Getting SMART about Developing Adaptive Intervention Strategies

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Outline

- Why are adaptive interventions useful?
- What is an adaptive intervention?
- How can SMART designs help us learn about adaptive interventions and improve them?
- What are some things to consider when designing a SMART trial?
- Where do SMARTs fit in the personalization process?
- What are some common misconceptions about adaptive interventions and SMART designs?

Case Studies

- **P**rogram for **LU**ng cancer screening and **TO**bacco cessation (PI: Jospeh, co-I Vock; smoking cessation for adults eligible for low-dose CT scan for lung cancer screening)
- An Adaptive Algorithm-Based Approach to Treatment for Adolescent Depression (PI: Gunlicks-Stoessel, co-I Vock; adolescent depression with IPT & meds)

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Motivation for AIS

- Not everyone responds to the same intervention in the same way (between person heterogeneity)
- Not everyone response to an intervention is consistent over time (within person heterogeneity)
  - Changes in adherence, engagement, burden
  - Accrual of toxicity or delayed side effects
- Many chronic or long-term conditions or diseases — cancer, smoking, substance use disorder, depression, obesity, ADHD, autism, or schizophrenia
- BUT we may have multiple different interventions (or dosages/intensities to try)

How do we treat chronic disease?

- Make an initial treatment decision, monitor for response/adherence, and adjusting treatment based on the individual's changing course

How do we treat chronic disease?

- Can we formalize this process to test different strategies improve outcomes?

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Adaptive Intervention Strategy

- Pre-specified sequence of decision rules
- One rule for each possible decision point
- Dictate what type of treatment/intervention, at what dosage/intensity, with what type of delivery (e.g., switch, augment, intensify, stay the same)
- Based on measured patient characteristics (including prior response to treatment)

Adaptive Intervention Strategy

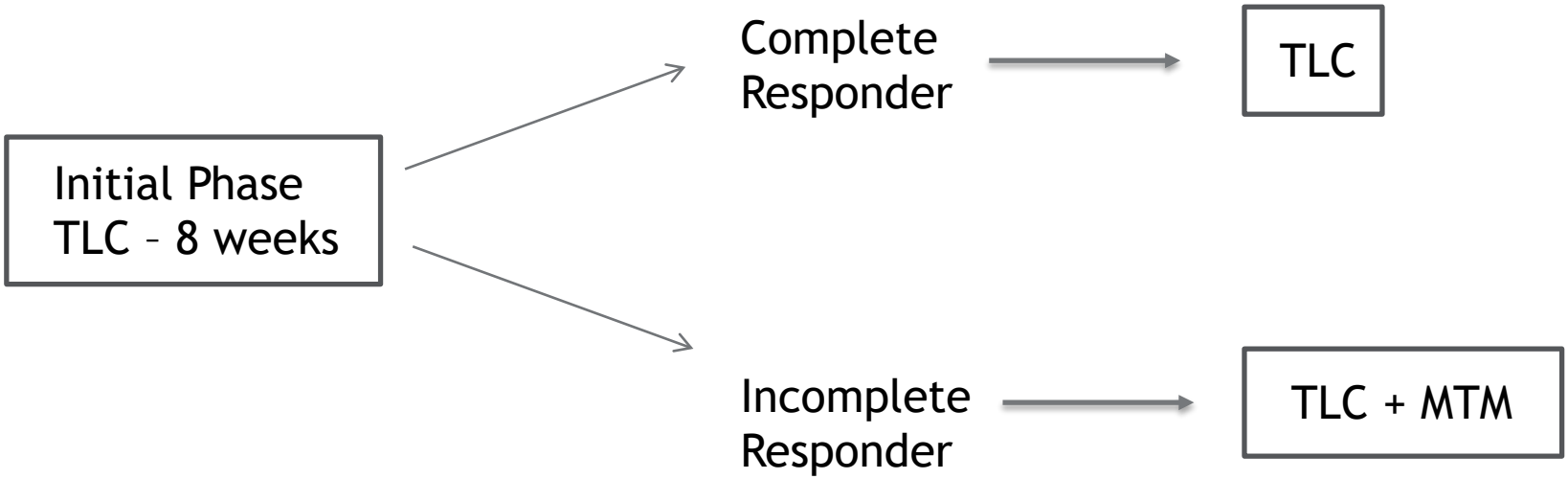
- The intervention/treatment strategy/regime/policy is said to be “adaptive” or “dynamic” or “tailored” because it depends on a person’s evolving characteristic
- Note: Stepped care intervention models are a special case of adaptive interventions

A Rose By Any Other Name

- Adaptive Intervention Strategy (AI or AIS)
- Adaptive Treatment Strategy (ATS)
- Dynamic Treatment Regime (DTR)
- Multistage Treatment Strategy (MTS)
- Treatment Policy (TP)

Example AIS in Smoking Cessation

- Stage 1: Initial Phase TLC (phone counseling + NRT) for 8 weeks
- Stage 2: At end of 8 weeks assess 7 day abstinence
  - IF abstinent (complete responder) continue with TLC (at least monthly phone counseling + NRT) for 48 weeks
  - ELSE combine TLC with pharmacotherapy (MTM)



Tailoring Variables

- The variable and cutoff which determine which intervention a participant should receive are known as tailoring variables and cutpoint
- Smoking cessation AIS: 7 day abstinence
- What can be a tailoring variable?
- Any variable which can be measured can be a tailoring variable
- This does not mean all are equally good ideas

Many Possible Adaptive Interventions

- Are these “good” adaptive interventions?
- How could these adaptive interventions be improved?

Unanswered Questions to Optimize an AIS

- Which treatment or intervention should be offered to individuals initially?
- How frequently should individuals be monitored for response/nonresponse to initial treatment?
- Among individuals who are not responding well to initial treatment, should their initial treatment be intensified, augmented, or switched?
- Among individuals responding to treatment, what maintenance/relapse prevention treatment should be offered?

Optimizing an AIS

- Typically used the following to develop AIS
  - Expert opinion
  - Clinical judgement
  - Piecing together an adaptive intervention using results from separate RCTs
- Can we collect data which would help inform development of an AIS?

