WHERE DO WE GO FROM HERE? NEXT GENERATION TREATMENT INTERVENTIONS

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LEGACY | The Schroeder Institute
FOR TOBACCO RESEARCH AND POLICY STUDIES

Outline

- Personalized treatment & personalized medicine
- Clinical algorithms
- RCTs
- Multiphase Optimization Strategy (MOST)
- Adaptive Treatment strategies
- Sequential multiple assignment randomized trial (SMART)
    - Example 1: ADHD
    - Example 2: Pharmacologic treatment for smoking in HIV+ smokers
- Analysis Approaches

Treatment Outcome: In Need of Tailoring?

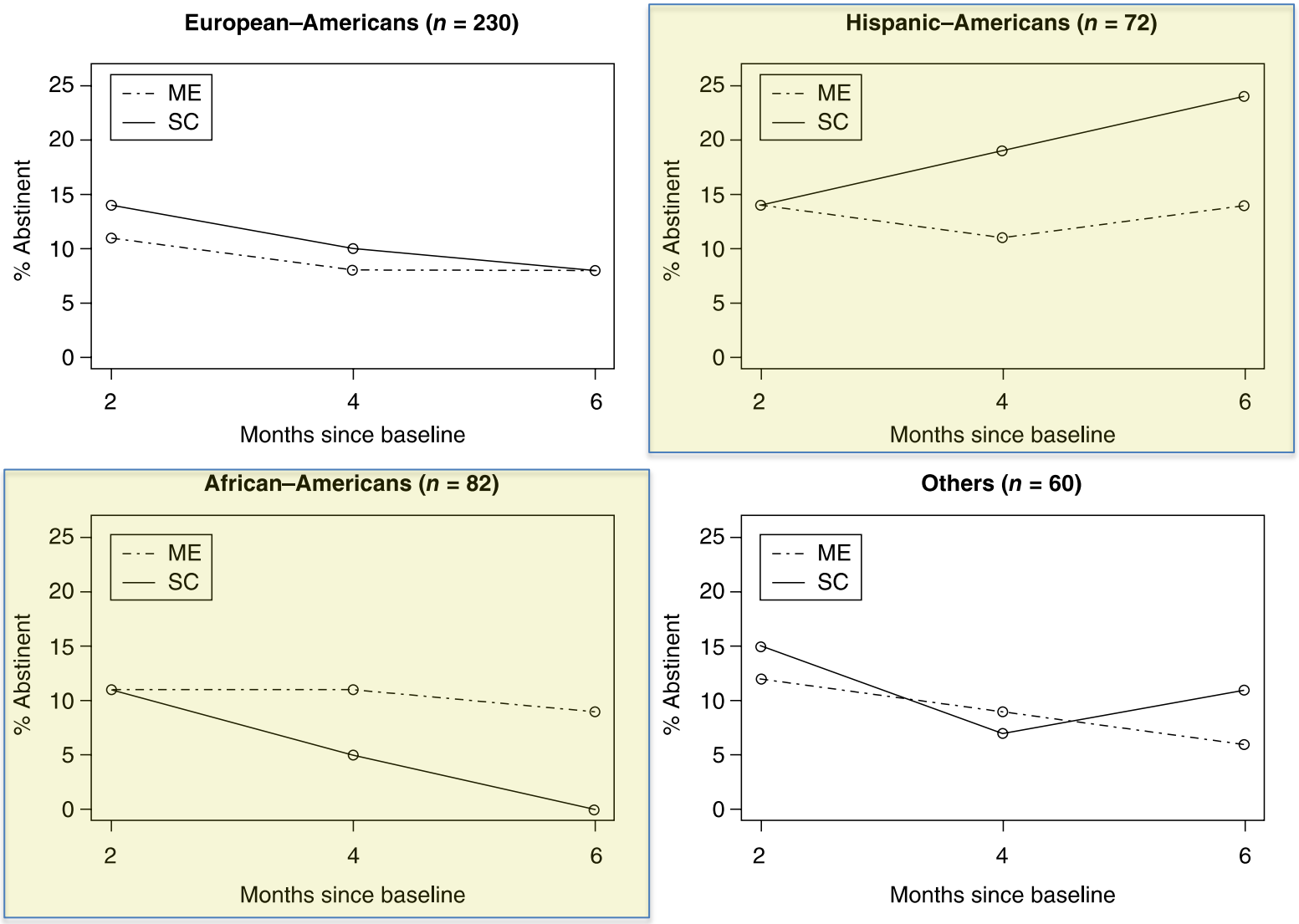


Figure 2 Intent-to-treat (ITT) quit rates over 2-month, 4-month and 6-month follow-up by study condition and race/ethnic group. ME: motivationally enhanced treatment; SC: standard care treatment

LESSONS LEARNED

Tailoring – To what?

- Race/ethnicity/culture/subculture/microculture
- HIV/AIDS unique needs (what are they, compared to other chronic illnesses?)
    - Reprieve of death sentence (ART/other advances)
    - Low SES (education; income; employment)
    - Social and welfare needs (housing; access to health care; social support)
    - Psychiatric and other medical comorbidities
    - Drug/alcohol use/risky behaviors
    - Sexual orientation/sexuality
    - Low health literacy/knowledge/awareness
    - Complicated treatment regimens (e.g., many meds)

PERSONALIZED TREATMENT

What is it?

Matching patient characteristics to choice of treatment options (initial treatment selection)

Adapting treatment to interim outcomes (dynamic treatment selection)

PERSONALIZED TREATMENT

Early efforts:

- Patient-treatment matching, tailoring based on clinical information
- Stepped care
- Clinical algorithms

Personalized medicine

PERSONALIZED MEDICINE

A medical model that proposes the customization of healthcare - with medical decisions, practices, and/or products being tailored to the individual patient.

PERSONALIZED MEDICINE

Pharmacogenetics

- Drug metabolism (e.g., warfarin)
- Disease subsets (cancers; schizophrenias)
- Targeted therapy (cellular; molecular)
- Safety and toxicity (risk of adverse events)
- Early treatment response/failure (biomarkers: imaging; proteomics)
- Prevention (risk stratification)

PERSONALIZED TREATMENT: CLINICAL ALGORITHMS

ELSEVIER

Journal of Substance Abuse Treatment 34 (2008) 426–432

Journal of Substance Abuse Treatment

Regular article

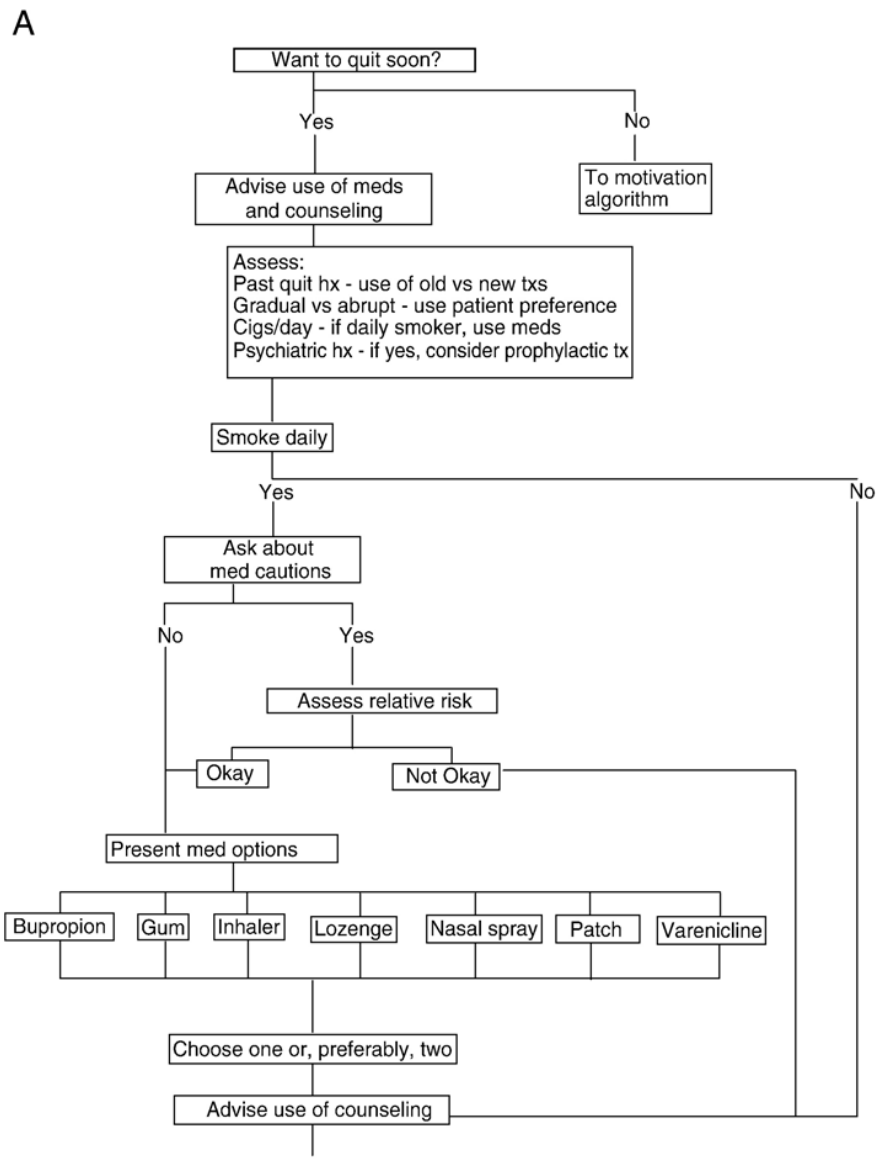
An algorithm for choosing among smoking cessation treatments

