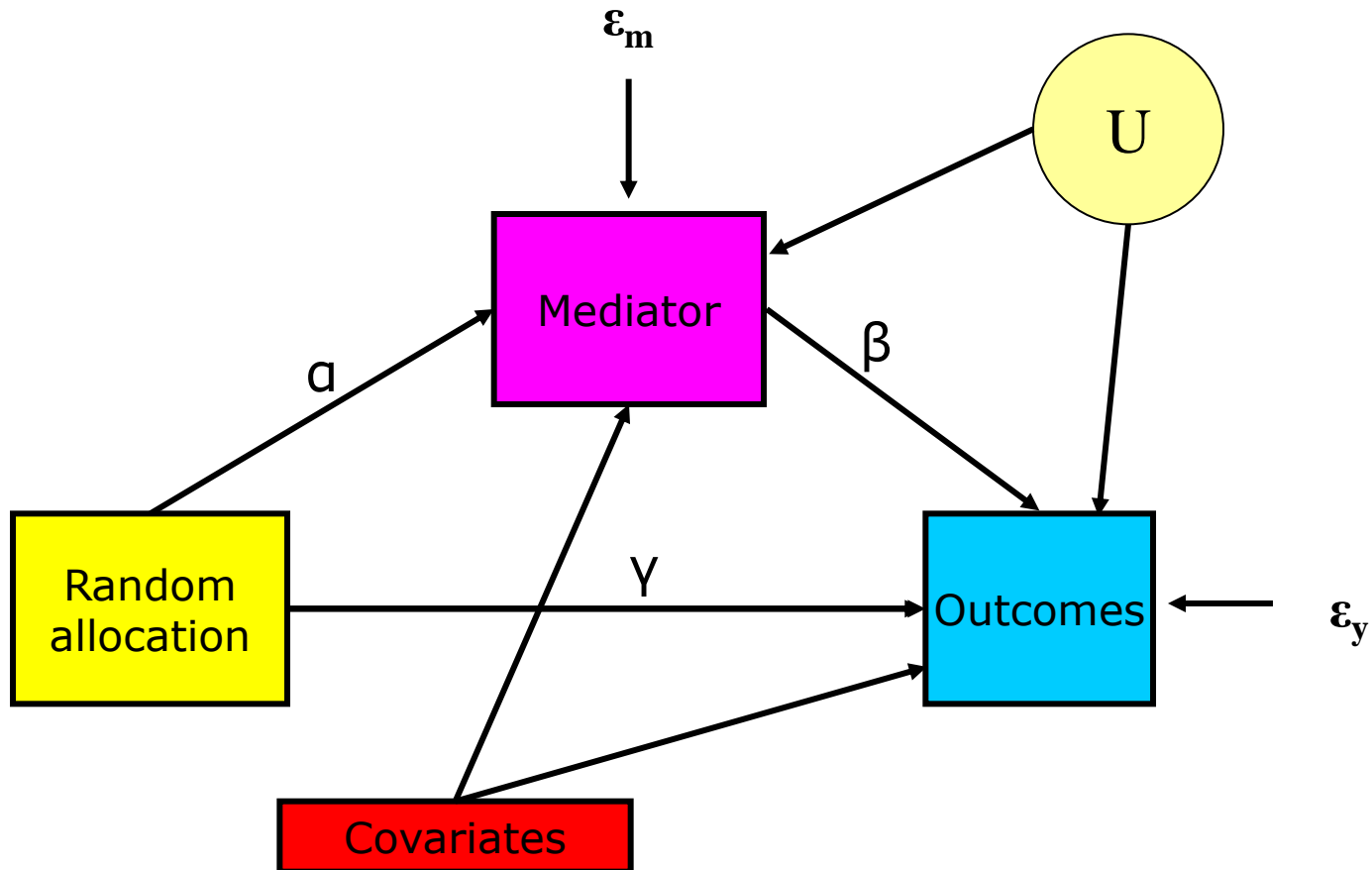
Baron RM & Kenny DA (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology* **51**, 1173-1182.

- As of 27th September 2011 on Web of Science:
16,391 citations and hundreds more each month!

(For comparison, Bland and Altman's 1986 agreement paper has 19,045)
- Depends on the implicitly-assumed **absence of hidden confounding** (non-ignorable selection) which is very **rarely stated**, let alone its validity discussed.
- One suspects that the majority of investigators are **oblivious** of the assumptions and their implications.
- One is left with the unsettling thought that the thousands of investigations of mediational mechanisms in the psychological and other literatures are of **unknown and questionable value**.