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Sequential Multiple Assignment Randomized Trial

- SMART Designs are type of trial design that scientists can use to optimize an AIS
- Can be used to answer any of the previously posed questions

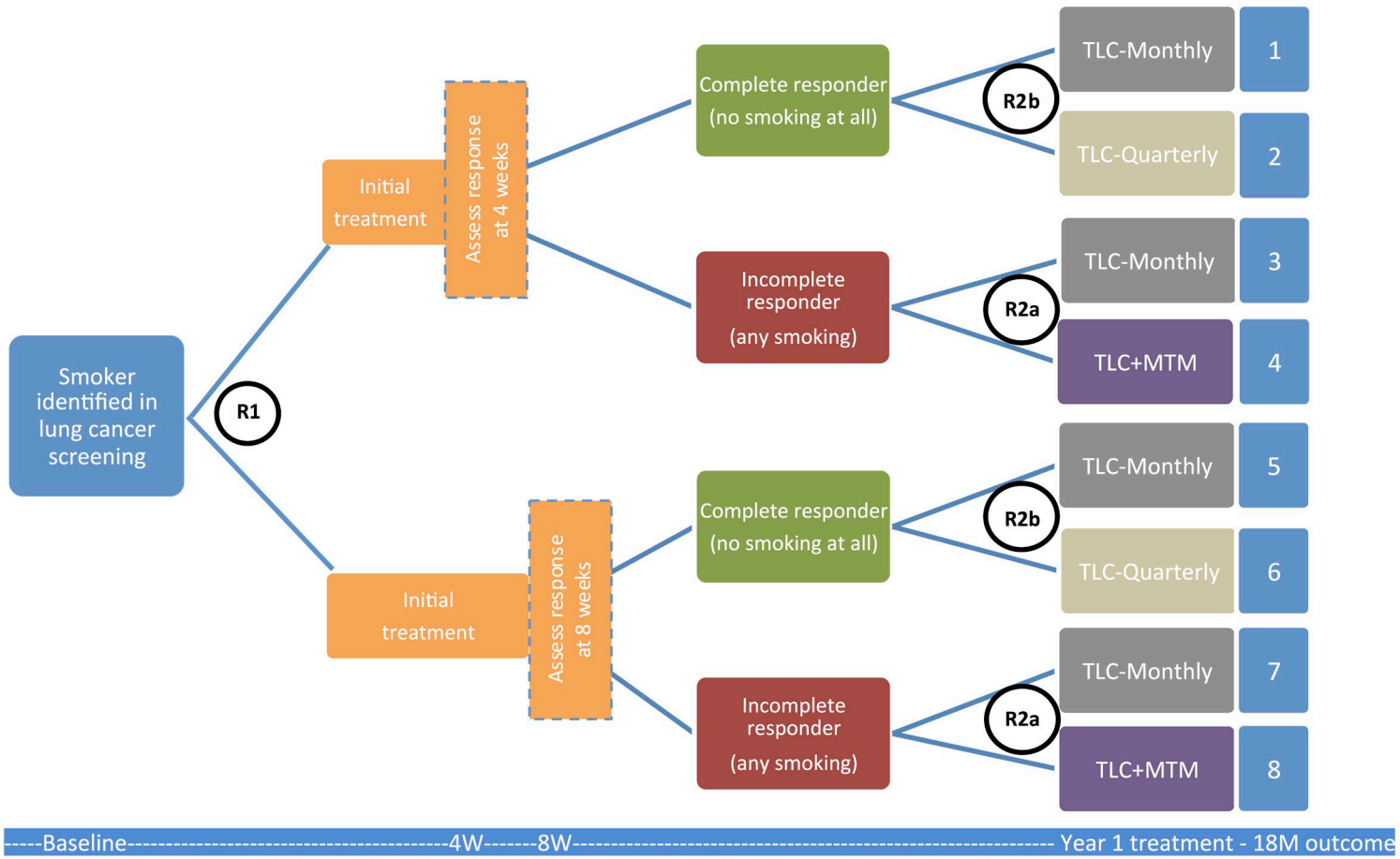
Sequential Multiple Assignment Randomized Trial

- Multi-stage trial design - each stage corresponds to a critical decision
- Participant can be randomly assigned to one of several intervention options at each stage
- Set of available interventions that a single participant may be randomized to at each stage may depend on prior treatment received and/or participant characteristics
- In a SMART, some or all participants are randomized at least twice; i.e., at two or more stages

Case Study #1: PLUTO

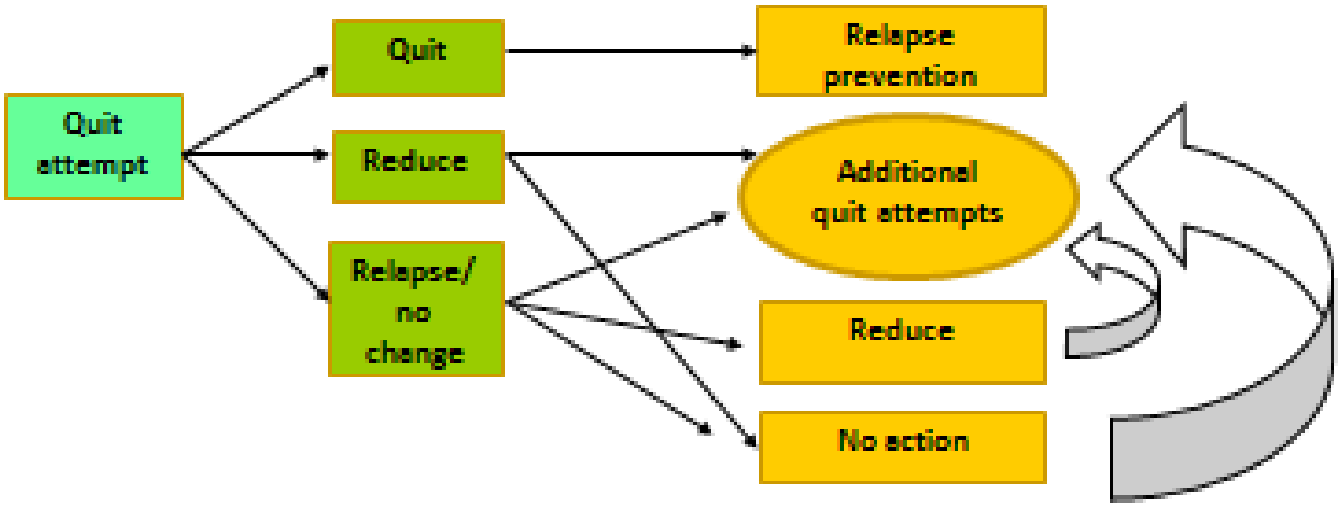
- Several behavioral, pharmacological, and combination treatment strategies for smoking cessation
- Treatments yield low rates of long-term abstinence (5-20%), and there is little evidence to help development of an AIS
- Pressing need: USPSTF recommends annual lung cancer screening for those age 55 to 80 years who have a 30 or more pack year history of smoking and who are current smokers or have quit within the last 15 years