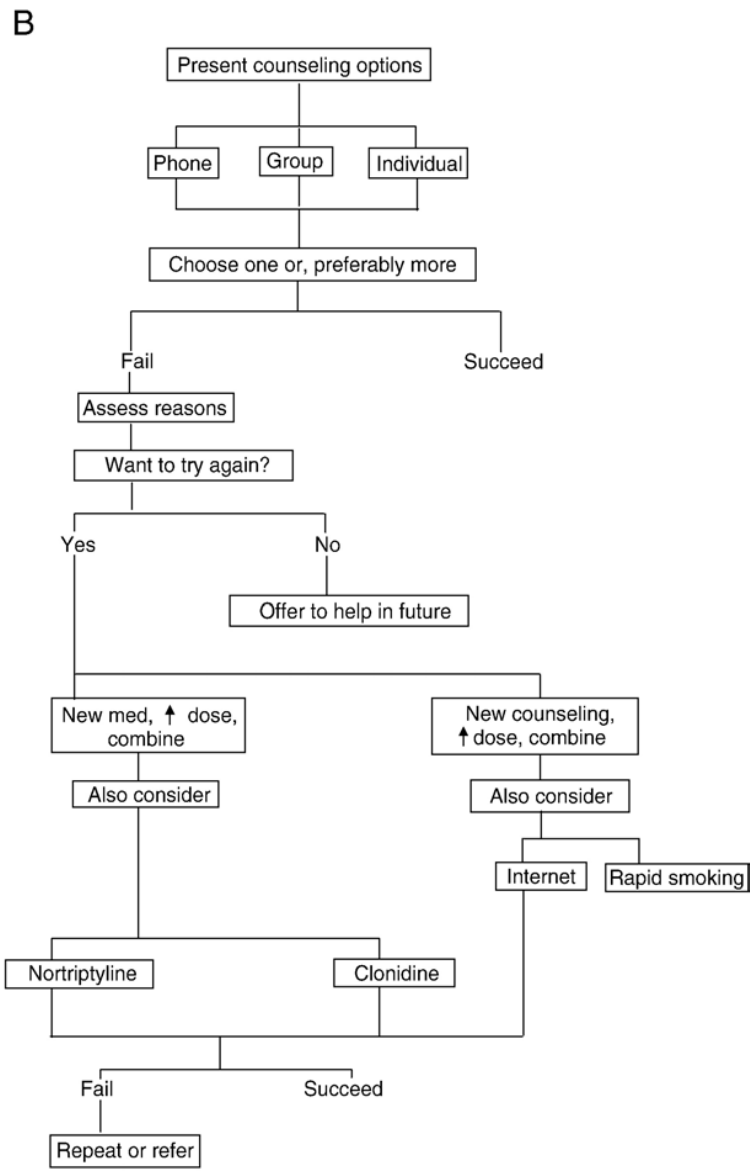
John Hughes, (M.D.)

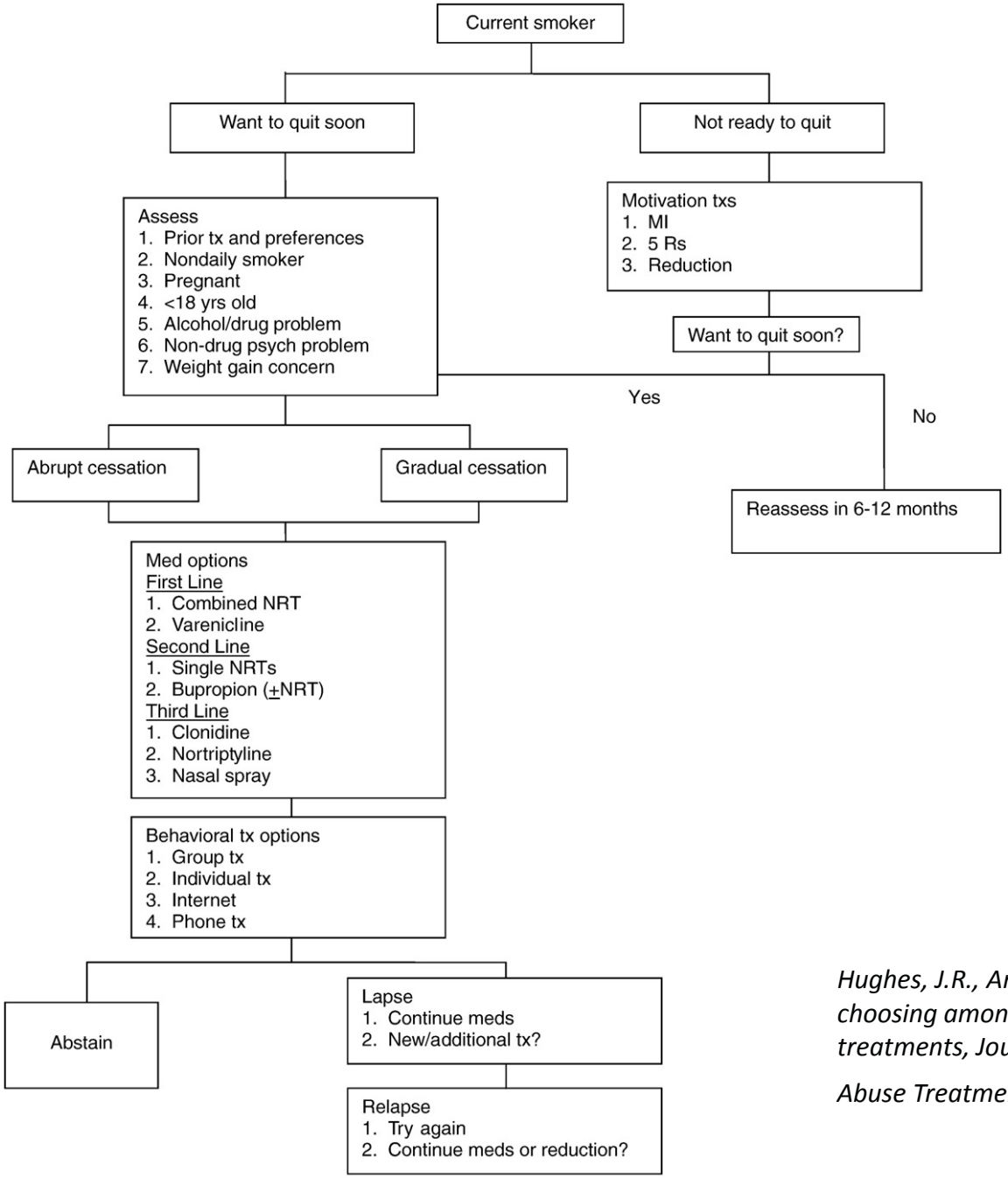
University of Vermont, Burlington, VT 05401-1419, USA

Received 13 March 2007; received in revised form 25 June 2007; accepted 1 July 2007

