LIHS Mini Master Class

Innovative RCT designs for evaluating complex interventions

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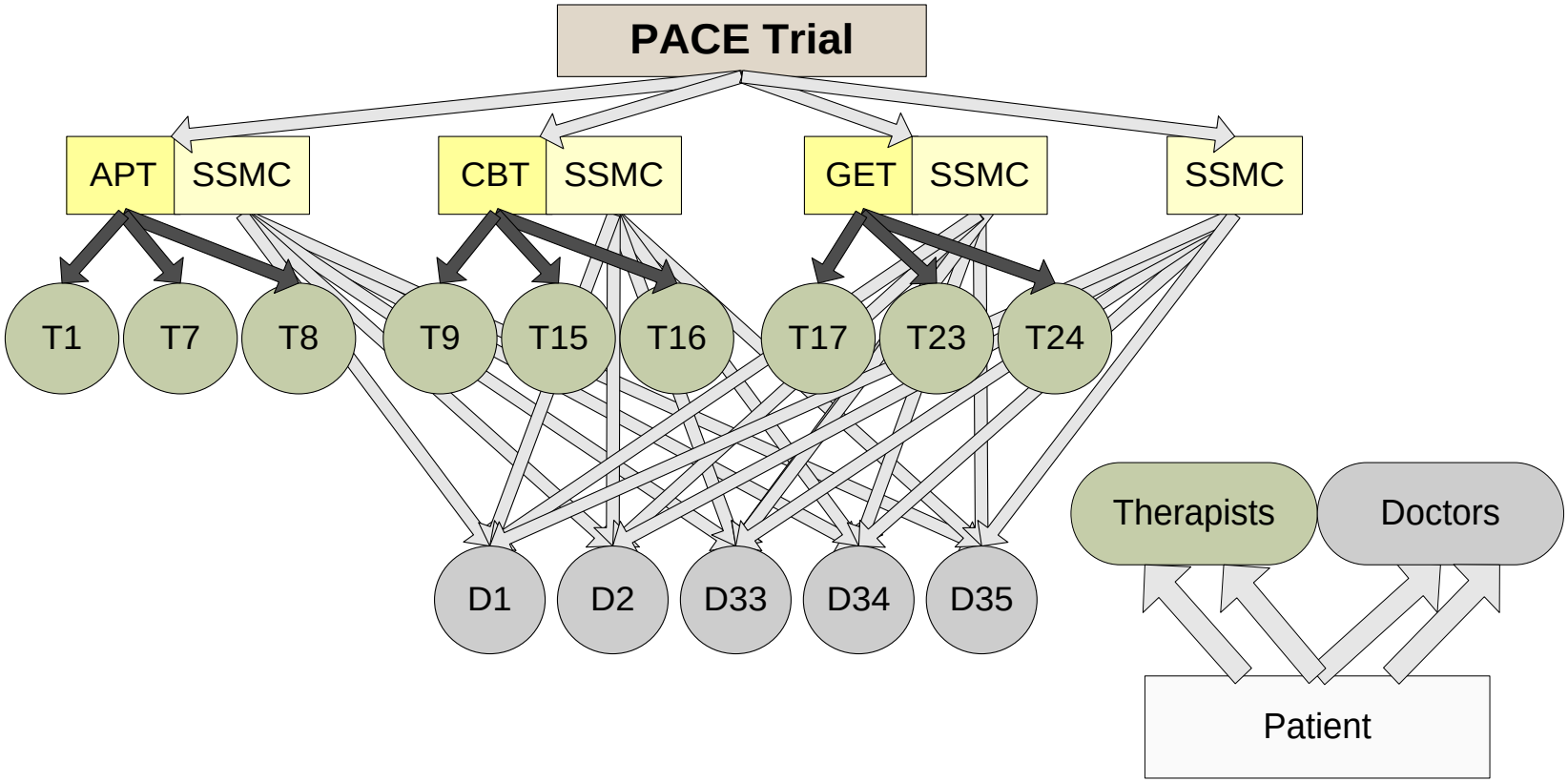
1. An example of a complex intervention trial



Therapists are nested (APT, CBT, GET; not SSMC)

Doctors are crossed with medical care (SSMC)

White *et al* (2011) *Lancet,* ***377***(9768): 823-836

2. A conceptual framework

- Walwyn & Roberts (2010) *Statistical Methods in Medical Research,* ***19***: 291-315.
- Walwyn R (2010) *Therapist Variation within Meta-Analyses of Psychotherapy Trials*. PhD Thesis. University of Manchester, UK.

a) What is therapist variation in psychotherapy trials?