Case Study #1: PLUTO



Case Study #1: PLUTO

- Usual care: 8 weeks of telephone counseling + NRT
- Tobacco longitudinal care: continue monthly calls for one year → recycle relapsers and reducers to make additional quit attempts
- TLC algorithm for treatment non-responders



Case Study #1: PLUTO

- TLC is an intensive intervention compared to state quit lines
- Other interventions which are evidence-based which could help those who are struggling
- Key questions:
  1. For those “doing well” can we reduce the frequency of phone counseling
  2. For those “struggling” will offering pharmacotherapy improve outcomes?

Embedded Tailoring Variable/AIS

- Response or nonresponse status at the end of initial-phase TLC is used to tailor the interventions that a subject may be randomized to in the second-phase
- Because this tailoring variable is part of the study design → "embedded tailoring variable"
- AIS which use this tailoring variable and intervention components in the study are known as "embedded adaptive intervention"

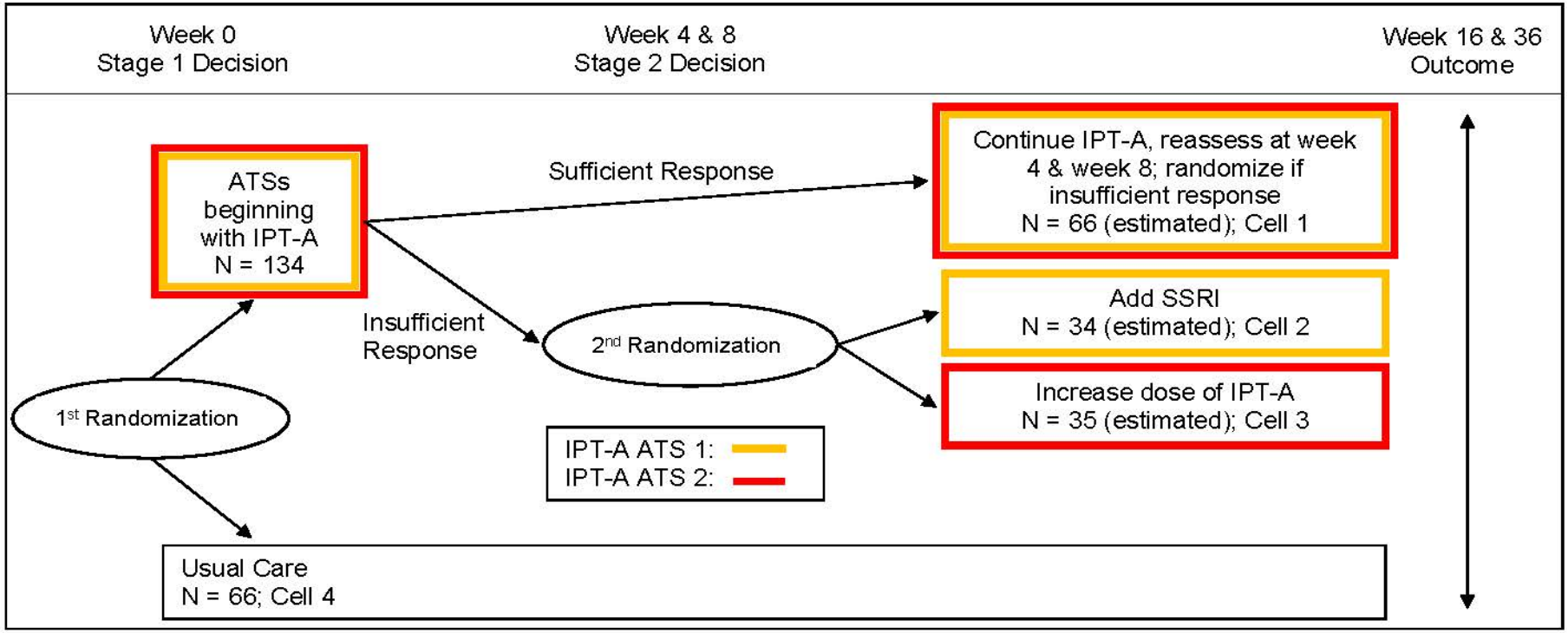
Embedded AIS in PLUTO

	Phase 1 Intervention	Phase 2 Intervention for Responders	Phase 2 Intervention for Nonresponders	Cells in Figure 1 Consistent with this DTR
1	4 weeks of Initial Phase of TLC	TLC-Monthly	TLC-Monthly	1 & 3
2	4 weeks of Initial Phase of TLC	TLC-Monthly	TLC+MTM	1 & 4
3	4 weeks of Initial Phase of TLC	TLC-Quarterly	TLC-Monthly	2 & 3
4	4 weeks of Initial Phase of TLC	TLC-Quarterly	TLC+MTM	2 & 4
5	8 weeks of Initial Phase of TLC	TLC-Monthly	TLC-Monthly	5 & 7
6	8 weeks of Initial Phase of TLC	TLC-Monthly	TLC+MTM	5 & 8
7	8 weeks of Initial Phase of TLC	TLC-Quarterly	TLC-Monthly	6 & 7
8	8 weeks of Initial Phase of TLC	TLC-Quarterly	TLC+MTM	6 & 8

