Overcoming the Challenges and Reaping the Benefits of SMARTs

IMPACT

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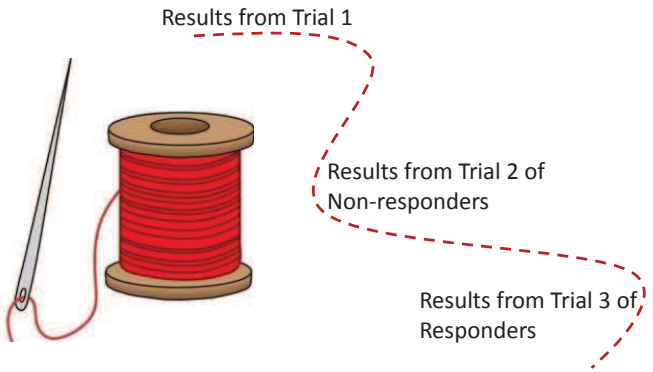
Top 10 List

Common challenges in SMART design and implementation

1

Why run a SMART when I can use observational data or piece together information from multiple trials?

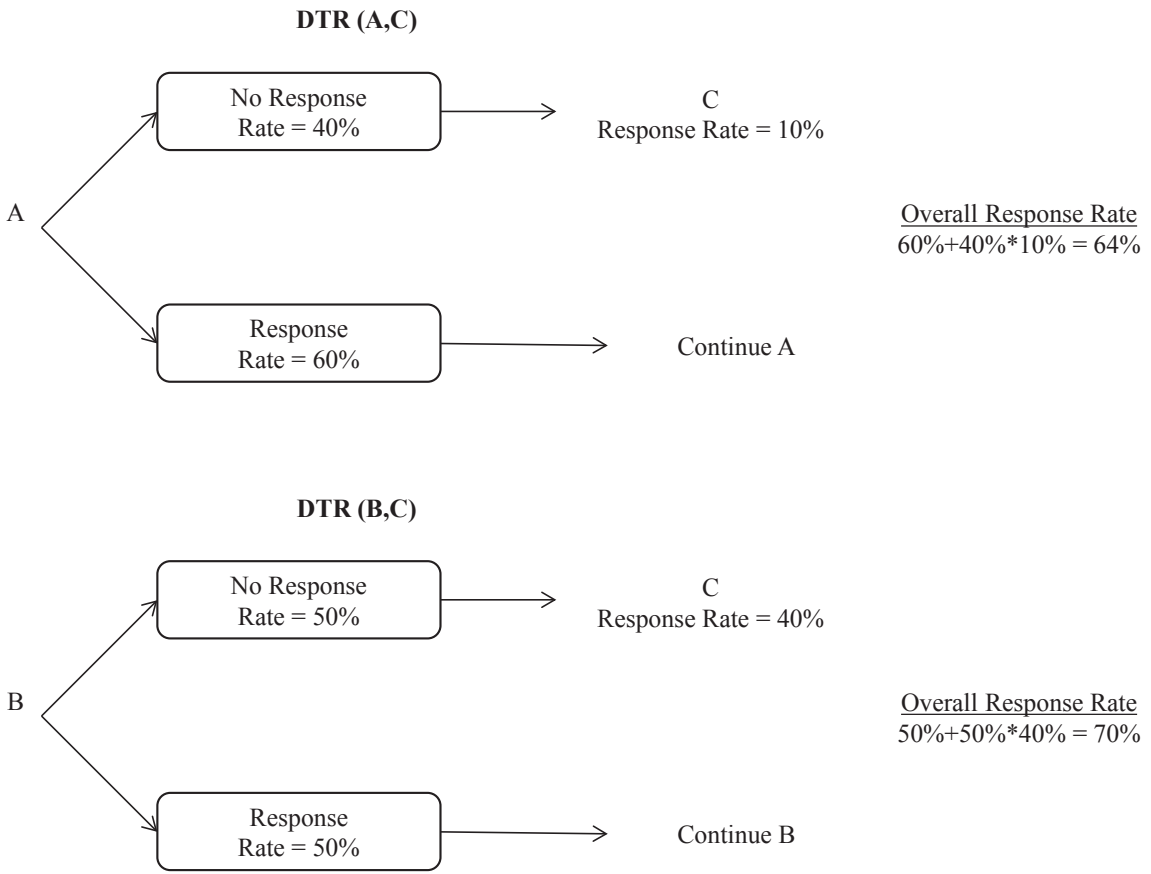


1: SMART vs. Observational Data

- Observational data analysis can provide insight
- May be appropriate in certain settings due to ethics and timing of interventions
- Issues with confounding, recall bias, positivity

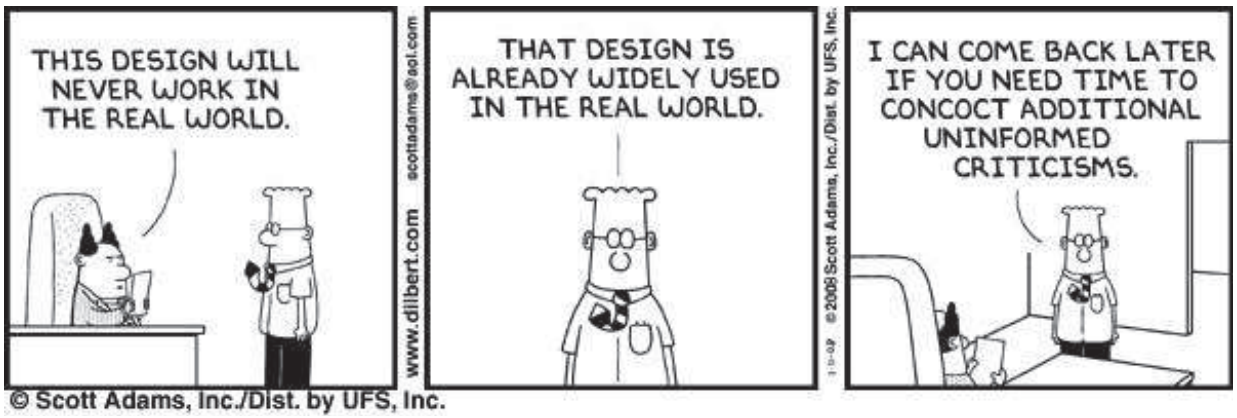
1: SMART vs. Piecing Together Trials

Myopic view of stage-specific trials may miss delayed effects



2

What makes a SMART different from a standard RCT, factorial trial, randomized discontinuation, or non-responder trial?