- It is the result of therapists being an important component of the intervention separate to but interacting with their behaviours

Psychotherapy =	Therapist	+	Behaviours	+	Interaction

- The therapist is a random treatment variable: "patient outcomes may vary systematically by therapist"
- Their behaviours are often a fixed treatment variable

2. A conceptual framework

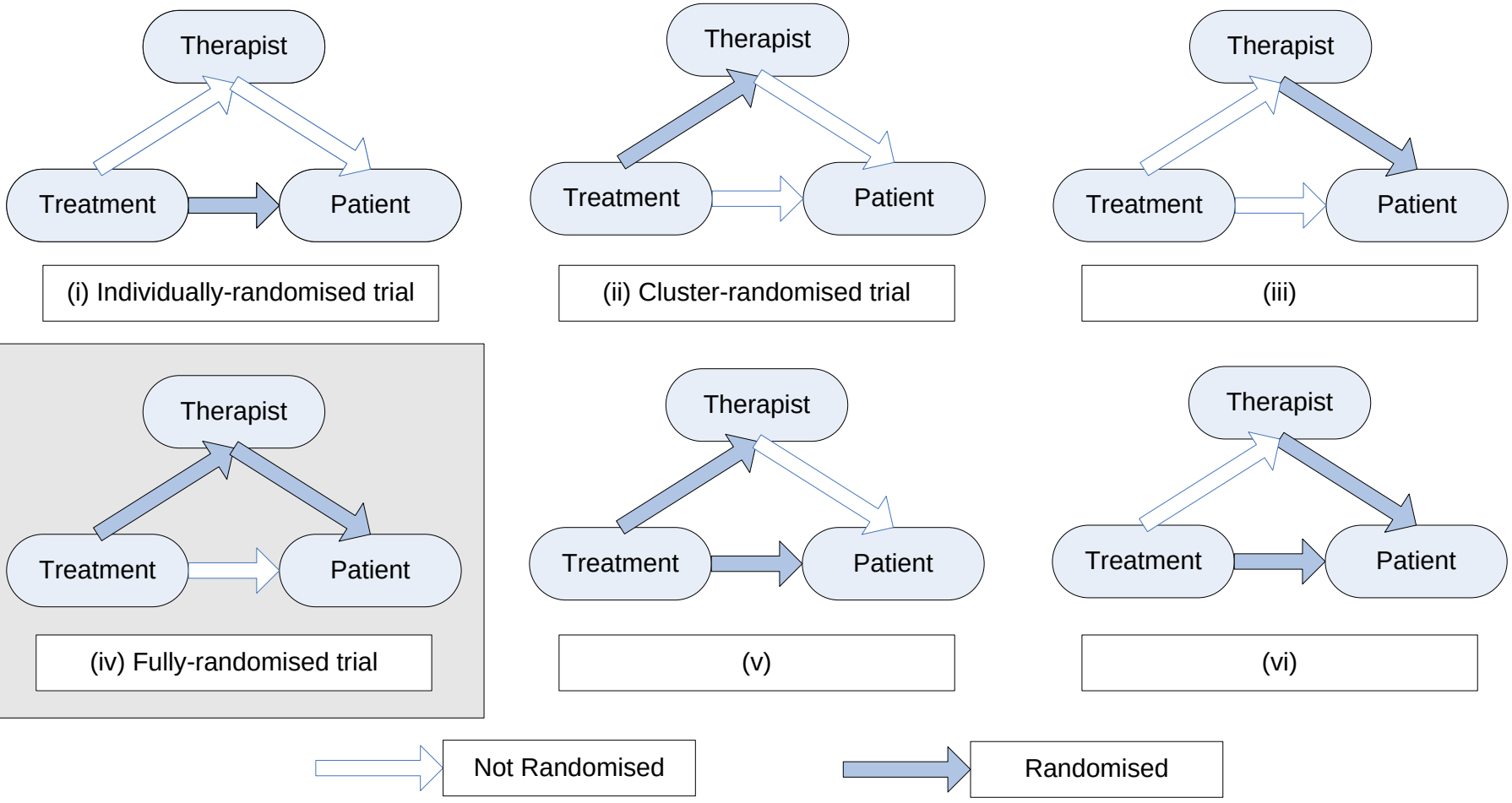
b) What are the implications for the research question?