Case Study #2: Algorithms for Adolescent Depression

- 20% of adolescents experiencing a depressive episode at some point
- Several evidence-based treatments including psychotherapy (interpersonal psychotherapy, cognitive behavioral therapy), antidepressant medication (SSRIs), and their combination.
- Approximately 30-50% of adolescents who receive these treatments do not respond
- Practice parameters recommend systematic and routine assessment and monitoring
- Currently no guidelines to direct therapists regarding how to use those symptom assessments to guide subsequent treatment decisions

Case Study #2: Algorithms for Adolescent Depression



Specific Aims of PLUTO

- Primary: Test whether *incomplete responders* to initial phase of TLC treatment benefit from the addition of MTM
- Secondary: Among *complete responders* compare the effect of more intensive (at least monthly) follow-up to less intensive (quarterly) follow-up
- Exploratory: Moderators of second-phase treatment (assessment time & # of days smoking in last week)
- Exploratory: Compare different embedded adaptive interventions
- Note: primary and secondary aim mirror the key questions outlined earlier

Stat Analysis and Power for Primary Aim

- As with factorial designs, common test the main effects of intervention components
- To test primary aim of PLUTO: pool data from all *incomplete responders* randomized to TLC (cells 3 & 7) or TLC+MTM (cells 4 & 8 and compare the outcomes using methods appropriate for the comparison of two groups
- Standard formulas can be used to estimate the sample size of nonresponders needed
- Overall study sample size: Dividing the sample size of nonresponders by the proportion of subjects one anticipates to be nonresponders

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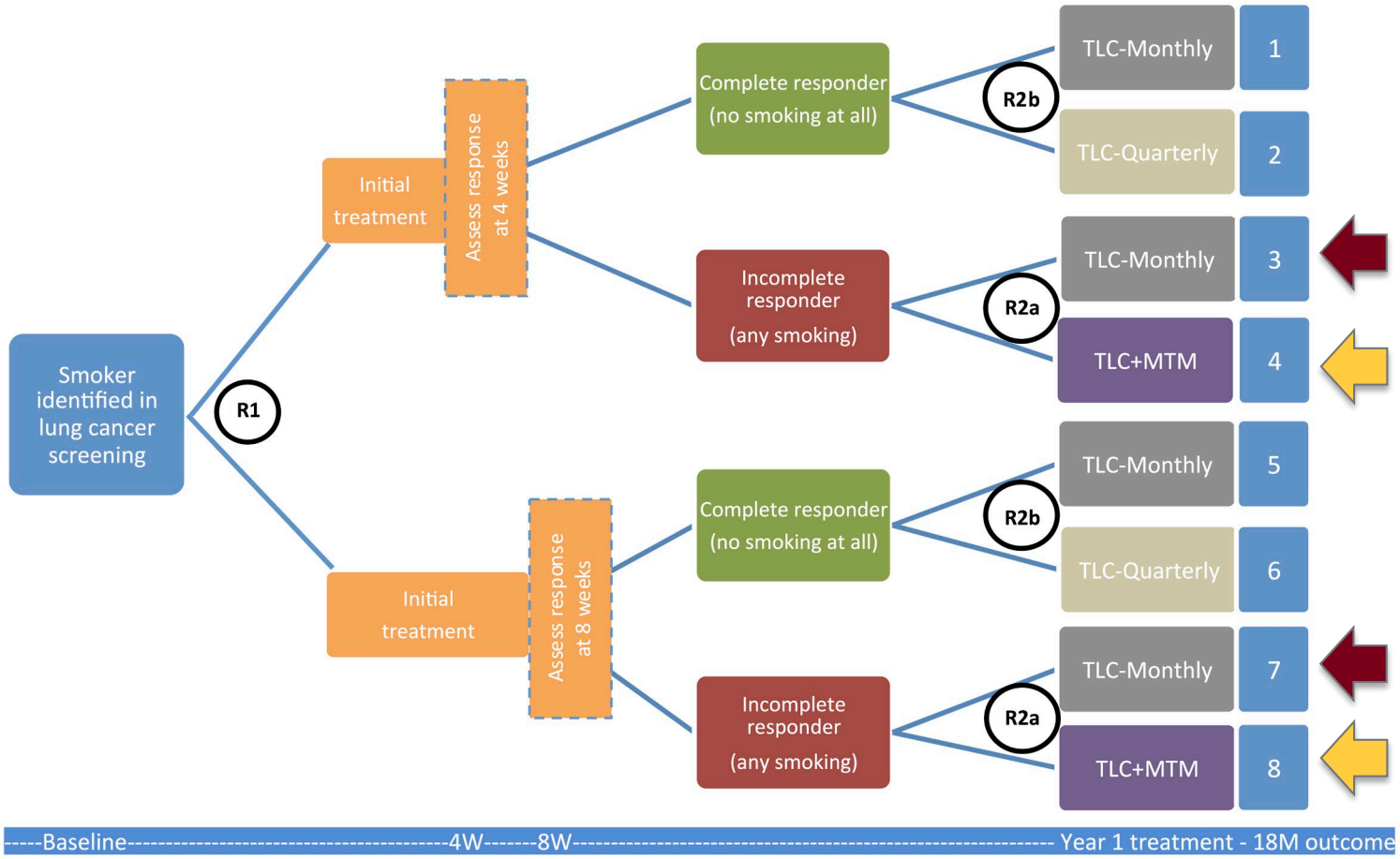
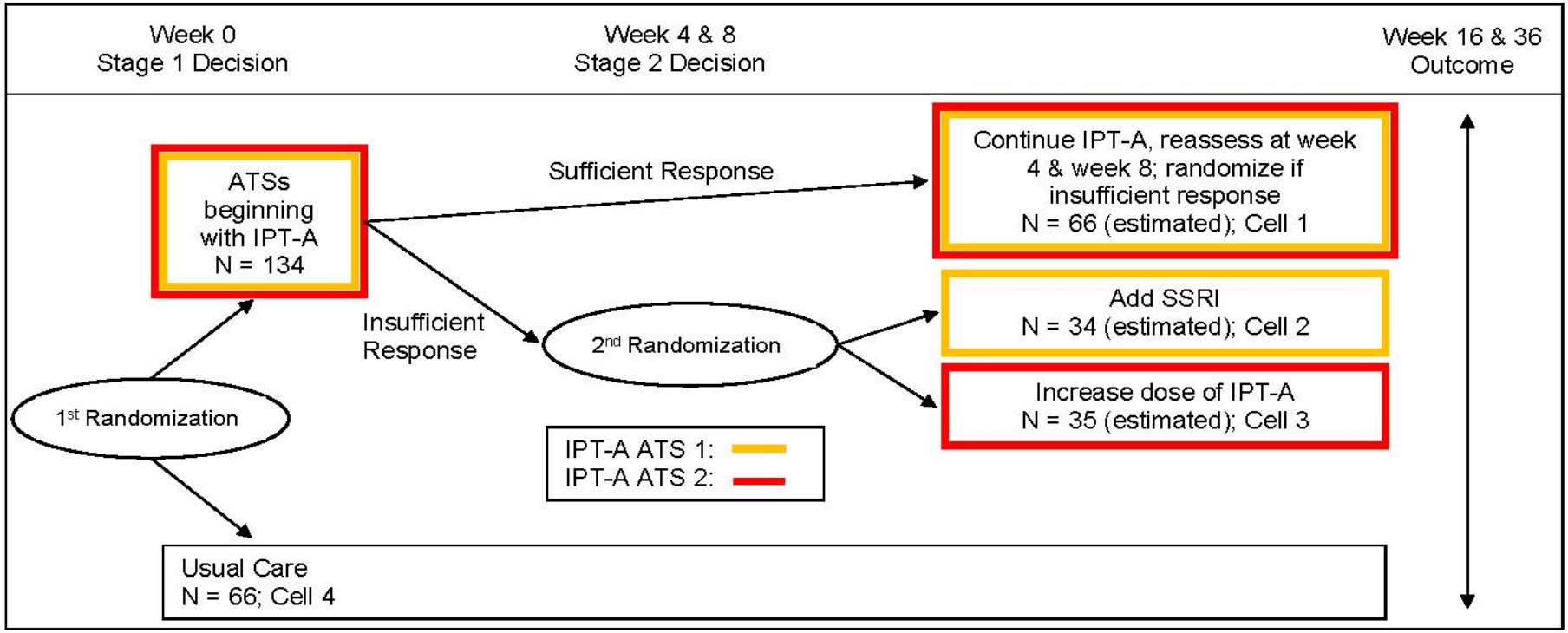