2: What does a SMART design have that others don't?

Design	Fixed parameters	Assess all enrolled	Washout Period	Sequential Treatment	Main Effects	Treatment Interactions	Tailored Strategies
RCT	X	X			X		
Adaptive		X			X		
Crossover	X	X	X		X		
Factorial	X	X			X	X	
Randomized Discontinuation	X			X	X		
Non-responder	X	O		O	X	O	
SMART	X	X		X	X	X	X

X: Yes ; O: Maybe


3

3

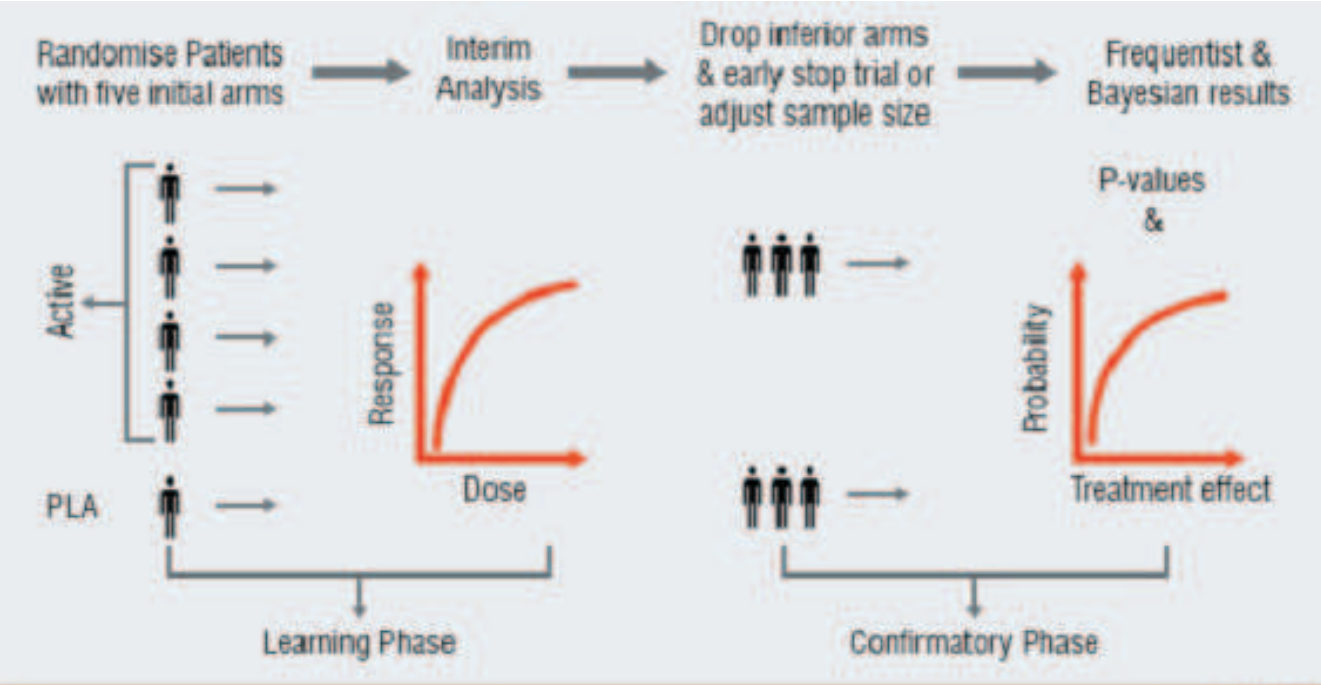
So a SMART is an adaptive design?

3: Adaptive?

- SMARTs are within-person adaptive
- Adaptive designs are between-person adaptive adjusting operational characteristics of the trial based on previous participants for future participants
- Two separate concepts that can be combined (see Lee, Thall, Ji, and Muller 2014, JASA; Cheung, Chakraborty, Davidson 2014, Biometrics)
- Follows the same participants throughout to develop effective DTRs

3: Adaptive?