Example:		**Techniques**	
		Counselling	Advice
Therapists	Counsellors	A	B
	GPs	C	D

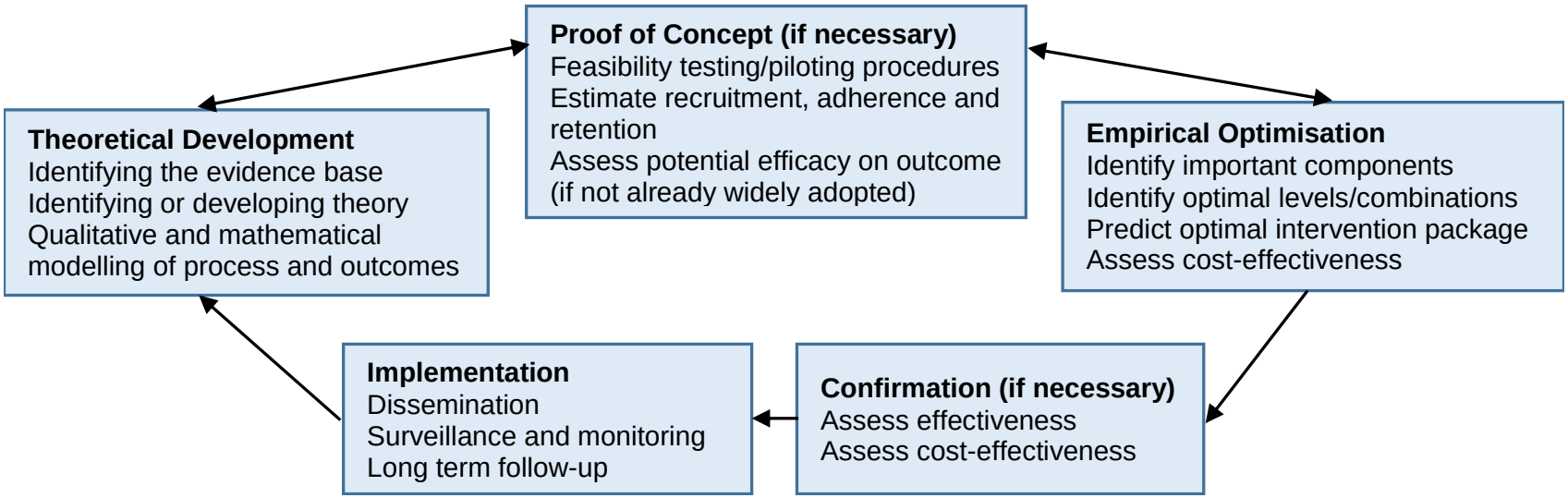
1. Techniques
2. Therapist characteristics
3. Packages

} "Complex" Interventions

2. A conceptual framework



3. A research strategy for developing and evaluating novel and widely adopted complex interventions



4. A more general conceptual framework

Four Features contributing to Intervention Complexity

- **MRC 2008 Guidance**
  - Number of interacting components within the intervention
  - Need to characterise the delivery of the intervention (by whom, and in what context)
  - Degree of tailoring of the intervention
  - (Perhaps multiple) levels at which an intervention might work

- **Statistical Features**
  - Multiple components (=> multiple treatment variables)

  1. Components are applied to different levels in a healthcare system
  2. Interventions may consist of a chain or cascade of components
  3. Interventions may be tailored to individuals or clusters based on their baseline characteristics or needs
  4. Interventions may consist of a series of decision rules dictating how subsequent treatment is tailored based on intermediate outcomes

Possible Components

Component	Area	Example: Audit & Feedback
What	Content	Feedback Reports Slide Show Support
How	Delivery mode	Web, face-to-face, telephone
Who	Providers	Audit lead (& group), NCA, TPs…
Where	Setting	Audit of blood transfusion practice in elective surgery / haematology
When	Timing	Reports, followed by support and slide show