Stat Analysis to Compare AIS

- Want to estimate the average response to the AIS "begin with IPT-A and nonresponders receive IPT-A + SSRI"
- Data from participants consistent with that embedded AIS (i.e., participants who follow the treatment paths ending in cells 1 and 2) would be used
- Subjects are compliant with more than one embedded AIS. Therefore, estimators of the anticipated outcome of different embedded AISs may be correlated → robust standard errors
- Responders who are consistent with an embedded AIS are over- or underrepresented relative to what we would expect if everyone in the population were to follow this regimen. Over- or underrepresentation in a sample can be corrected using a weighted analysis

Case Study #2: Algorithms for Adolescent Depression



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Design Considerations

- Old adage: “Protocolize what you know, randomize what you don’t know”
- Lots to consider as part of SMART
  - Initial phase treatment type, intensity, and duration
  - Tailoring variable, cutpoint, and assessment time
  - Second phase treatment type, intensity, and duration for both “responders” and “nonresponders”
- Cannot randomize them all and usually infeasible to randomize to more than 2-3 levels

Design Considerations: Selecting Treatment Types

- SMARTs are about testing the sequence of interventions not establishing new ones
- Frequently start with a single longitudinal evidence-based intervention and then consider ways to augment/intensify/switch
  - PLUTO: start with TLC and test augmenting with MTM
  - Adolescent depression: start with IPT-A and testing intensifying versus augmenting with SSRI
- Need to consider safety and tolerability (may need pilot)

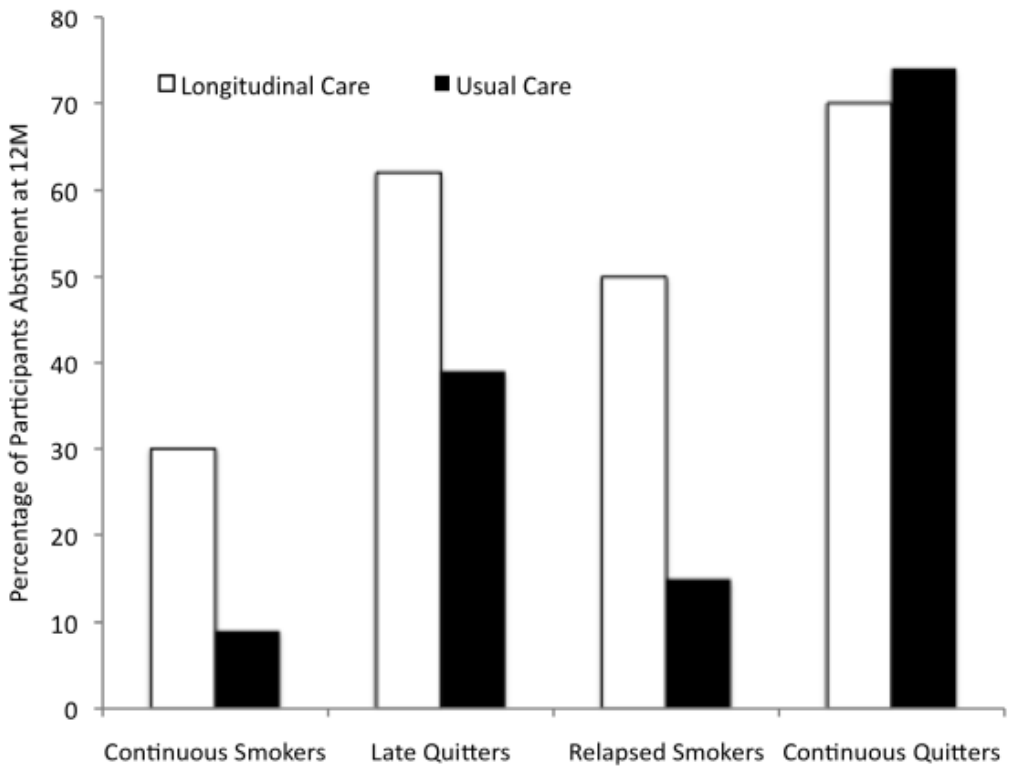
Design Considerations: Tailoring Variable & Cutpoint