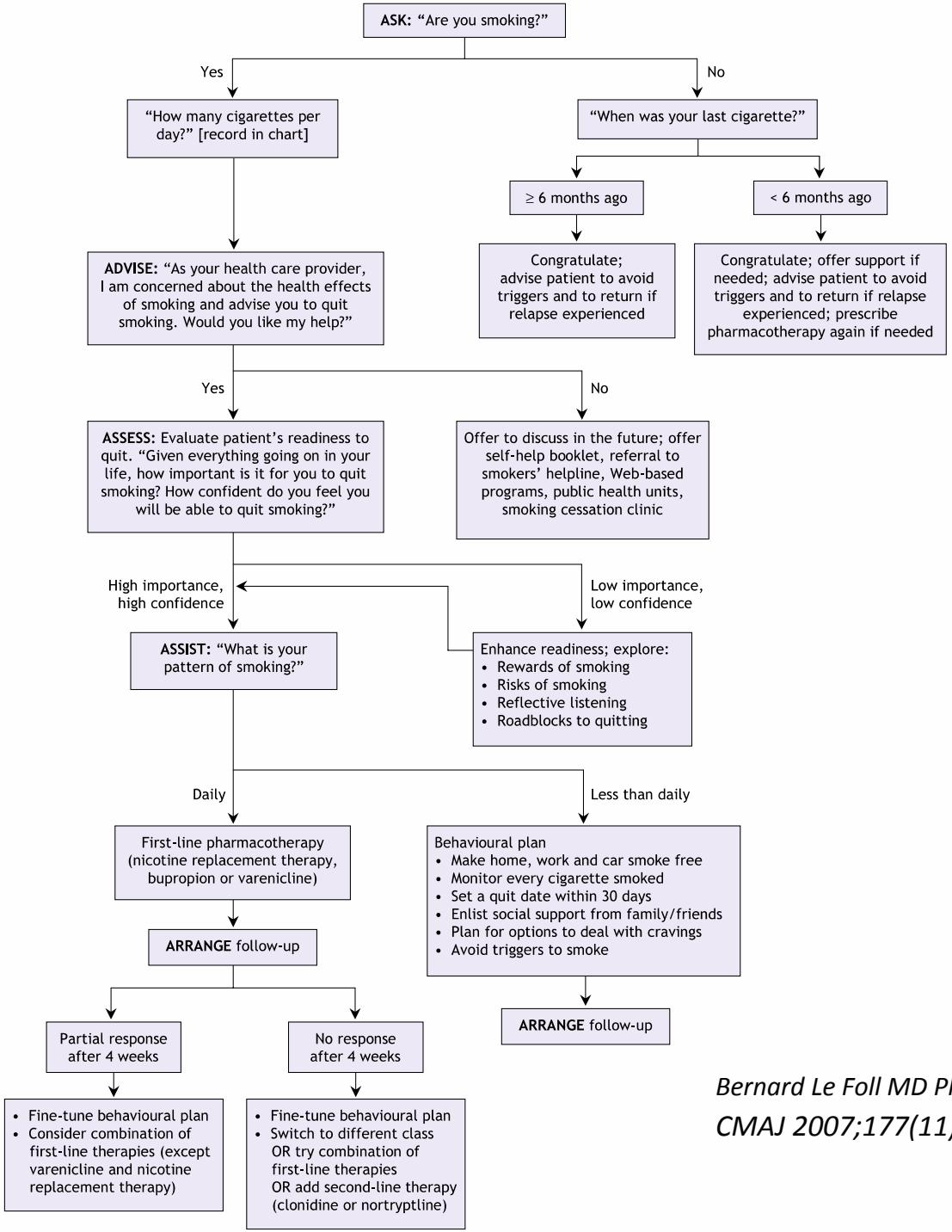
PERSONALIZED TREATMENT: CLINICAL ALGORITHMS



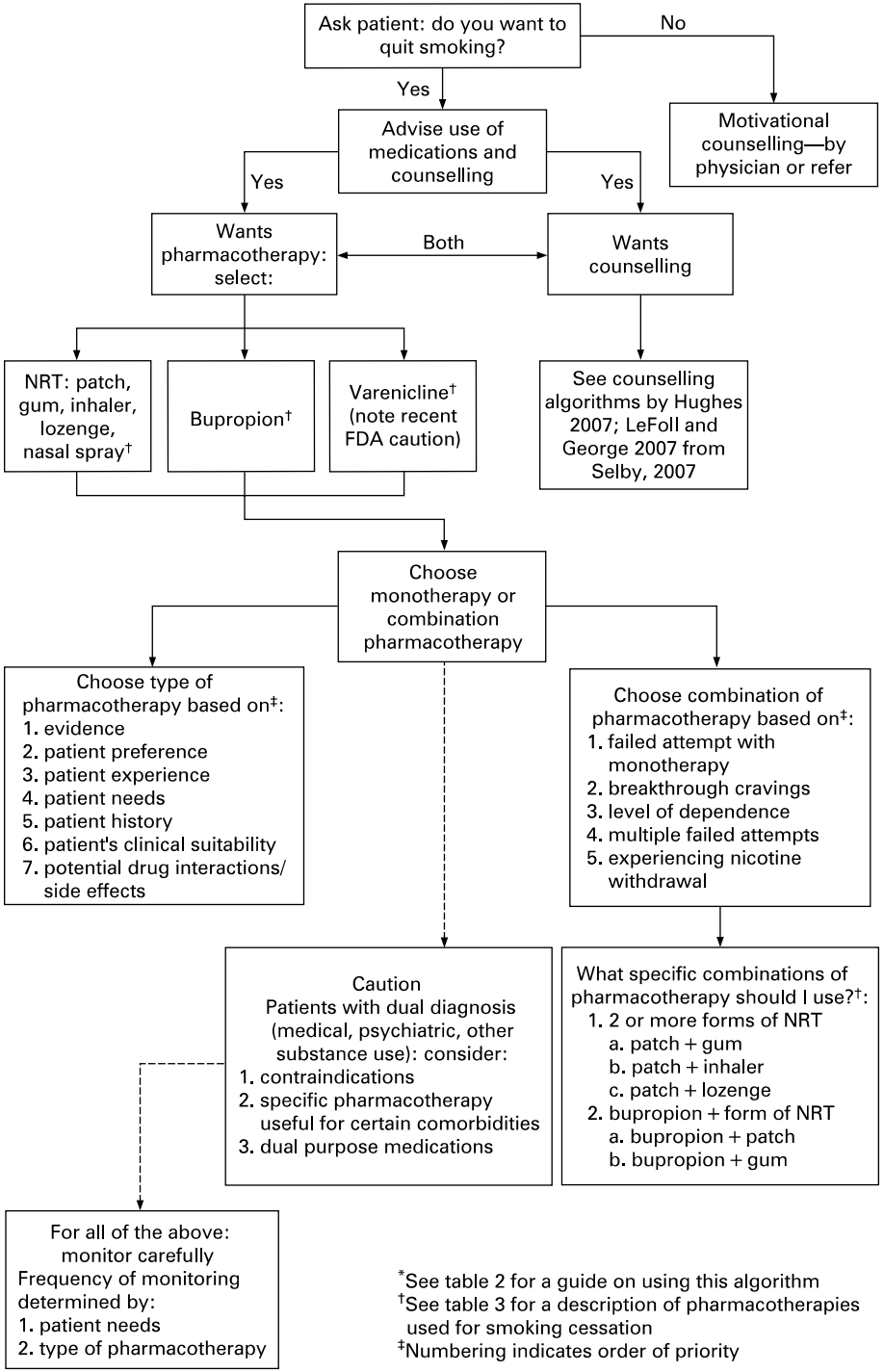




Hughes, J.R., An updated algorithm for choosing among smoking cessation treatments, Journal of Substance Abuse Treatment (2013),



Bernard Le Foll MD PhD, Tony P. George MD
CMAJ 2007;177(11):1373-80



P Bader, P McDonald, P Selby,

Tobacco Control 2009;18:34–42.

PERSONALIZED TREATMENT

How do we learn how to decide?

PERSONALIZED TREATMENT

How do we learn how to decide?

RCT's!
(sort of)

PERSONALIZED TREATMENT:RCT'S

RCT's are best for:

Determining whether a treatment package performs better than

- A control or comparison group (placebo; no treatment; usual care)
- An alternative intervention (comparative effectiveness)

PERSONALIZED TREATMENT:RCT'S

(Conventional) RCT's are not as good for:

- Evaluating components in multicomponent treatments (black box treatment packages)
- Stratified effects (matching)
- Evaluating sequential treatments

MULTICOMPONENT RCT'S

An RCT that finds a <u>significant</u> effect DOES NOT tell us

- *Which components* are making positive contributions to overall effect
- Whether the inclusion of one component has an impact on the effect of another
- Whether a component's contribution offsets its cost
- Whether all the components are really needed
- How to make the intervention more effective, efficient, and scalable

MULTICOMPONENT RCT'S

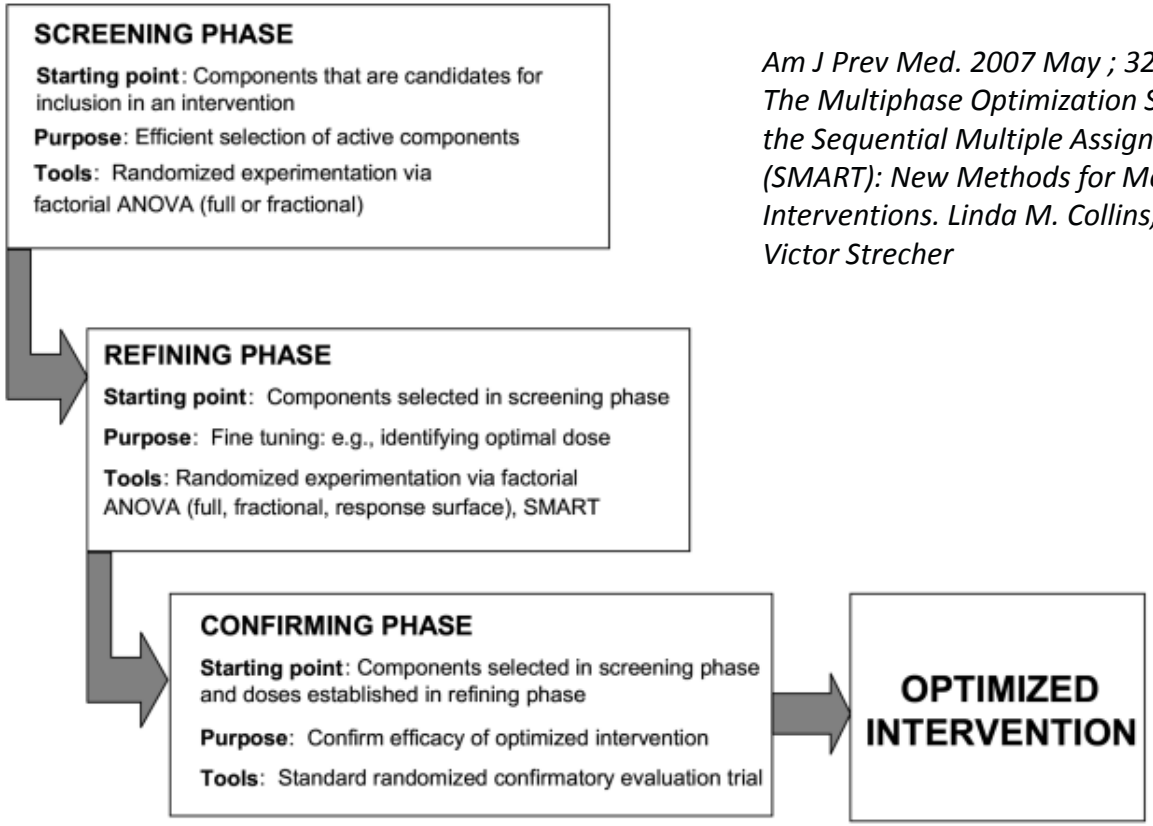
An RCT that finds a <u>non-significant</u> effect DOES NOT tell us