Lend themselves to **factorial** and **response surface designs**

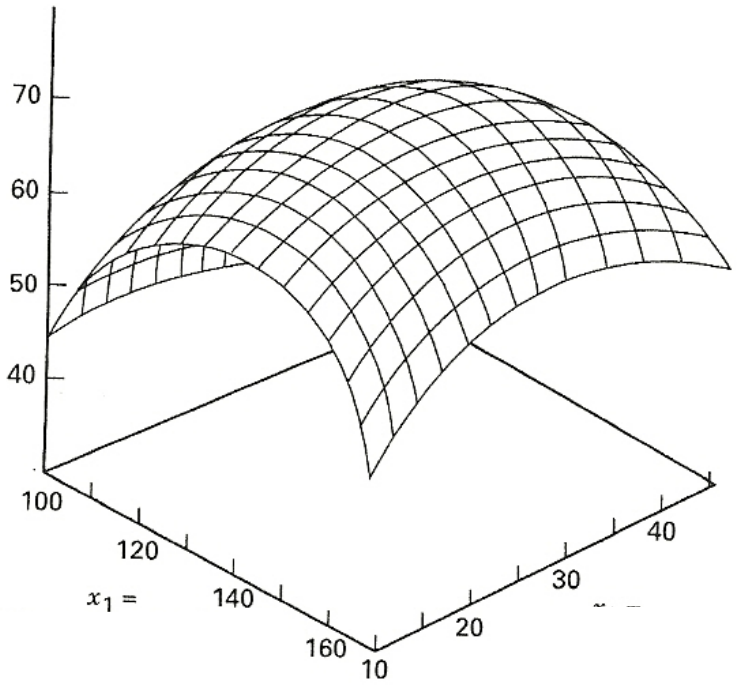
A second example of a complex intervention trial (AFFINITE)

	Usual Content	Enhanced Content	Marginal
Usual Follow-On Support	A_0B_0 = 20%	A_1B_0 = 14%	AB_0 = 17%
Enhanced Follow-On Support	A_0B_1 = 14%	A_1B_1 = 10% (8% to 12%)	AB_1 = 12%
Marginal	A_0B = 17%	A_1B = 12%	Effect A = 5% Effect B = 5% Effect AB =4/6%

Factorial and Response Surface Designs

- Treatments are made up of packages of different components

	Feedback Content	
Support	**Usual**	**Enhanced**
Usual	Package A	Package B
Enhanced	Package C	Package D



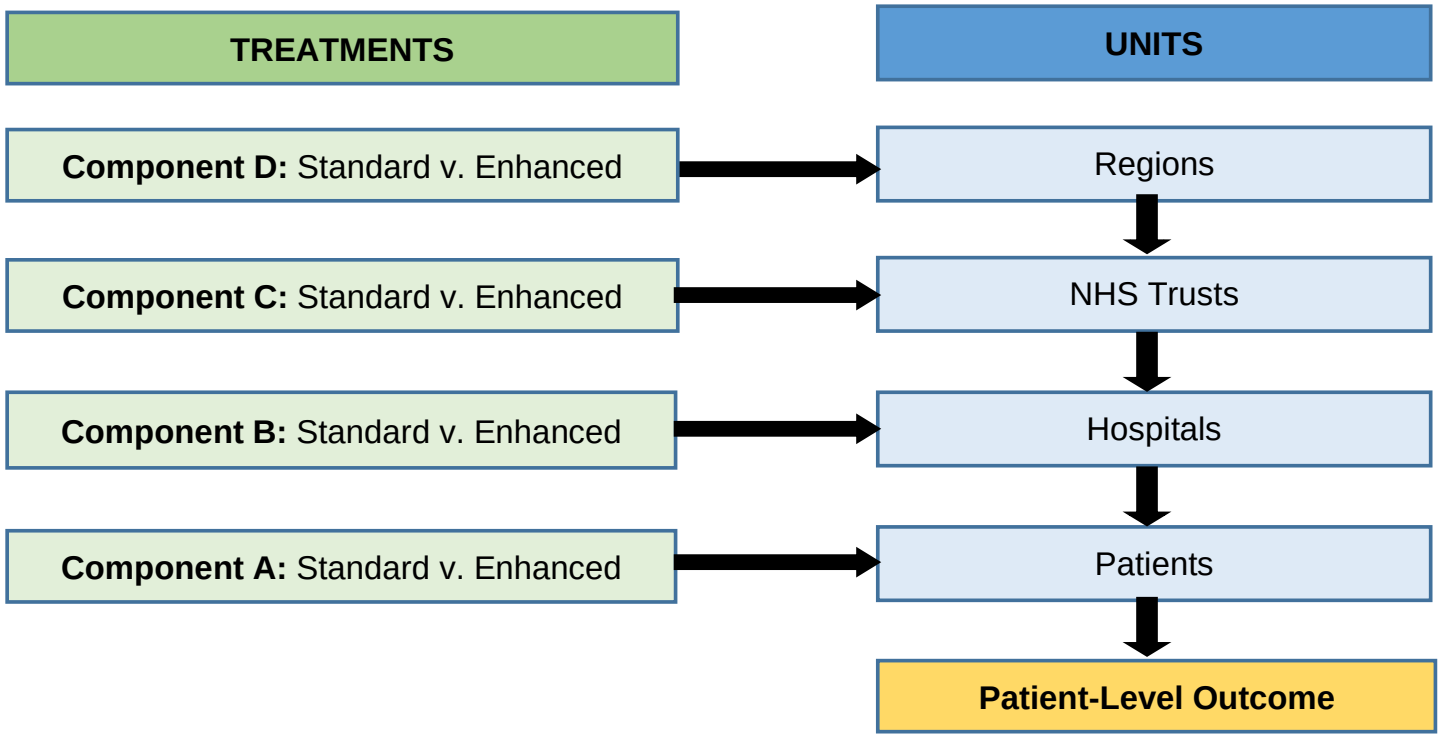
- Note. Both of these factors are fixed. It is also possible to use a factorial design if one (or more of the factors were random (e.g. provider). If a further component had been the time from audit to feedback (i.e. continuous) then a response surface design would have been appropriate.