- Often second phase treatment will intensify for those with poor prognosis and focus on maintenance/relapse prevention
- Tailoring variable should
  - Be easily measurable (in the real world)
  - Have good predictive value of the final outcome (e.g., C-index)
- Cutpoint can be chosen to balance sensitivity and specificity

Design Considerations: Tailoring Variable & Cutpoint

- Adolescent Depression
  - Tailoring variable: Hamilton Rating Scale for Depression (week 4: AUC=.78, p=.01; week 8: AUC=.81, p<.01).
  - At week 4 & 8, a cutoff of 20% and 40% reduction in HRSD from baseline represented the best combined sensitivity (72.7% & 72.7%) and specificity (71.4% & 83.3%)
- PLUTO
  - Tailoring variable: 7 day abstinence
  - Cutpoint chosen to identify subgroup where TLC was no better than usual care

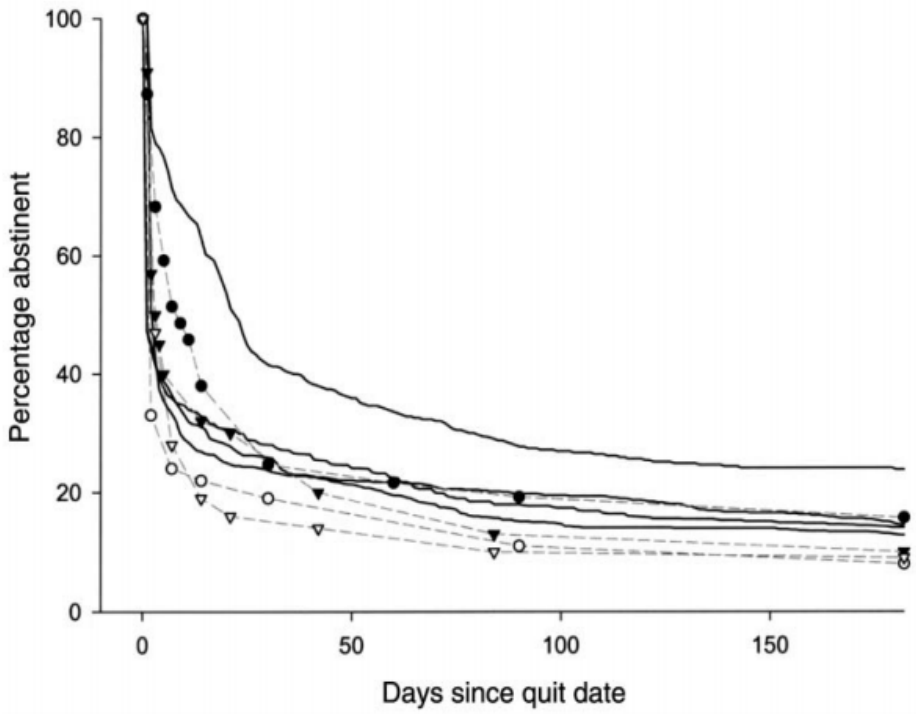
Design Considerations: Tailoring Variable & Cutpoint



Design Considerations: Assessment Time

- Operating characteristics of tailoring variable depend on when it is measured
- Need to assess nonresponse early enough to avoid discouragement but late enough to catch late relapsers
- Adolescent depression: Assess response to IPT-A twice (4 and 8 weeks). Based on pilot data.
- PLUTO: Randomization to 4 and 8 weeks was based on historical data

Design Considerations: Assessment Time



Sample survival curves from smoking cessation studies

Control Conditions Within a SMART

- Many SMARTs do not include a “control” or “unpersonalized” condition → goal is to test efficacy of several AIS one of which could be carried forward
- SMARTs can be designed to include a suitable control intervention
  - As part of the embedded AIS
  - As part of the initial randomization
- Effect sizes will be smaller comparing two different high quality AISs than comparing AIS to usual care