The basic underlying problem – estimating valid causal effects

U – the unmeasured confounders



Statistical solutions to unmeasured confounding

- Statistical Mediation Analysis vs. Causal Mediation Analysis
- We've previously proposed three solutions to analyse mediation allowing for the unmeasured confounding:
 1. Measure and adjust for potential confounders (sounds obvious, not always done);
 2. Instrumental variables;
 3. Principal stratification.

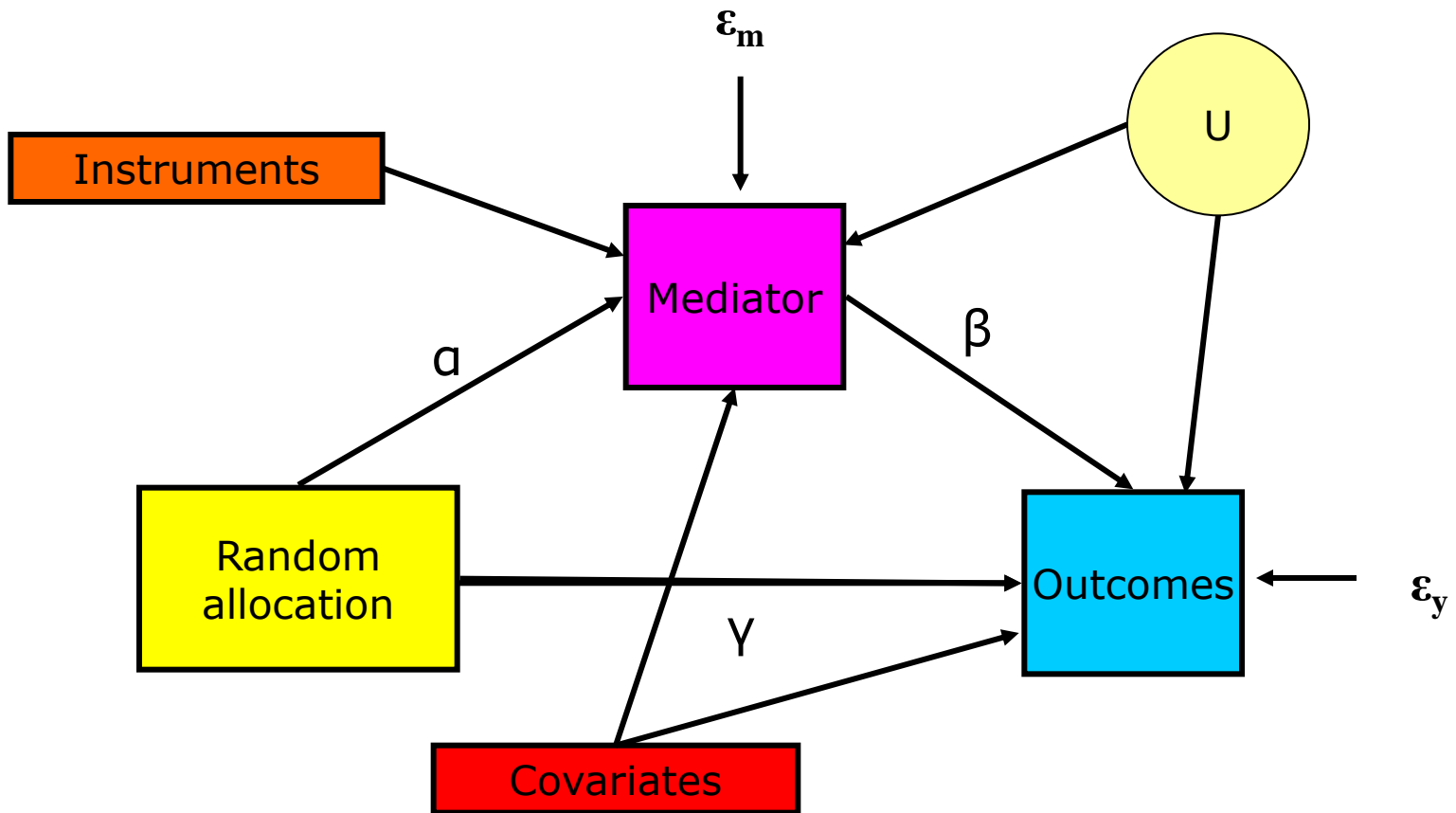
Explained in detail in:

Emsley, R., Dunn, G. & White I.R. (2010). Modelling mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Statistical Methods in Medical Research*, 19(3), pp.237-270.