- Whether any components are worth retaining
- Whether one component had a negative effect that offset the positive effect of others
- Specifically what went wrong and how to do it better the next time

MULTICOMPONENT RCT'S

What's the alternative?

- MOST: Preparation, Optimization, Evaluation



Am J Prev Med. 2007 May ; 32(5 Suppl): S112–S118. The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent eHealth Interventions. Linda M. Collins, Susan A. Murphy, and Victor Strecher

Figure 1. Outline of the Multiphase Optimization Strategy (MOST)
ANOVA, analysis of variance; SMART, sequential multiple assignment randomized trial

PERSONALIZED TREATMENT:RCT'S

(Conventional) RCT's are not as good for:

- Evaluating components in multicomponent treatments (black box treatment packages)
- Stratified effects (matching)
- Evaluating sequential treatments

ADAPTIVE TREATMENT STRATEGIES (ATS) *AKA* DYNAMIC TREATMENT REGIMES (DTR) *AKA* ADAPTIVE INTERVENTIONS

- Evaluating sequential treatments

ADAPTIVE TREATMENT STRATEGIES (ATS)

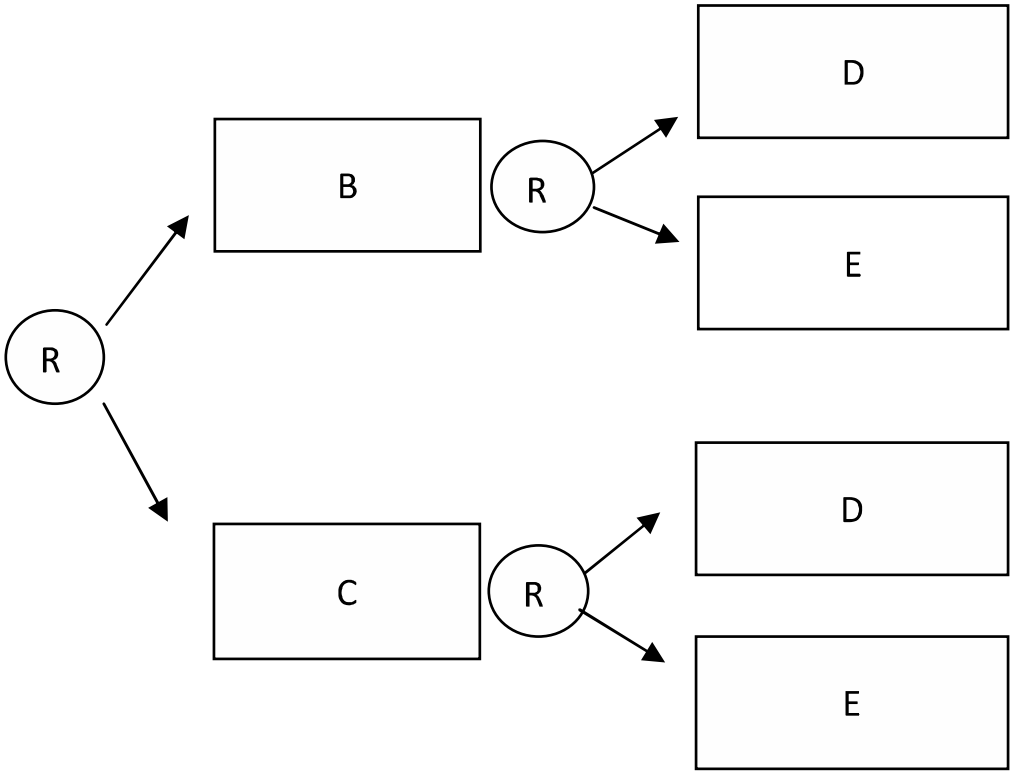
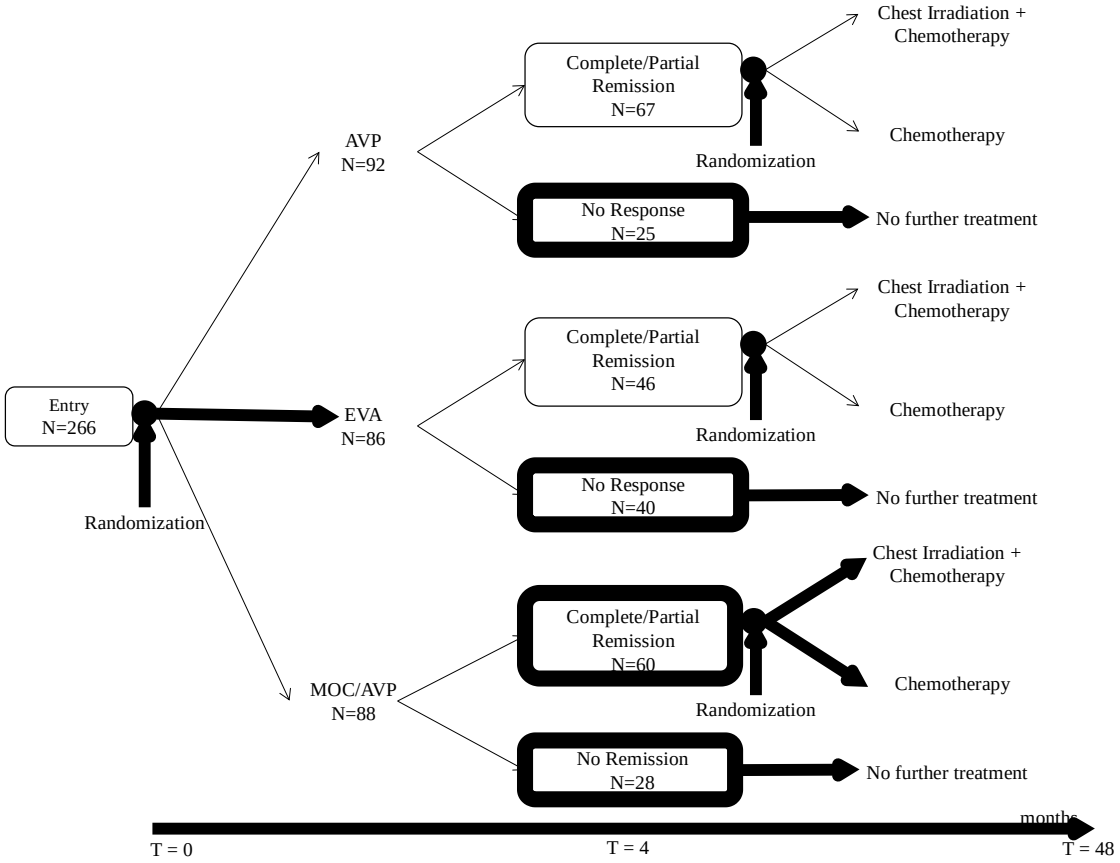


Figure 2. Sequential multiple assignment randomized trial (SMART) with no embedded tailoring variables.