Adaptive Design

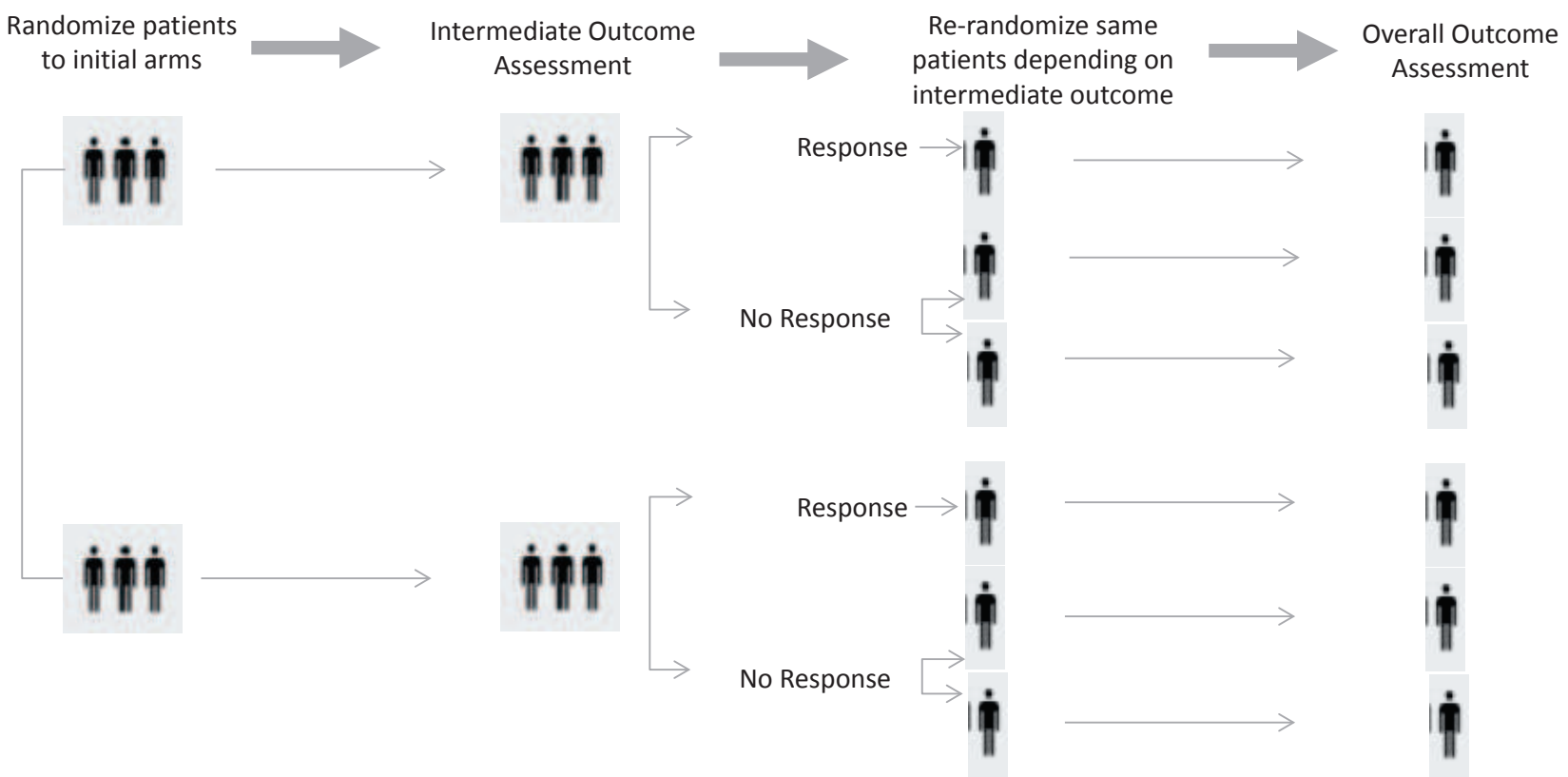


http://www.pharmafocusasia.com/clinical_trials/adaptive_trial_design.htm

Figure 1

3: Adaptive?

SMART



4

Dynamic treatment what?

4: Vocabulary

- Dynamic treatment regime, adaptive treatment strategy, treatment policy, adaptive intervention
- Use terminology your collaborator will understand best
- Describe in simple terms: intervention guideline over the intervention process including sequential treatment where treatment can depend on previous treatments, response to previous treatments and other individual behaviors and characteristics
- It is what you do in clinic

4: Vocabulary

Dynamic treatment regimen includes:

- Sequence of critical decision
- Intervention options at each decision point
- Tailoring variable to identify when and for whom intervention should be altered
- Sequence of decision rules


5

5

What is a tailoring variable?

5: Tailoring Variable

- a.k.a. intermediate outcome, response
- Intermediate outcome that can guide subsequent treatment decisions
- Early signal of ultimate success or failure
- Low dimensional (usually dichotomous)
- Examples: lab values, defined criteria (RECIST), adherence, questionnaire or interview results, number of red flags, composite measure
- Well defined with expert consensus and implementable in practice

5: Tailoring Variable

- Used in a DTR to adaptively determine the next treatment
- Used in a SMART to determine set of randomized treatment options

6

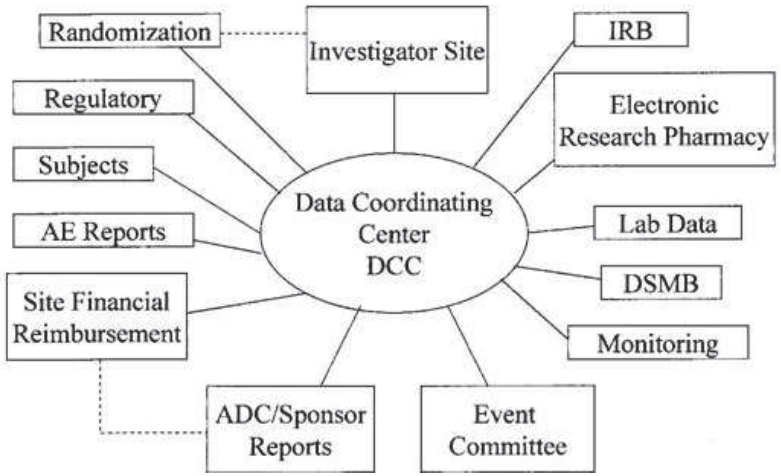
Multiple randomizations = multiple headaches

6: Multiple randomizations

- Can randomize upfront to follow specific DTR
- Ideal to randomize in time to stratify on important factors
- Technology and support provides timely information so should not add much more difficulty to trial

7

SMARTs appear to require a lot of infrastructure- how can we be sure this is in place?



7: Infrastructure

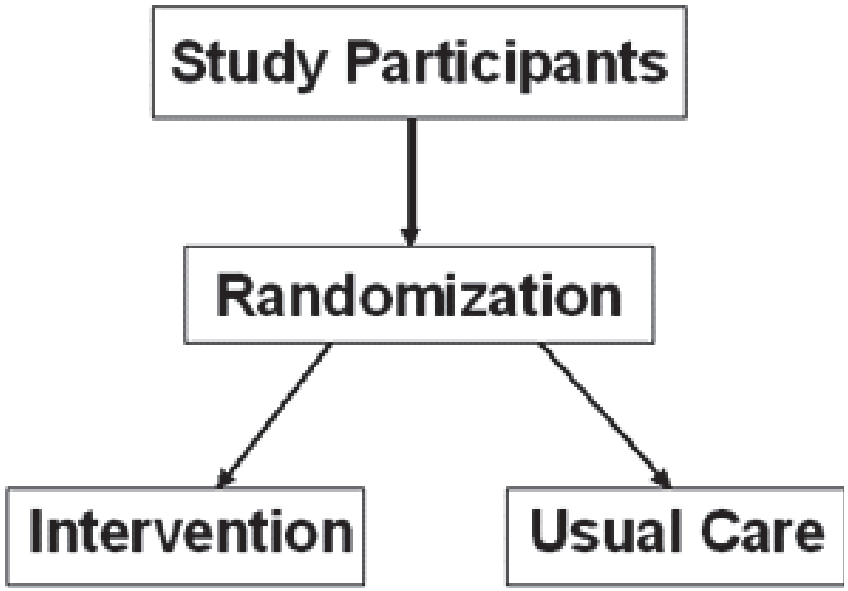
- Statistician is integral, trained staff is necessary
- To ensure feasibility, fidelity, and buy-in run a pilot study
- Pilots are publishable, require smaller sample
- Almirall et al. 2012: Designing a Pilot Sequential Multiple Assignment Randomized Trial for Developing an Adaptive Treatment Strategy

8

So I need a million patients to enroll in a SMART?