4a. Components may be applied to different levels

Level	Example: Audit & Feedback
Setting/Time	Audit Topic
Audit Lead	Training
Regions	Slide show
Trusts	Support (& Policies)
Hospitals	Feedback Reports
Patients	Blood Transfusion

Lend themselves to **multi-stratum designs** (e.g. cluster randomised, split-plot, split-split-plot, split-block etc.)

Simple Example #1: Multilevel Intervention



Entire treatments, or selected treatment components, randomized to clusters (at possibly more than one level) while responses are measured on individual patients

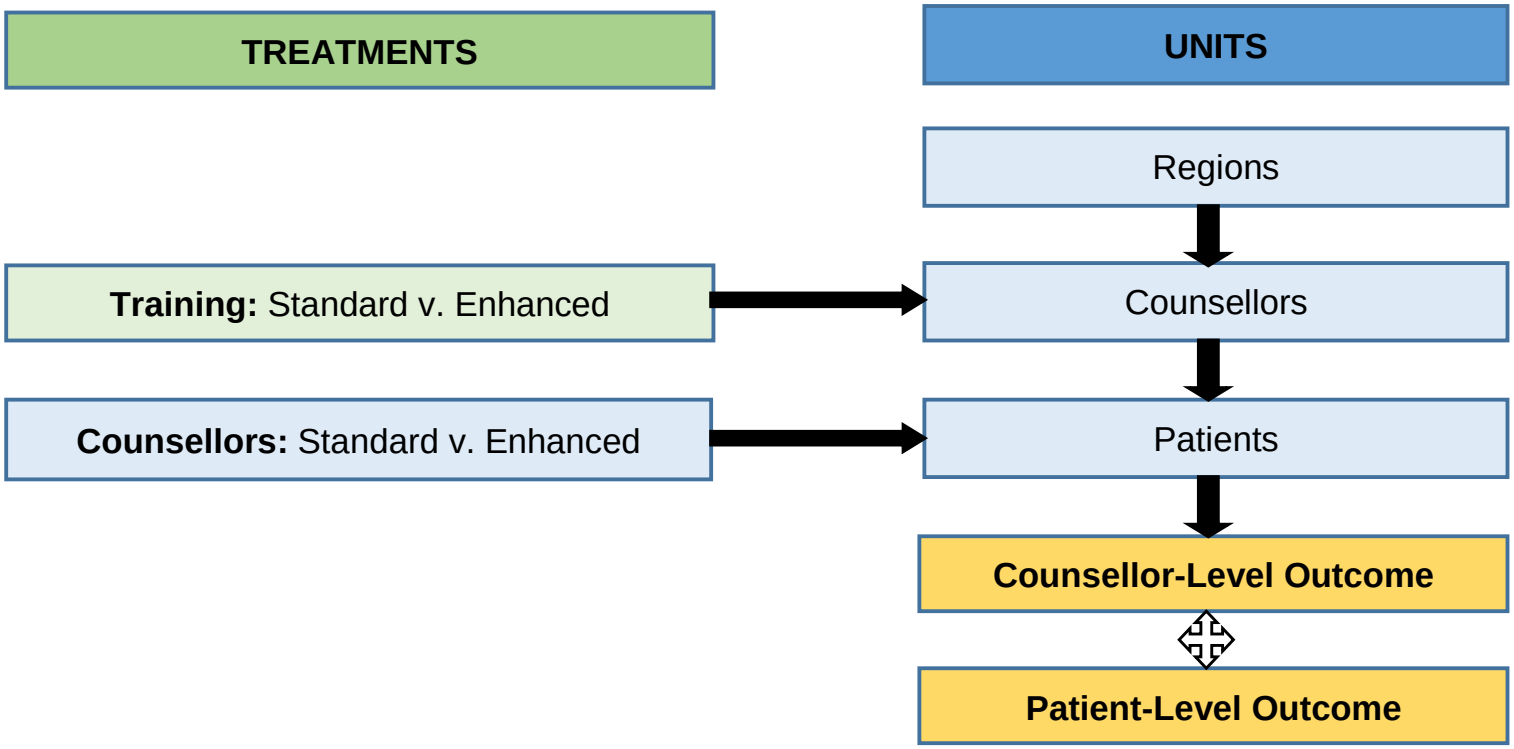
4b. Interventions may be a chain/cascade of components