Instrumental variables

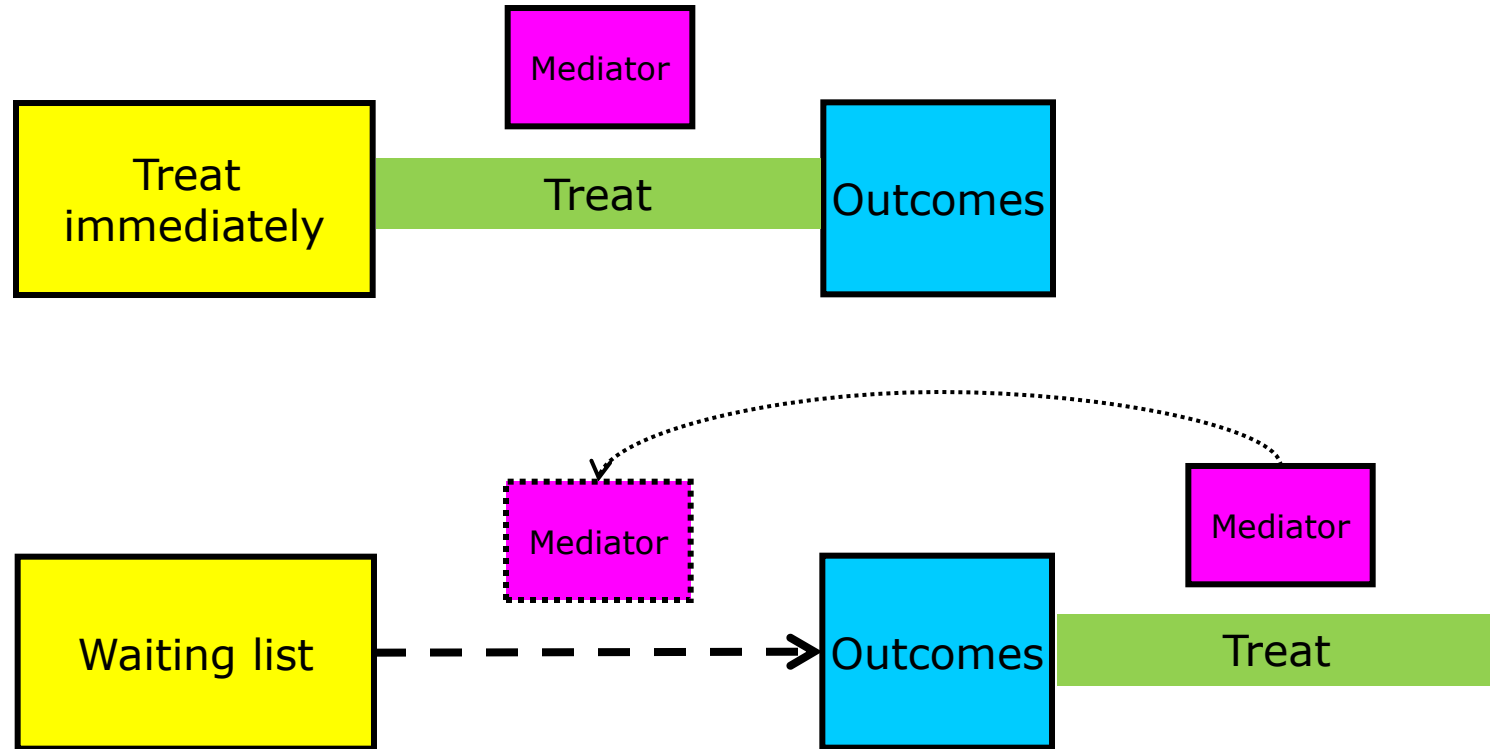
- We need to find a variable which is:
 1. (Strongly) predictive of the mediator;
 2. Has no direct effect on the outcome, except through the mediator;
 3. Does not share common causes with the outcome.
- If these conditions hold, in addition to one further assumption (no interactions or monotonicity), then such a variable can be used as an **instrumental variable**.
- If we consider this at the design stage of the complex intervention trial, we can measure variables that MIGHT meet these requirements.