Control AIS in PLUTO

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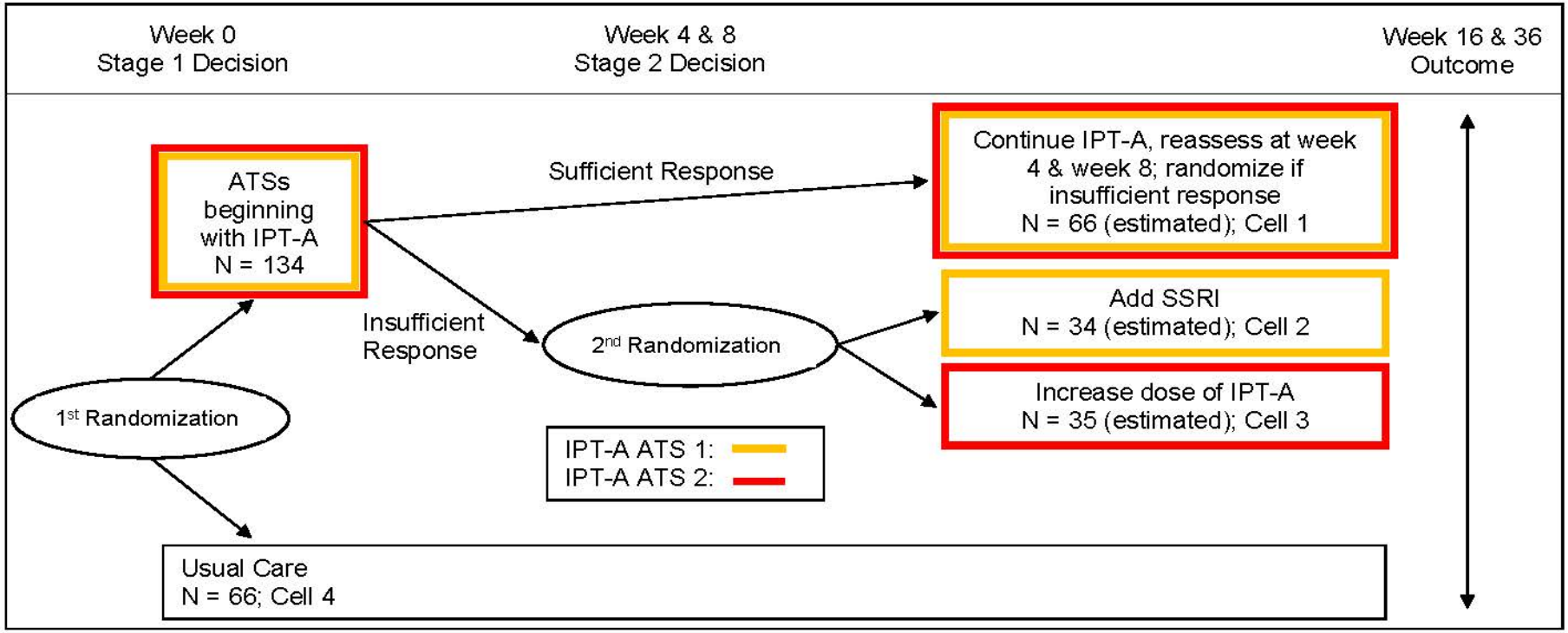
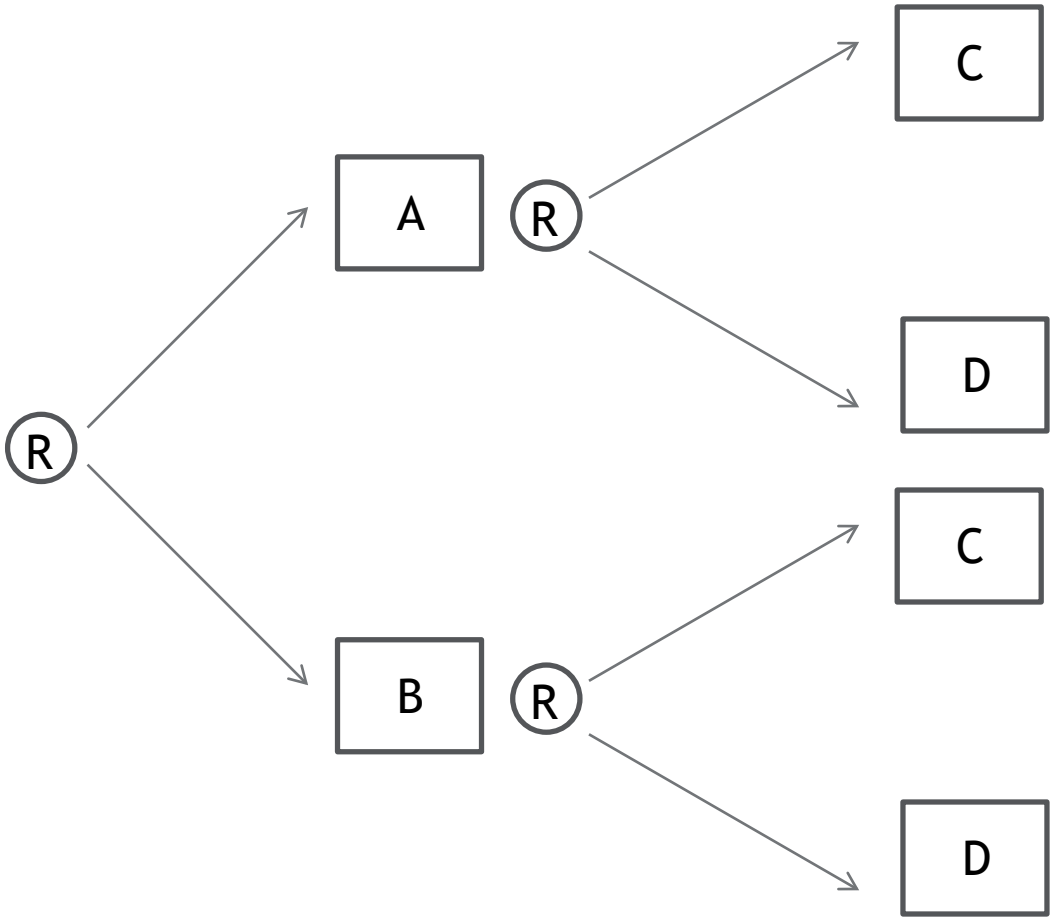