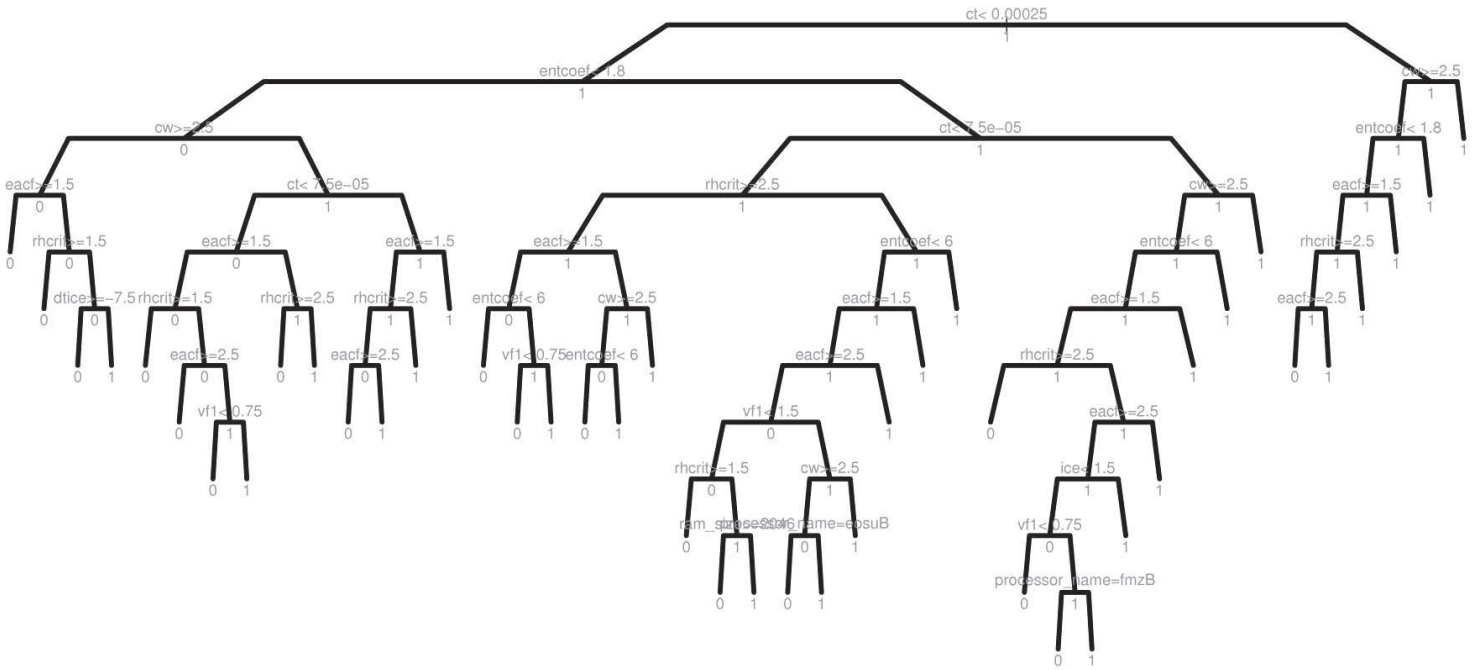
8: Sample Size

Comfortable Trial Design



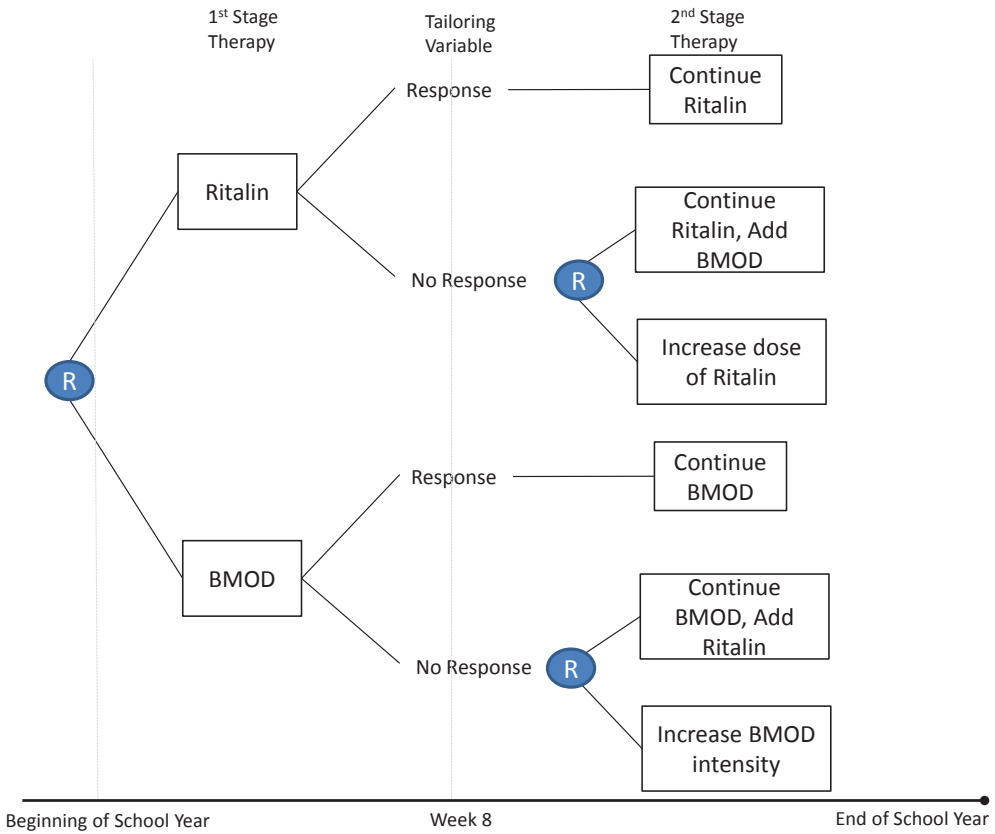
8: Sample Size

What a SMART looks like to someone for the first time



8: Sample Size

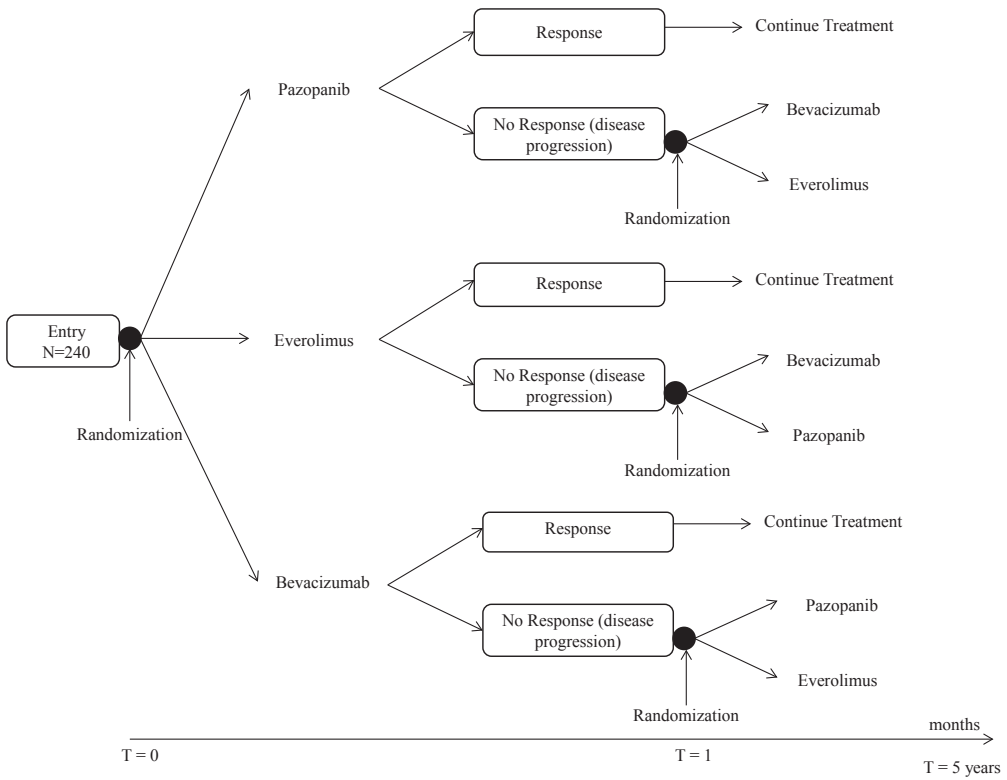
What a SMART really looks like: ADHD (n=153)