Mediation diagram with instrumental variables



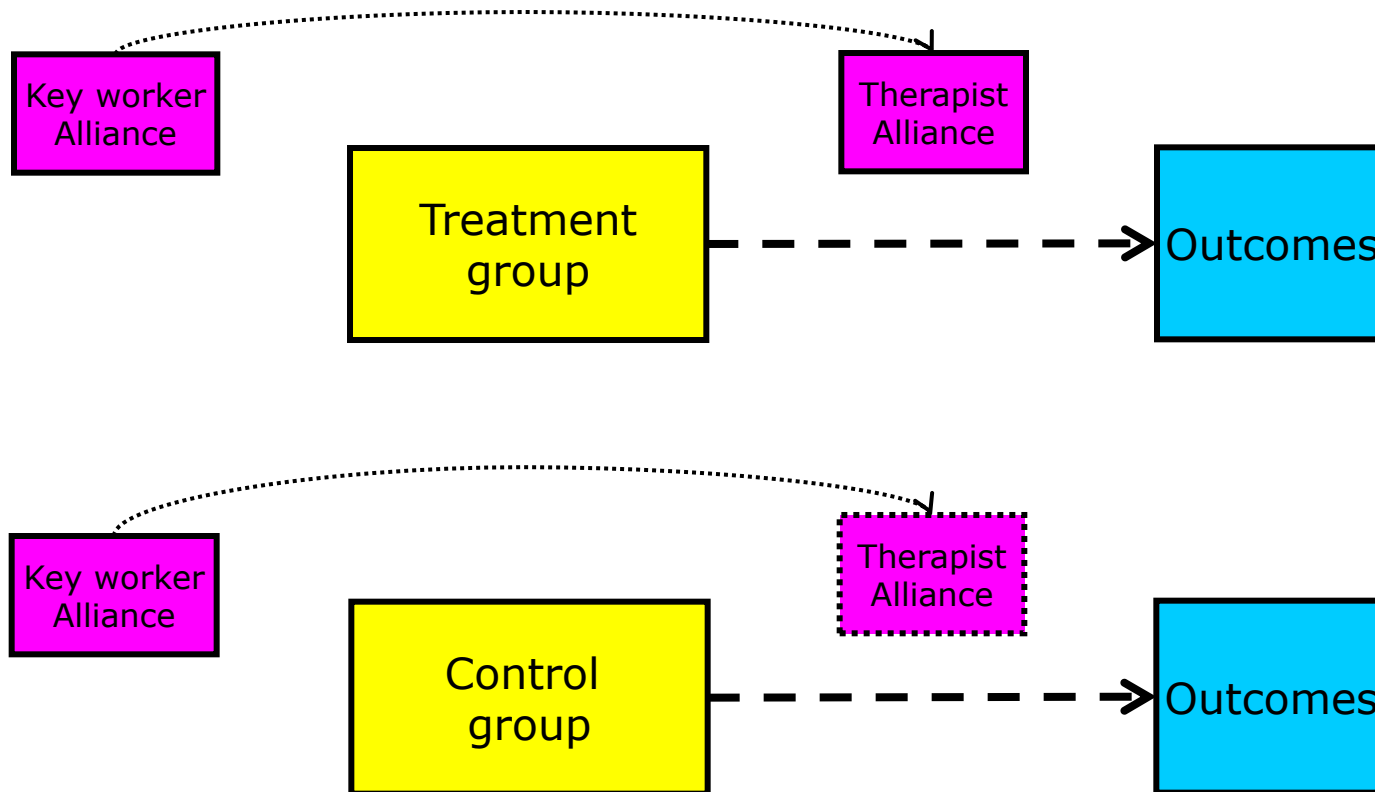
Design 1: "Waiting list control"