Nahum-Shani, I., Qian, M., Almirall, D., Pelham, W. E., Gnagy, B., Fabiano, G. A., Waxmonsky, J. G., Yu, J., & Murphy, S. A. Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. Psychological Methods. 2012, Vol. 17, No. 4, 457–477

Sequential multiple assignment randomized trial (SMART)

Small-Cell Lung Cancer



Joss RA, Alberto P, Bleher EA, et al. 1994. Combined-modality treatment of small-cell lung cancer: randomized comparison of three induction chemotherapies followed by maintenance chemotherapy with or without radiotherapy to the chest. Ann. Oncol. 5:921-28

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART) ADHD

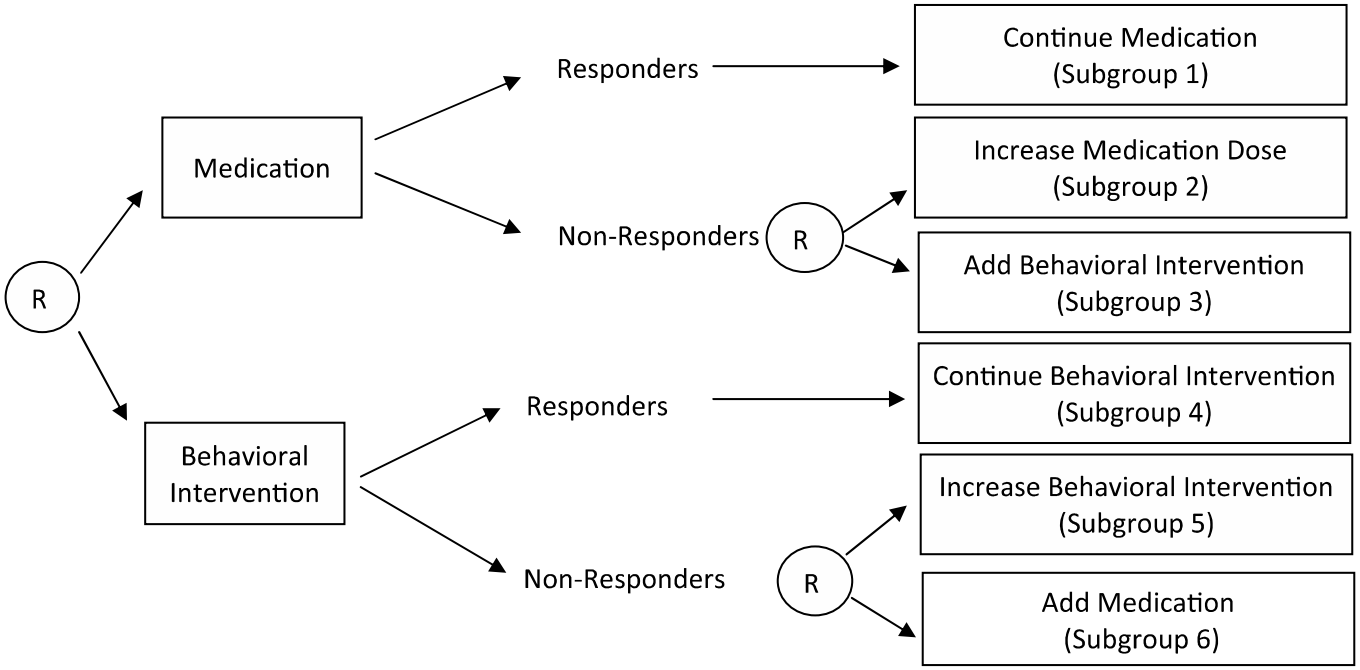


Figure 1. Sequential multiple assignment randomized trial for attention-deficit/hyperactivity disorder (ADHD) study.

Nahum-Shani, I., Qian, M., Almirall, D., Pelham, W. E., Gnagy, B., Fabiano, G. A., Waxmonsky, J. G., Yu, J., & Murphy, S. A. Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. Psychological Methods. 2012, Vol. 17, No. 4, 457–477

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Adaptive Treatment Strategies:

Are individually tailored time-varying treatments composed of:

- a sequence of critical treatment decisions
- tailoring variables decision rules, one per critical decision; decision rules input tailoring variables and output an individualized treatment recommendation.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Operationalize clinical practice:

- From the *individual/patient/client's* point of view:
  A sequence of (individualized) treatments

- From the *clinical scientist's* point of view:
  A sequence of **decision rules** that recommend one or more treatments at each critical decision.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Critical treatment decisions:

- How long to try the first treatment?
- How should a treatment be delivered?
- How intensive should a treatment be?
- When to stop/start treatment?

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Tailoring variables:

- severity of illness,
- presence of comorbid mental or physical conditions,
- adherence to present treatment,
- side effects resulting from present treatment,
- symptoms while in treatment.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why Adaptive Treatment Strategies?

- High heterogeneity in response to any one treatment: What works for one person may not work for another
- Improvement often marred by relapse
- Lack of adherence or excessive burden is common
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

Treatment incurs side effects and burden, particularly over longer time periods.

Problems with adherence:

- Variations of treatment or different delivery mechanisms may increase adherence

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

Excessive treatment may lead to non-adherence

Treatment is costly (allocate resources to patients with more severe problems)

More is not always better!

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Parts of the Adaptive Treatment Strategy:

- Choice of the Tailoring Variable
- Measurement of the Tailoring Variable
- Decision Rules linking Tailoring Variables to Treatment Decisions
- Implementation of the Decision Rules

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

What is a sequential multiple assignment randomized trial (SMART)?

- Multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

- Goal is to inform the construction of adaptive treatment strategies.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Subset of adaptive designs

Brown, C. H., Ten Have, T. R., Jo, B., Dagne, G., Wyman, P. A., Muthén, B., & Gibbons, R. D. (2009). Adaptive designs for randomized trials in public health. *Annual Review of Public Health*, *30*, 1-25.

Lei, H., Nahum-Shani, I., Lynch, K., Oslin, D., & Murphy, S. A. (2012). A "SMART" design for building individualized treatment sequences. *Annual Review of Clinical Psychology*, *8*, 21-48.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not use data from multiple trials to construct the adaptive treatment strategy?

- Choose the best initial treatment on the basis of a RCT of initial treatments and choose the best secondary treatment on the basis of a RCT of secondary treatments.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not use data from multiple trials to construct the adaptive treatment strategy?

Delayed Therapeutic Effects

Positive synergies:

- Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment.

- Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Delayed Therapeutic Effects

Negative synergies:

- Treatment A may produce a higher proportion of responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond.

- Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Prescriptive Effects

- Treatment A may not produce as high a proportion of responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Sample Selection Effects

- Subjects who will enroll in, who remain in, or who are adherent in the trial of the initial treatments, may be quite different from the subjects in SMART.

e.g., maintenance and retreatment strategies in smoking cessation.

Latest News

- NIH Funding Announcement Calls for SMART
  January 17, 2013
- Articles: Building adaptive interventions
  December 05, 2012

More SMART news

Free Software

- SAS PROC QLEARN: for analyzing data from a SMART
- R code: Construct adaptive interventions using data from a SMART

All SMART software and other Center software

Researchers

Lead researcher: Susan Murphy

Other researchers: Daniel Almirall, Inbal Nahum-Shani, and Linda Collins

Adaptive Interventions

Behavioral interventions for prevention and treatment are an important part of the fight against drug abuse and conditions such as HIV/AIDS and mental illness. Among the challenges faced by scientists is how and when to alter the course of treatment for participants in the intervention.

Sequential, Multiple Assignment, Randomized Trials (SMART)

Adaptive interventions (also known as "adaptive treatment strategies" or "dynamic treatment regimes") are individually tailored treatments. Formally, an adaptive intervention is a sequence of decision rules that specify how the intensity or type of treatment should change depending on the patient's needs. We are developing sequential, multiple assignment, randomized trials (SMART) to enable scientists to build adaptive interventions.

Why Conduct a SMART to Build an Adaptive Intervention?

Interventions that adapt at the right times can improve participant outcomes (e.g., intensifying for people who do not respond to the initial treatment) while decreasing the cost and burden of the intervention (e.g., stepping down treatment for responsive participants). SMART designs provide the data needed to construct high-quality adaptive interventions.

Read more

Introductory Example: Using Medication to Prevent Alcoholism Relapse

Resources

- Recommended reading
- NIH PAs calling for SMART designs
- Podcast: Adaptive interventions
- Online SMART presentations

Center Collaborations

This work began as a collaboration between Susan Murphy and Linda Collins, which led to two projects: work on optimizing interventions, and SMART.

Definitions

View All

Adaptive Intervention,
Adaptive Treatment Strategy,
Dynamic Treatment Regime,
Treatment Policies, Inference,
Multi-Stage Decision Making,
Reinforcement Learning,
Tailoring Variable

EXAMPLE 1: ADHD

- Dynamic treatment regime for children with ADHD

- W. Pelham is the intervention scientist

Slides courtesy of Linda Collins

http://methodology.psu.edu

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DYNAMIC TREATMENT REGIMES FOR CHILDREN WITH ADHD

- Two approaches to treatment of ADHD
  - Behavior modification (BMOD)
  - Medication
- They can be combined into a dynamic treatment regime
- What is the best set of decision rules?

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DYNAMIC TREATMENT REGIMES FOR CHILDREN WITH ADHD

Research questions that must be addressed for optimization:

- Is it better to start with BMOD or medication?
  - Note: BMOD much more expensive
- For those who do not respond to initial treatment, is it better to
  - Remain with the same strategy but enhance?
  - Augment with the other strategy?
- What is the best overall strategy?