Step	Component	Example: Feedback Reports
1	Development	Theoretical development of enhancements Example report & guidance document
2	Training	Intervention developer trains audit lead and audit statistician
3	Delivery	Audit lead develops template reports Audit statistician programs site reports
4	Receipt	Hospital teams (transfusion practitioners et al) download site reports from website
5	Enactment	Hospital teams read and digest feedback, write and implement action plans
6	Outcome	Blood transfusions are given only where necessary, in accordance with guidelines

Borrelli B (2011) The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. Journal of Public Health Dentistry 71: S52–S63

Lend themselves to **composed multi-tiered designs**

Simple Example #2: Cascading Intervention



There might be a chain of interventions over time, generally with more than one randomisation.

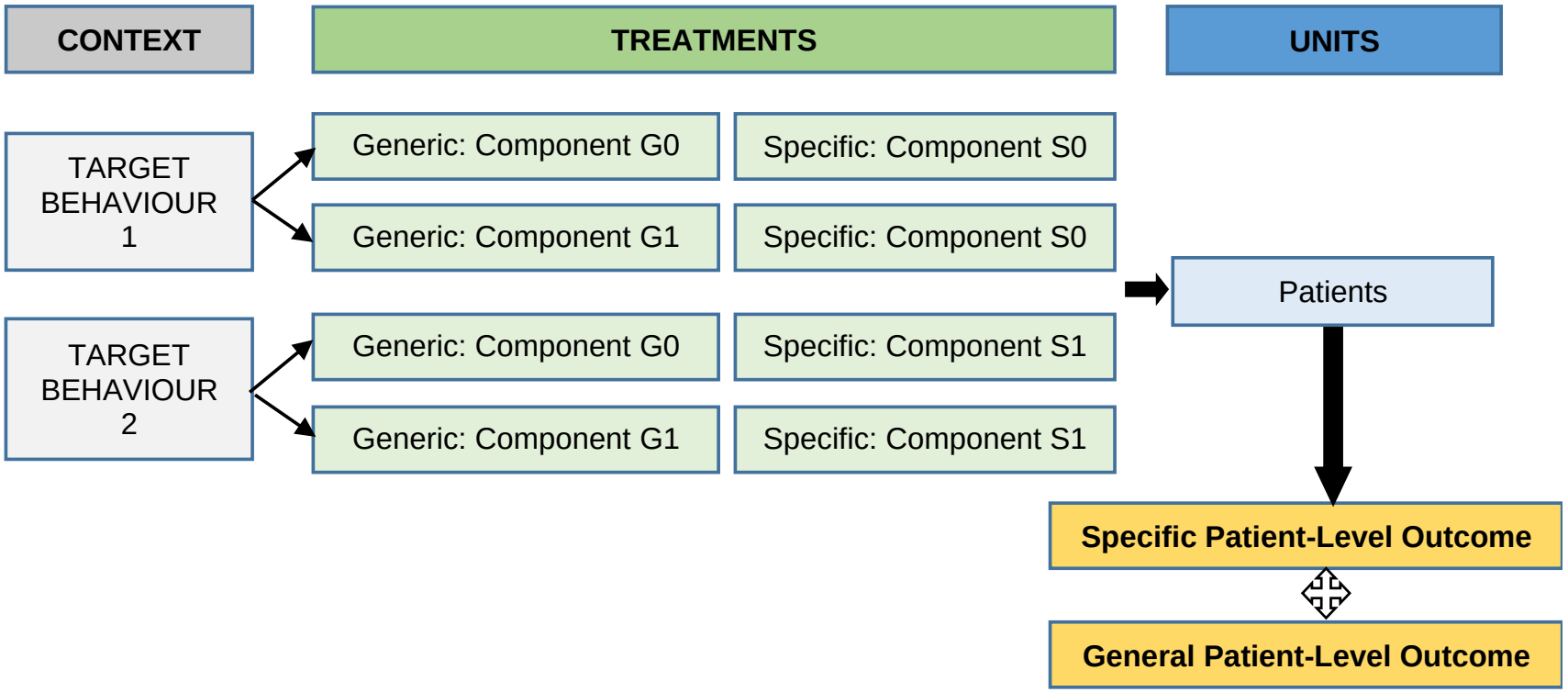
4c. Interventions may be targeted at clusters/patients