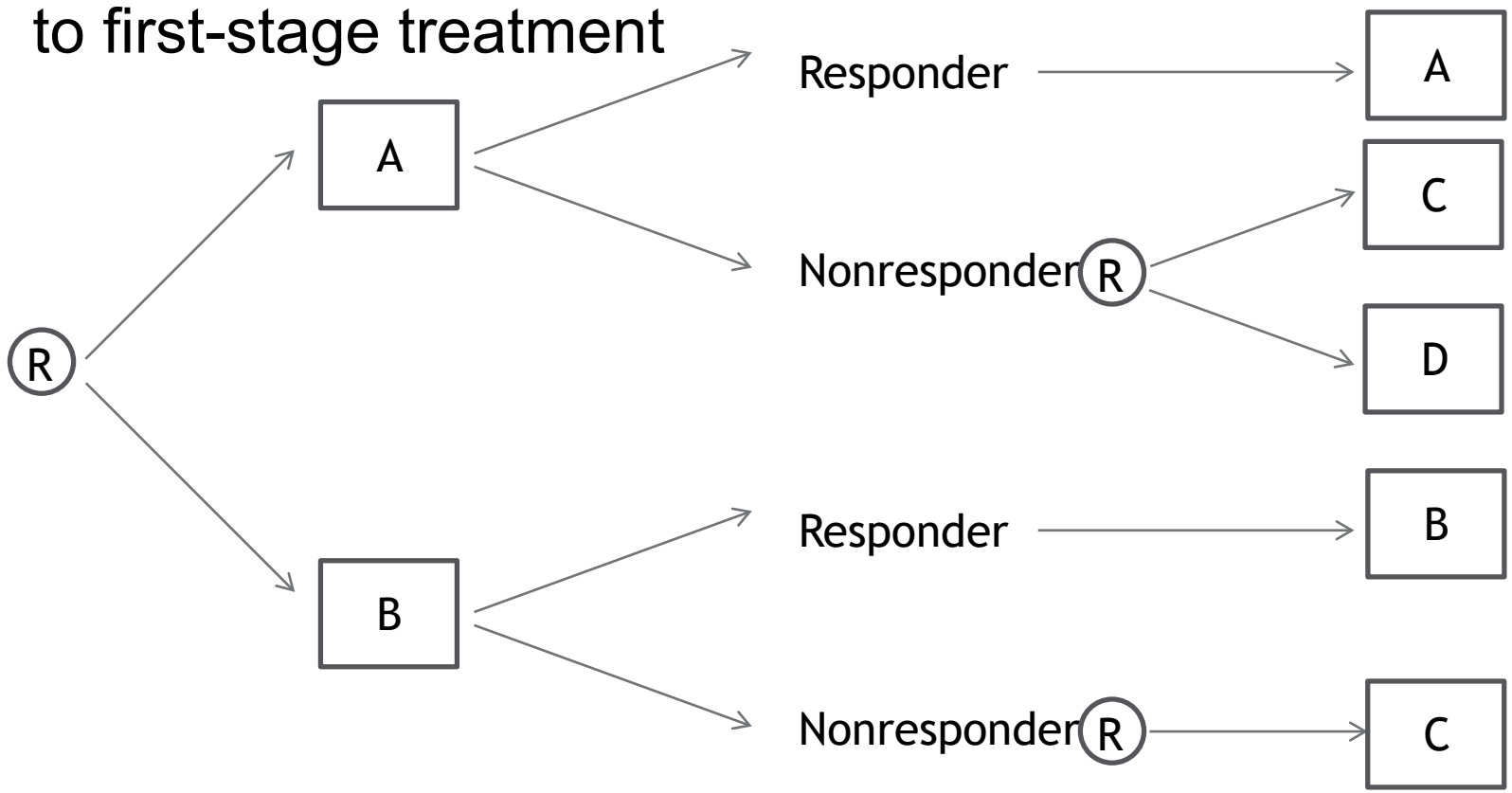
Other Common SMART Designs

- SMART with no embedded tailoring variable



Other Common SMART Designs

- SMART in which re-randomization depends on a combination of first-stage treatment and nonresponse to first-stage treatment



Other Experimental Designs

- Factorial Design
- Multi-arm RCT
- Standard RCT or series of two-arm RCTs comparing different adaptive intervention strategies
- Single-stage-at-a-time experimental approach (e.g., nonresponder trial, discontinuation trial, etc.)

Other Experimental Designs: Drawbacks

- Factorial Design – Does not allow embedded tailoring variables
- Multi-arm RCT – Requires larger sample size
- Standard RCT or series of two-arm RCTs comparing different adaptive intervention strategies – Requires MUCH larger sample size
- Single-stage-at-a-time experimental approach (e.g., nonresponder trial, discontinuation trial, etc.) – 1) interventions may have delayed effects or interact with later-stage treatments 2) the types of nonresponding subjects who agree to participant in a trial testing two second-stage treatments may differ from the population of nonresponders

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Personalization Process and Next Steps

- Drug development and approval does not happen as the result of a single randomized experiment → Neither should a personalized intervention algorithm
- Need to think of personalized intervention development in terms of phases analogous to drug development

Phases of Personalization

- Phase I: Pilot SMARTs
  - Willing to have intervention re-randomized?
  - Adhere to the proposed interventions?
  - How do we handle participants who don't have tailoring variable measured?
- Phase II: SMART study
  - Establish that the personalized interventions have some amount of efficacy
  - Use the data collected to refine personalized algorithms
- Phase II: Confirmatory Trial

More Deeply Tailored Interventions

- Example: “Start with initial phase TLC and assess response status at 4 weeks. If a responder, continue with TLC-Q; else if a nonresponder who has smoked on two or fewer days in the past week continue with TLC-M; else continue with TLC+MTM.”

More Deeply Tailored Interventions

- How do we find more deeply tailored interventions which improve outcomes?
- Short answer: moderators, effect modifiers, interaction which are qualitative in nature
- Long answer: reinforcement learning/machine learning techniques which account for delayed effects - Q-learning, A-learning, C-learning, and outcome weighted learning

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Common Misconceptions of AIS

- Tailoring variables cannot differ based on previous intervention
- An adaptive intervention must recommend a single intervention component at each decision point
- Adaptive interventions seek to replace clinical judgement
- Adaptive interventions are only relevant in treatment settings
- Adaptive interventions are non-standard because they involve randomization

Common Misconceptions of SMART

- SMARTs require prohibitively large sample sizes
- All SMARTs require Multiple-Comparisons Adjustments
- All research on adaptive interventions requires a SMART
- All SMARTs must include an embedded tailoring variable
- All aspects of an embedded adaptive intervention must be randomized
- SMARTs are a form of adaptive research design
- SMARTs never include a control group
- SMARTs require multiple consents
- SMARTs are susceptible to high levels of study drop-out

Next Frontiers for AIS and SMART

- What should the next trial be after a SMART (more deeply tailored AIS or best embedded AIS)?
- How to handle missing data in SMARTs?
- Can we combine some of the phases of personalization?
- How does one recommend a set of possible treatment options which are equivalent?
- How to combine different outcomes and weight patient preference (efficacy vs. toxicity)?

Summary

- Defined Adaptive Interventions and discussed why they are important
- Demonstrated that SMART study designs can be used to develop and improve adaptive intervention as part of a personalization process
- Highlighted 2 SMARTs in the field

Collaborators

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