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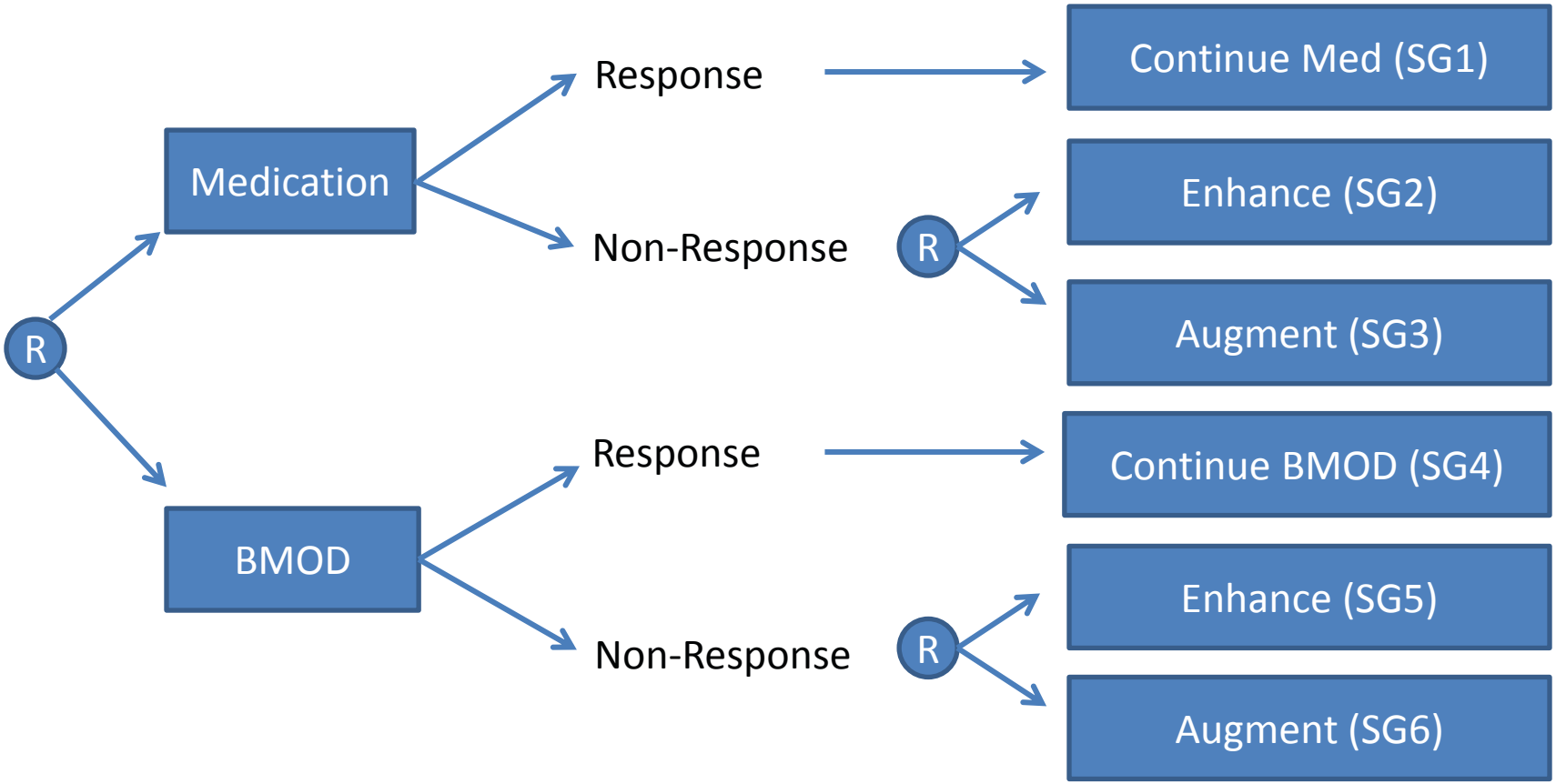
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)



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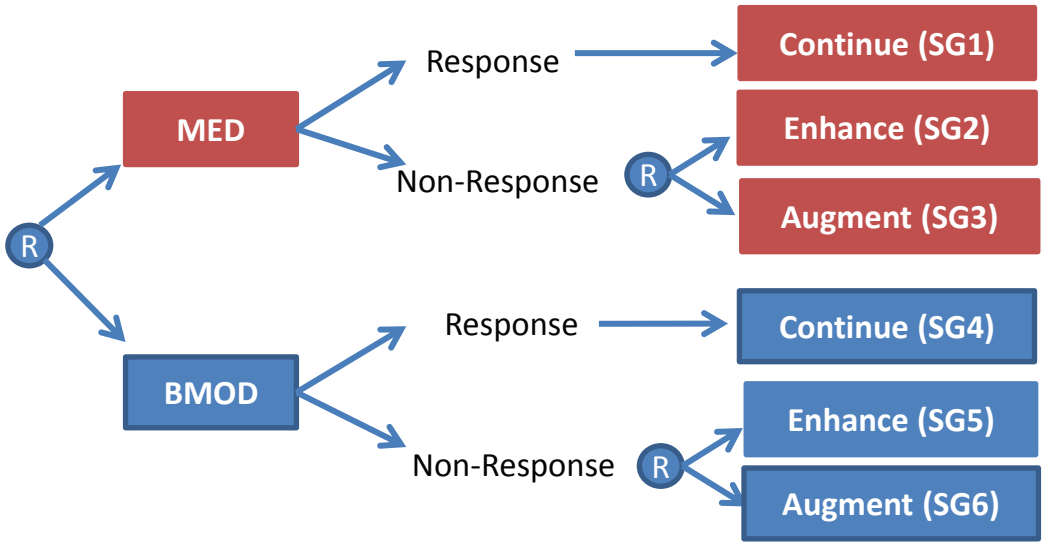
QUESTIONS WE CAN ADDRESS WITH SMART

Is it better to start with BMOD or MED?

- **(SG1+SG2+SG3)** vs. **(SG4+SG5+SG6)**
- **Medication vs. BMOD**
  - Averaging over subsequent treatment



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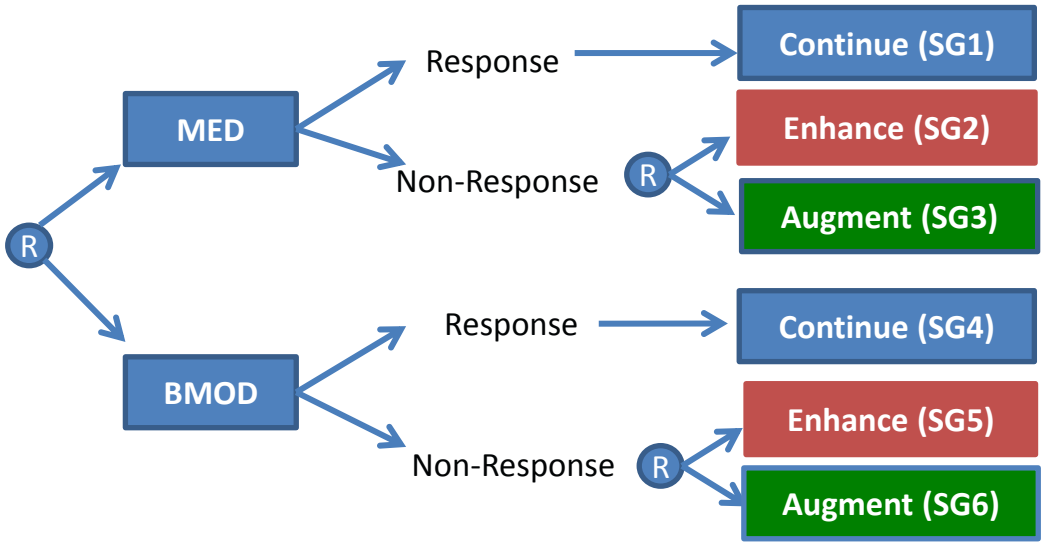
QUESTIONS WE CAN ADDRESS WITH SMART

Is it better to Enhance or Augment for non-responders?