Cluster Baseline Characteristic	Generic Component	Example: Feedback Reports
N/A	Layout/Comparator	One long feedback report comparing performance nationally
N/A	Layout/Comparator	Tiered feedback reports comparing performance nationally/locally

Cluster Baseline Characteristic	Specific Component	Example: Feedback Reports
High performing	Recommendation	Individualised feedback to maintain baseline performance
Low performing	Recommendation	Individualised feedback to improve baseline performance

Lend themselves to **conditional randomisations**

Simple Example #3: Targeted Intervention



Note: Interventions delivered to patients are made up of two components: one is randomised, the second is contingent on randomisation and baseline characteristics. Patients are allocated to:

1) G0 plus S0 if target = 1 or S1 if target = 2
2) G1 plus S0 if target = 1 or S1 if target = 2

4d. Intervention packages may evolve over time

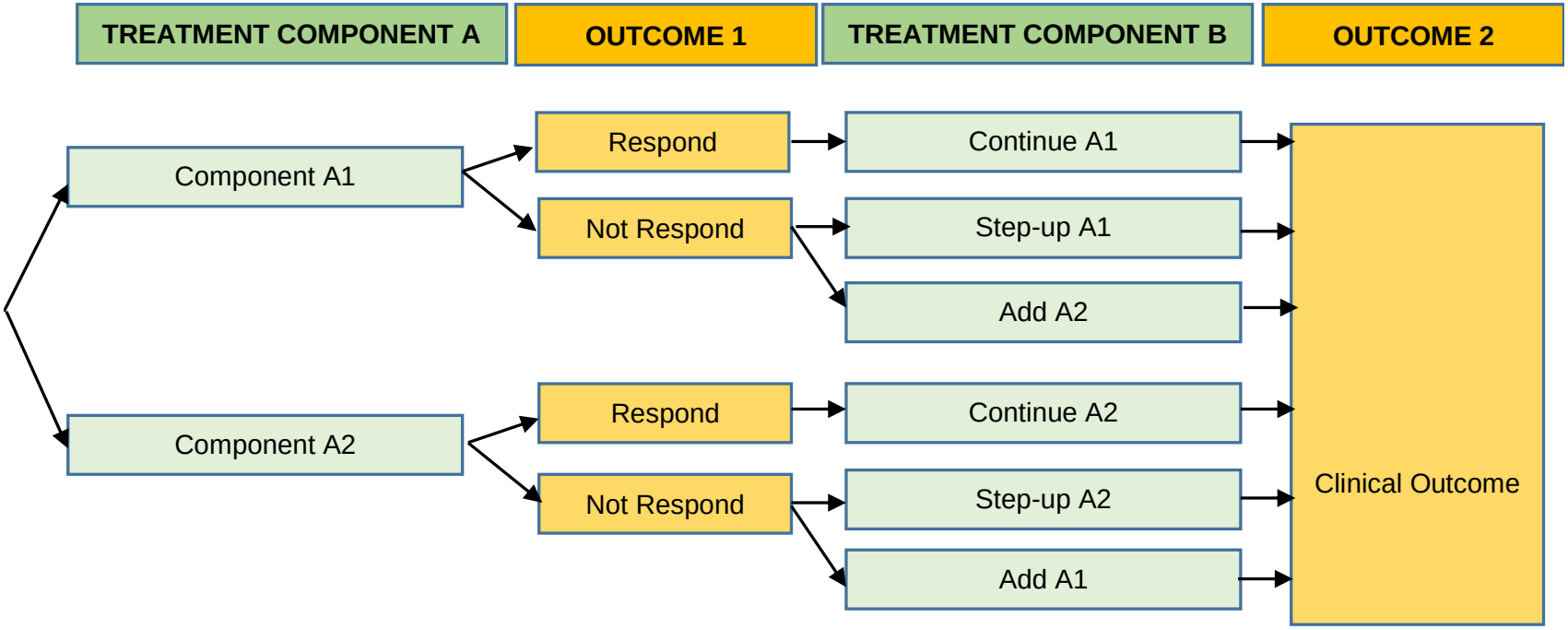
Decision Type	Example: Audit & Feedback
Repeated	Repeat an existing audit annually
Dynamic	Stepped feedback: e.g. increasing intensity of feedback depending on providers response to previous feedback cycles