Time →



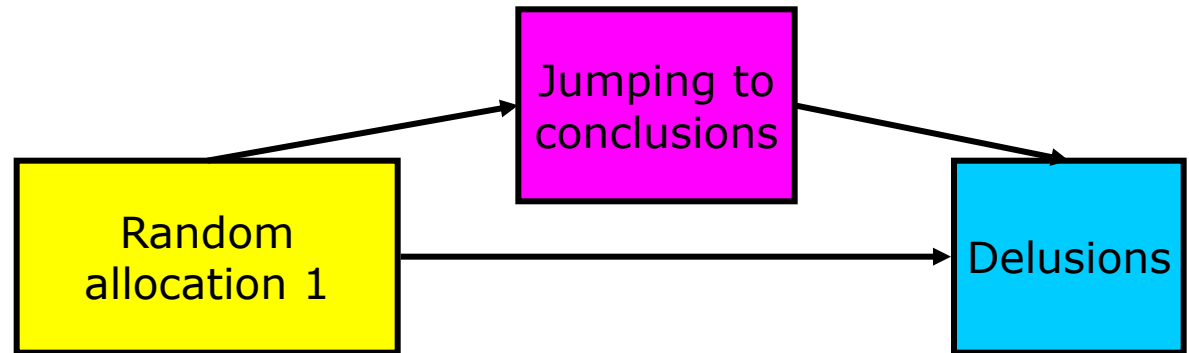
Design 2: "Innocuous vaccine" – MIDAS trial