William Pelham, see `http://methodology.psu.edu/ra/smart/projects`

8: Sample Size

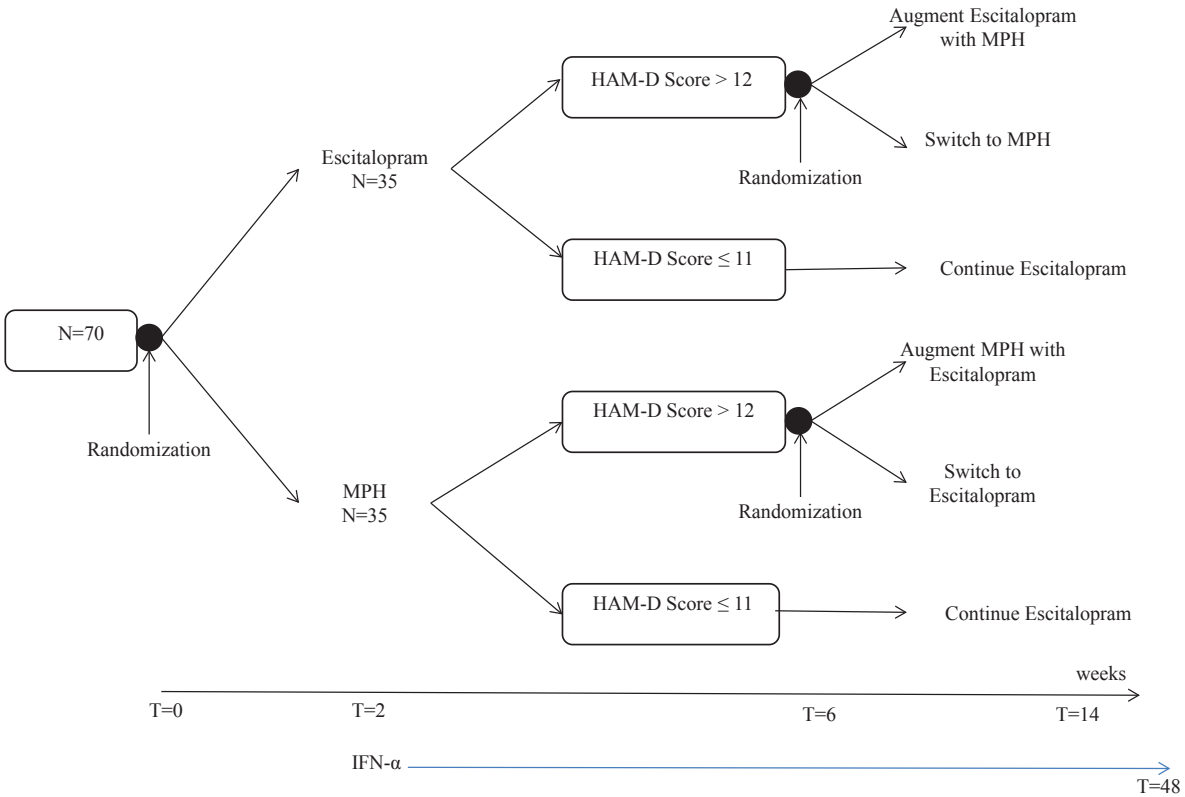
What a SMART really looks like: Kidney Cancer (n=240)



Tannir, see Thall et al Stat in Med 2007

8: Sample Size

What a SMART really looks like: Mental Health in Cancer (n=70)