- **(SG2+SG5) vs. (SG3+SG6)**
- **Enhance vs. Augment**



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QUESTIONS WE CAN ADDRESS WITH SMART

- ***What is the best overall strategy?*** **There are FOUR embedded here:**

Stage 1 = {MED},
IF *response = {NO}*
THEN *stage 2 = {AUGMENT}*
ELSE *continue stage 1*

Stage 1 = {MED},
IF *response = {NO}*
THEN *stage 2 = {ENHANCE}*
ELSE *continue stage 1*

Stage 1 = {BMOD},
IF *response = {NO}*
THEN *stage 2 = {ENHANCE}*
ELSE *continue stage 1*

Stage 1 = {BMOD},
IF *response = {NO}*
THEN *stage 2 = {AUGMENT}*
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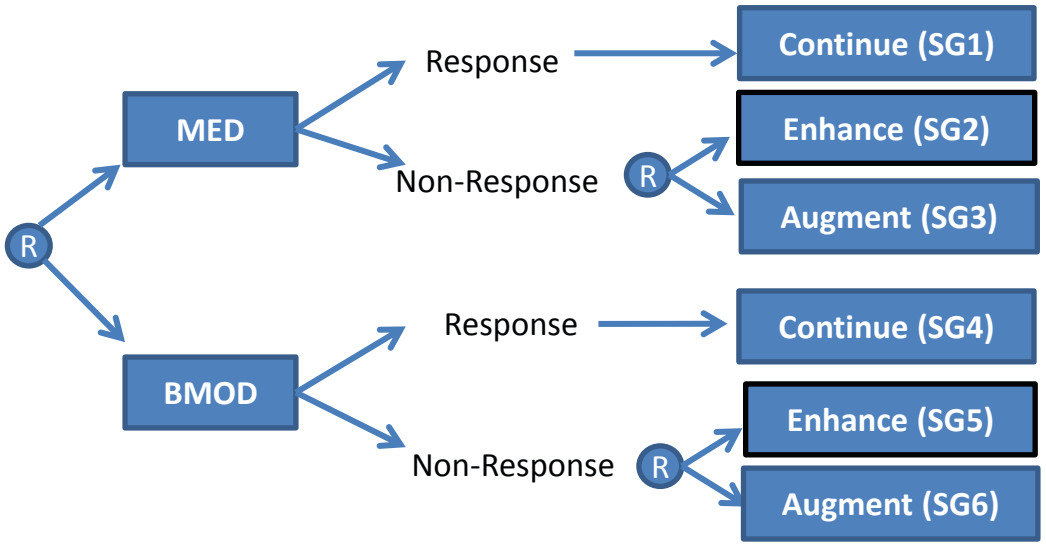

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QUESTIONS WE CAN ADDRESS WITH SMART

Example 2: Pharmacologic treatment for smoking in HIV+ smokers

Niaura, R., Chander, G., Hutton, H., & Stanton, C. (2012). Interventions to address chronic disease and HIV: Strategies to promote smoking cessation among HIV-infected individuals. Current HIV/AIDS Reports.

SMOKING CESSATION: WHAT WORKS? PHARMACOTHERAPIES

Drug	Comparison	# Trials	N	RR (95% CI)
NRT	Placebo/no treatment	111	40,000	1.58 (1.50-1.66)
Varenicline (Chantix)	Placebo	10	4,443	2.13 (2.01-2.66)
Bupropion (Zyban)	Placebo/no treatment	36	11,140	1.69 (1.53-1.85)
Varenicline	Bupropion	3	1,622	1.52 (1.22-1.88)

SMOKING CESSATION: WHAT WORKS?
MAJOR QUESTIONS

(1) What does one do when smokers fail to quit or relapse?

(2) What does one do when smokers quit?

SMOKING CESSATION: WHAT WORKS?
MAJOR QUESTIONS

(1) What does one do when smokers fail to quit or relapse?

-Continue same treatment
-Re-treat: Switch or augment

(2) What does one do when smokers successfully quit?

-Monitor progress
-Relapse prevention intervention
-Continue to treat (maintenance treatment)

sMOKING CESSATION: WHAT WORKS?
MAJOR QUESTIONS

(1) What does one do when smokers fail to quit or relapse?

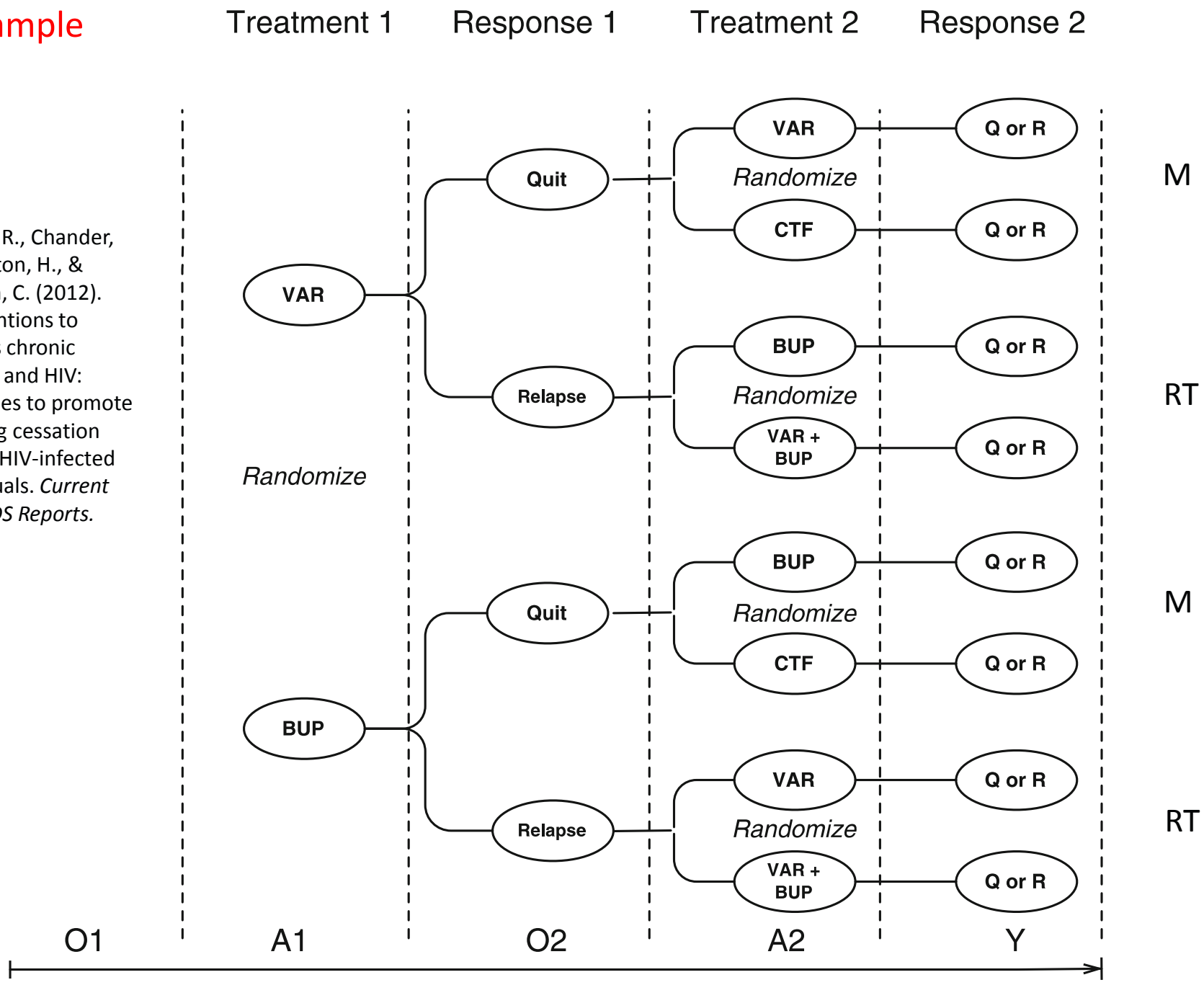
-Re-treat: Switch or augment

(2) What does one do when smokers successfully quit?

-Monitor progress
-Relapse prevention intervention
-Continue to treat (maintenance treatment)

How do you test these strategies?
The SMART way

Example



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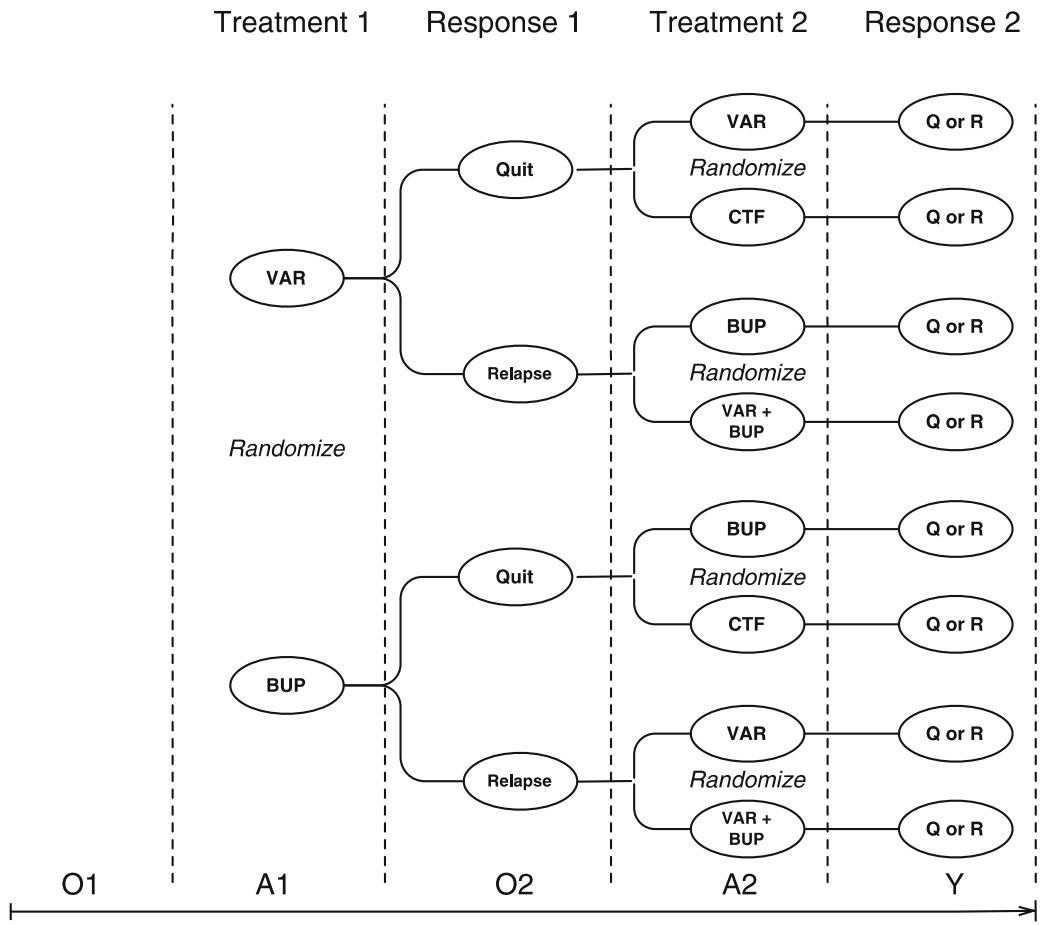