Time →

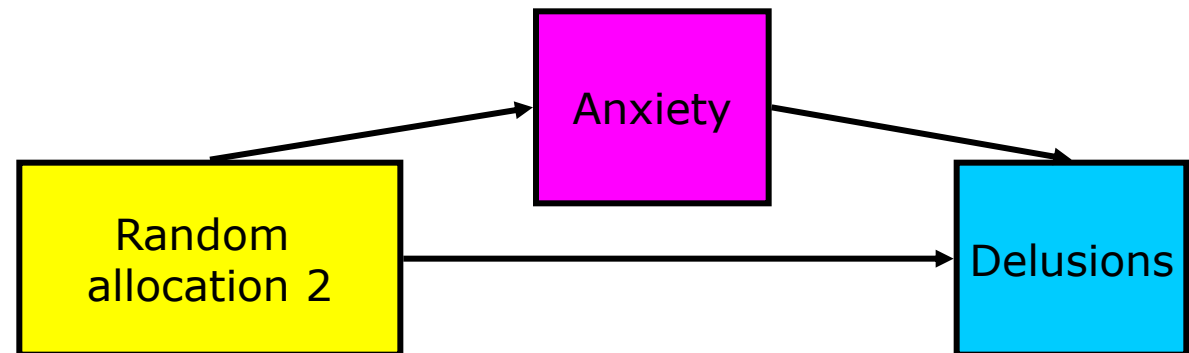


Design 3: “Parallel trials” – Psychosis Research Partnership experiments

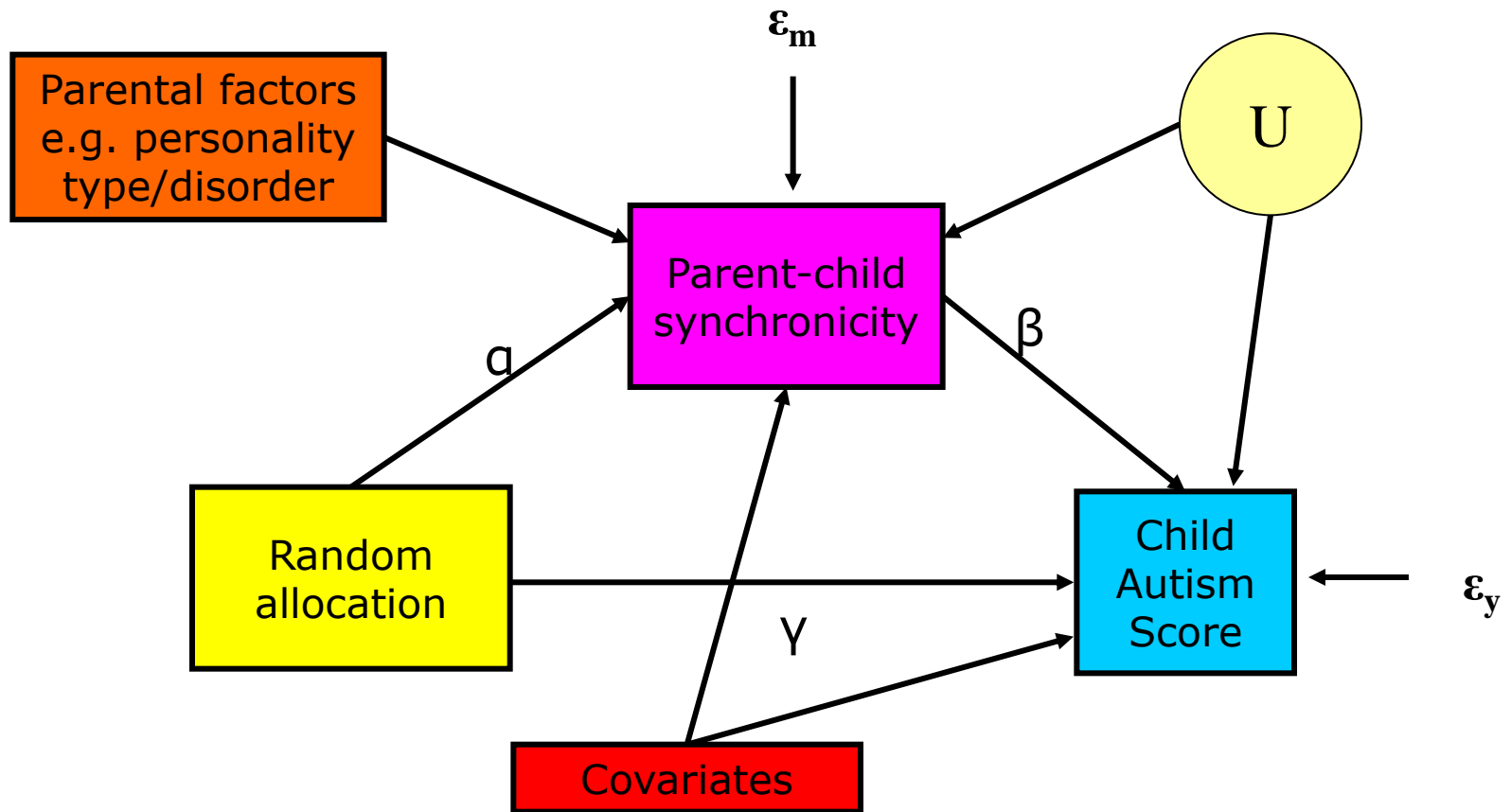
Trial 1:
Reasoning
training
component



Trial 2:
Anxiety
manipulation
component



Design 4: “Mediated Moderation” – Preschool Autism Communication Trial (PACT)



Summary: Designing complex intervention trials for mediation analysis

- Statistical mediation analysis relies on untestable assumptions such as no unmeasured confounding or no correlated measurement errors.
- Instrumental variables estimation can be use alternative assumptions, provided valid instruments can be found. Method uses random allocation by other variable interactions on mediator, but not outcome.
- This can be considered at the design stage:
 1. Augmented designs (waiting list control; “innocuous vaccine”).
 2. Joint analysis of several similar trials.
 3. Use of a multi-centre trial.
 4. Measure baseline variables which predict variation in the mediators but not the outcome (mediated moderation; genes).
 5. Randomize to multiple treatments.

Research Programme: Learning More From Randomised Trials of Complex Interventions

Funded by MRC Methodology Research Programme

- **Design and methods of explanatory (causal) analysis for randomised trials of complex interventions in mental health (2006-2009)**
 - Graham Dunn (PI), Richard Emsley, Linda Davies, Jonathan Green, Andrew Pickles, Chris Roberts, Ian White & Frank Windmeijer.
- **Estimation of causal effects of complex interventions in longitudinal studies with intermediate variables (2009-2012)**
 - Richard Emsley (MRC Fellow), Graham Dunn.
- **Designs and analysis for the evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health (2010-12)**
 - Graham Dunn (PI), Richard Emsley, Linda Davies, Jonathan Green, Andrew Pickles, Chris Roberts, Ian White & Frank Windmeijer with **Hanhua Liu**.
- PhD students, **Lucy Goldsmith** and **Clare Flach** (2010 – 2013).

Selected references

- Emsley RA, Dunn G & White IR. (2010). Modelling mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Statistical Methods in Medical Research*, 19(3), pp.237-270
- Emsley RA & Dunn G. (2011) Evaluation of potential mediators in randomized trials of complex interventions (psychotherapies). In: *Causal Inference: Statistical perspectives and applications*. Eds: Berzuini C, Dawid P & Bernardinelli, L. Wiley. (forthcoming in 2011).
- Emsley RA, Green J, Dunn G. (2011). Designing trials of complex interventions in mental health for efficacy and mechanisms evaluation. In preparation for Archives of General Psychiatry.
- And work in preparation with the next speaker...