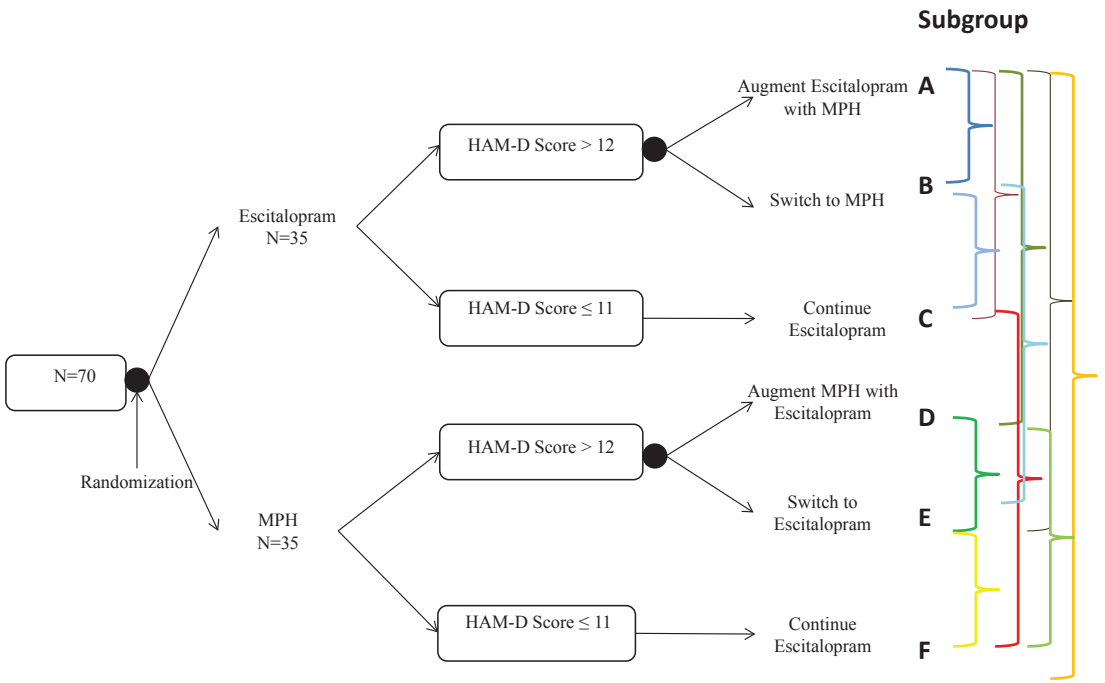
Auyeung et al, Clinical Trials, 2009

8: Sample Size

- Depends on primary objective
- Easy to use sample size calculators when dealing with DTR:
  `http://methodology.psu.edu/downloads`,
  `https://sites.google.com/a/umich.edu/kidwell/home/tools-for-design-and-analysis`
- Cannot be compared to standard RCT size

9

So I can compare all the subgroups in a SMART?

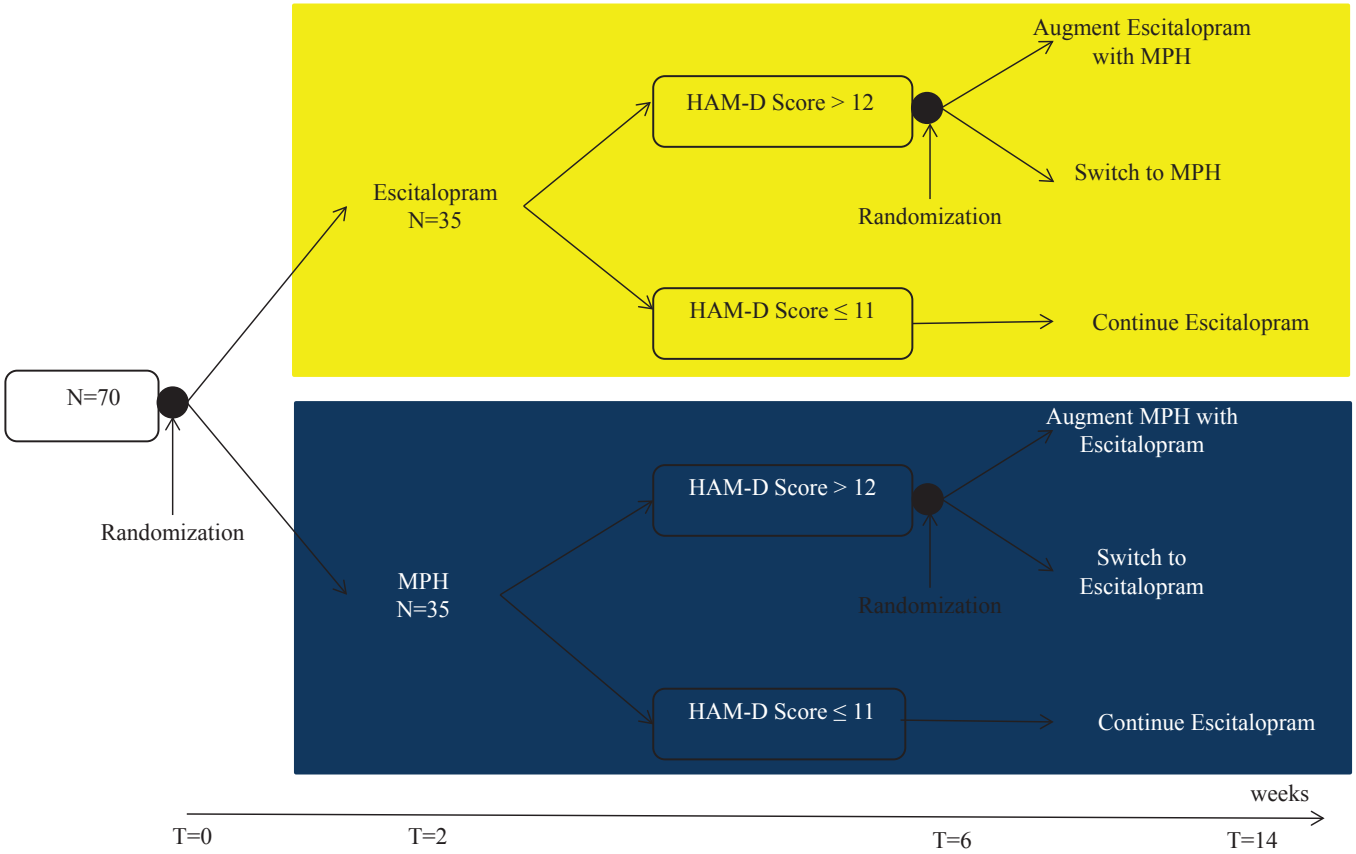


9: Subgroup comparison?