Entire treatments, or selected treatment components, might be repeated over time or tailored to responses to earlier components

Dynamic treatments lend themselves to **sequential multiple assignment randomised trial designs** (i.e. SMART designs)

Murphy S (2005) An experimental design for the development of adaptive treatment strategies. Statistics in Medicine, 24: 1455-81

Simple Example #4: Serial Intervention



4d. Intervention packages may evolve over time

- Six intervention packages (dependent on Outcome 1)
  - Component A1 then Continue A1 if Respond
  - Component A1 then Step Up A1 if Not Respond
  - Component A1 then Add A2 if Not Respond
  - Component A2 then Continue A2 if Respond
  - Component A2 then Step Up A2 if Not Respond
  - Component A2 then Add A1 if Not Respond

- 2x2 factorial trial (with conditional randomisation at start)
  - Component A1 then A1 if Respond or A1+ if Not Respond
  - Component A1 then A1 if Respond or Add A2 if Not Respond
  - Component A2 then A2 if Respond or A2+ if Not Respond
  - Component A2 then A2 if Respond or Add A1 if Not Respond

Key points

1. Complex healthcare interventions can be described as having one or more often several of the characteristics:
   - Multilevel, Cascading, Targeted, Serial

2. The overall aim is to understand the fixed and random, discrete and continuous, components of a complex medical, social or physical intervention for a defined problem or system of problems, which are causally and incidentally important, in what combination and circumstances, to what extent, why and for whom.

3. Experimental designs exist to handle each complexity in isolation but these have rarely been used in clinical trials…

Further Information

- **Murphy S** (2005) An experimental design for the development of adaptive treatment strategies. Statistics in Medicine, 24: 1455-81
- **Collins LM, Murphy SA, Strecher V** (2005) A strategy for optimizing and evaluating behavioural interventions. Annals of Behavioural Medicine, 30(1): 65-73
- **Brien CJ, Bailey RA** (2006) Multiple randomisations. Journal of the Royal Statistical Society, Series B. 68(4): 571-609
- **Craig P, Dieppe S, Macintyre S, Michie S, Nazareth I, Petticrew M** (2008) Developing and evaluating complex interventions: The new medical research council guidance. BMJ, 337: 9
- **Walwyn R, Roberts C** (2010) Therapist variation within randomised trials of psychotherapy: Implications for precision, internal and external validity. Statistical Methods in Medical Research, 19: 291-315
- **Borrelli B** (2011) The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. Journal of Public Health Dentistry 71: S52–S63
- **Trinca LA, Gilmour SG** (2014) Improved split-plot and multi-stratum designs. Technometrics, 1-20.