- SMARTs generally compare combinations of subgroups, not individual subgroups
- Not a causal comparison to compare two subgroups that begin with different first stage treatments and/or different response status

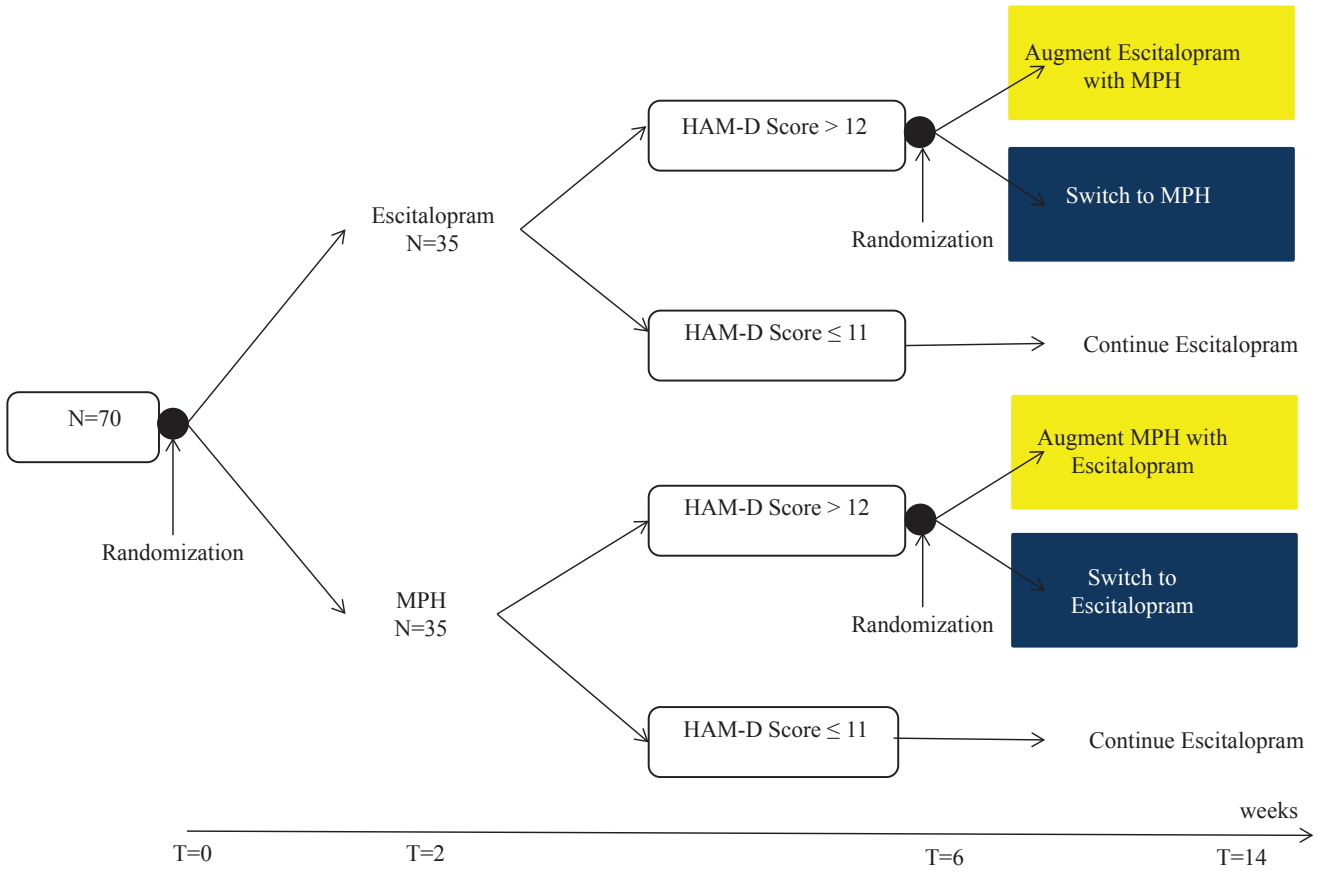
9: Subgroup comparison?

First-stage Intervention Main Effects Comparison



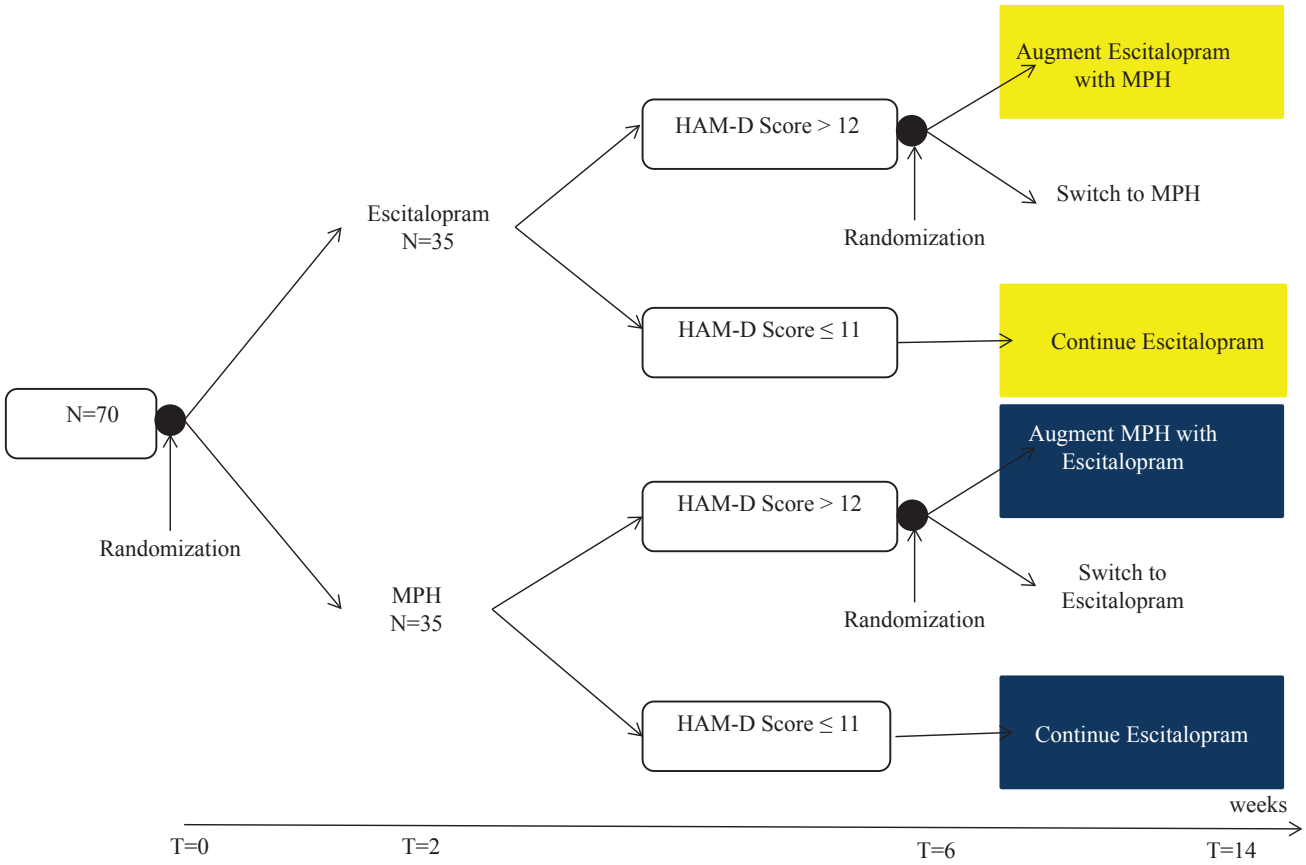
9: Subgroup comparison?

Second-stage Intervention Main Effects Comparison



9: Subgroup comparison?

Embedded DTR Comparison



10

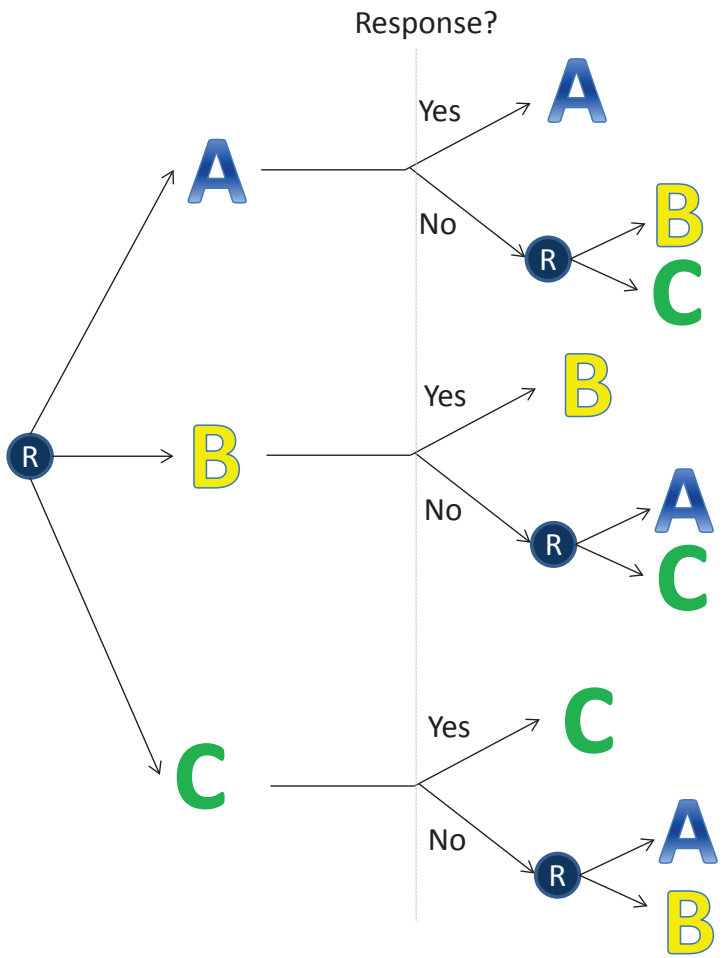
10

Will companies participate if several medications are used from different companies?

10: Company Participation

- STAR*D, CATIE
- Scope of study, interesting question
- FDA label for regimen?
- Can give medications opportunities for off-label use
- Test different duration or deliveries of treatment as opposed to different meds
- Need not focus on medication only trials

10: Company Participation



Regimens

(A,B)

(A,C)

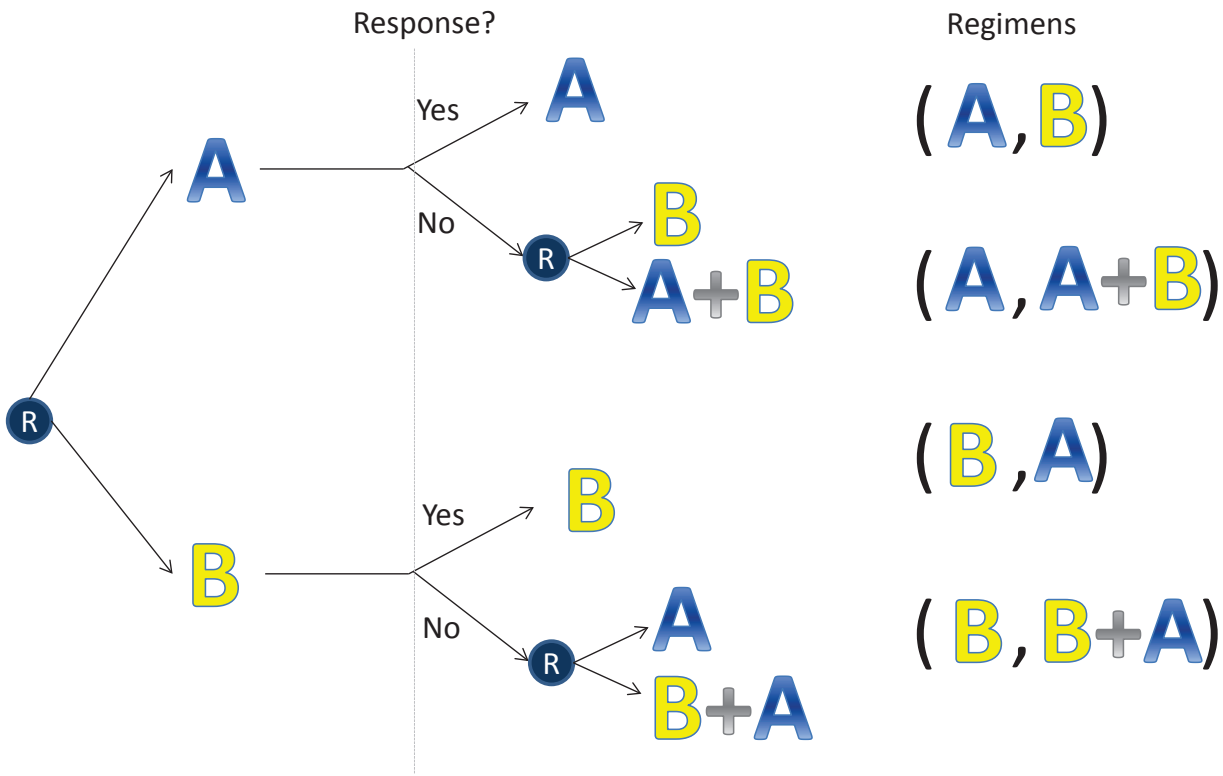
(B,A)

(B,C)

(C,A)

(C,B)

10: Company Participation



The End

Thank you

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