O1: Tailoring variables (e.g., prior tx response; adverse events; depression)

A2: Initial treatment

O2: Initial response (e.g., withdrawal symptoms; side effects; lack of efficacy; lack of adherence)

A2: Choice of next treatment based on O2 – better drug or behavioral tx?

Y: Outcome (quit or relapse)

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Tailoring variables:

- severity of illness
- presence of comorbid mental or physical conditions
- adherence to present treatment
- side effects resulting from present treatment
- symptoms while in treatment

Analysis Approaches:

IPTW; G-computation

Q-learning (Watkins, 1989; Murphy, 2005)

- Popular method from computer science.
- Regression-based:
  - Sequence of regressions
  - One regression for each stage
- Rationale:
  - Base your decision on what you know up to that point
  - Assume best future decisions

Nahum-Shani et al., (2012). Q-learning: A secondary data analysis method for developing adaptive interventions. Psychological Methods, 17(4), 478-494

PENNSTATE

The Methodology Center
advancing methods, improving health

SAS PROC QLEARN Users' Guide
Version 1.0.0

Ashkan Ertefaie
Daniel Almirall
Liying Huang
John J. Dziak
Aaron Wagner
Susan Murphy

R

Package 'qLearn'

February 15, 2013

Type Package

Title Estimation and inference for Q-learning

Version 1.0

Date 2012-03-01

Author Jingyi Xin, Bibhas Chakraborty, and Eric B. Laber

Maintainer Bibhas Chakraborty <bc2425@columbia.edu>

Description Functions to implement Q-learning for estimating optimal dynamic treatment regimes from two stage sequentially randomized trials, and to perform inference via m-out-of-n bootstrap for parameters indexing the optimal regime.

AFTER THE SMART

Results of analyses will be used to decide on best decision rules, i.e. optimized intervention

This does not tell us whether the optimized intervention has a statistically significant effect as compared to a control

Must move to the evaluation phase for that: (RCT)

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It's
Challenge
Time


CHALLENGE ACCEPTED

THANK YOU

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ADAPTIVE TREATMENT STRATEGIES (ATS)

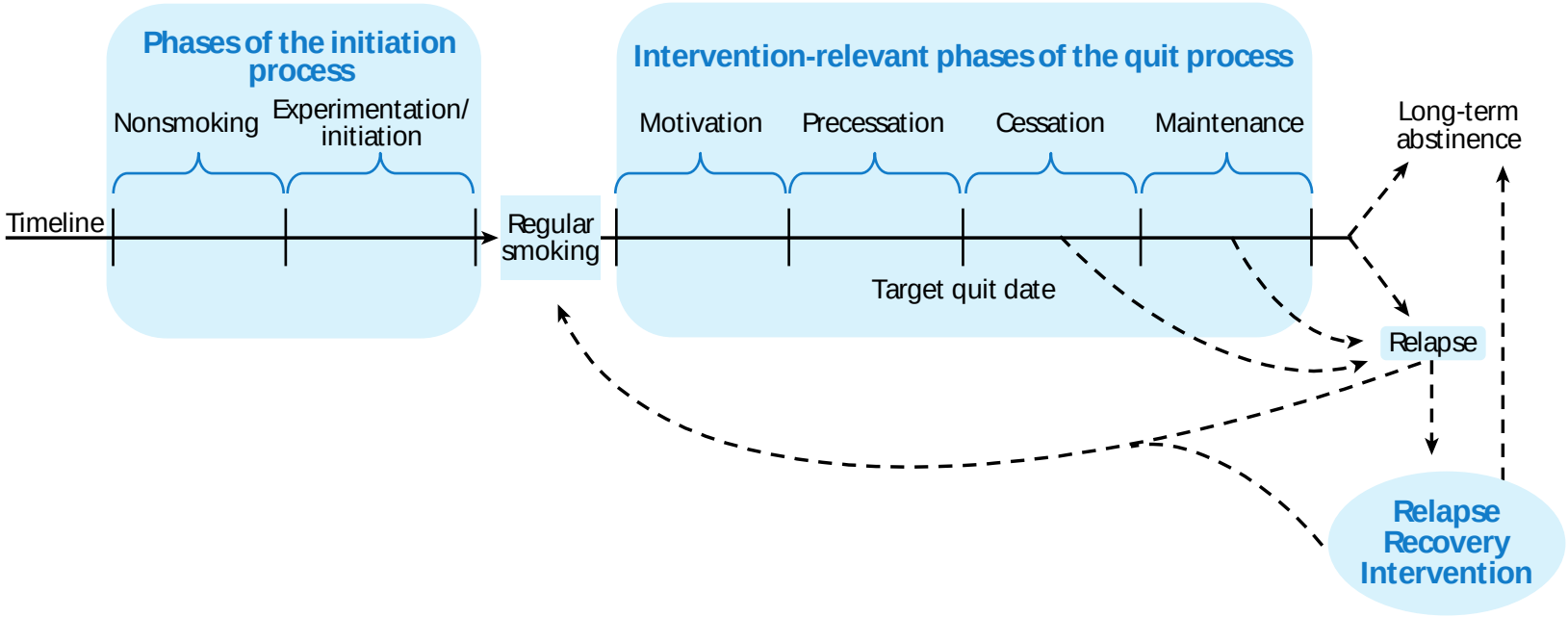

Figure 1

The longitudinal phase-based model of tobacco use initiation and cessation.

*Tanya R Schlam and Timothy B Baker, 2103, Annu Rev Clin Psychol **9**, 675-702*

Table 1 Exemplar challenges, intervention components, mechanisms, and treatment selection measures for the suggested four smoking cessation phases

Phase	Exemplar challenges	Exemplar intervention components	Exemplar measures of mechanism	Exemplary treatment selection measures
Motivation	1. Low motivation	1. Prequit medication	1. Craving/withdrawal	1. Stated intention to quit
	2. High dependence	2. Behavioral intervention to reduce smoking/contingencies	2. Nicotine dependence	2. Quit attempts
	3. Low self-efficacy	3. Motivational counseling	3. Smoking rate and contingencies	3. Early quitting success
	4. Lack of support		4. Self-efficacy	
			5. Intrinsic motivation	
Precessation	1. Smoking cues and contexts	1. Prequit medication	1. Perceived support	1. Abstinence attainment
	2. Withdrawal and craving	2. Behavioral intervention to reduce smoking contingencies, make practice quit attempts, practice coping, lifestyle changes	2. Smoking rate and contingencies (cue exposure)	2. Number of days smoking early in attempt
	3. Coping skill practice	3. Motivational and supportive counseling	3. Practice quit attempts and coping and symptomatic reactions	
Cessation	1. Withdrawal and craving	1. Medication (intensive, combination)	1. Withdrawal and craving increase and trajectory	1. Abstinence attainment
	2. Decline in positive affect	2. Supportive counseling	2. Positive affect	2. Number of days smoking early in attempt
	3. Smoking cues		3. Perceived support (buffered temptations and stressors)	
	4. Lapses		4. Self-efficacy	
Maintenance	1. Lapses	1. Medication (extended)	1. Medication use	1. Lapses and lapse latency
	2. Relapse	2. Adherence interventions	2. Withdrawal and craving (levels, volatility)	2. Relapse and relapse latency
	3. Resurgent withdrawal and craving	3. Supportive counseling	3. Anhedonia	3. Number of days smoking
	4. Anhedonia	4. Maintenance skill training (coping, lifestyle change)	4. Intrinsic motivation	4. Point-prevalence abstinence
	5. Declines in motivation		5. Lapse response (self-efficacy, motivation, craving)	
	6. Stressors		6. Perceived support	
	7. Non-adherence		7. Response to smoking cues (craving, lapsing)	

Baker, T. B., Mermelstein, R., Collins, L. M., Piper, M. E., Jorenby, D. E., Smith, S. S., . . . Fiore, M. C. (2010). New methods for tobacco dependence treatment research. Annals of Behavioral Medicine

SMOKING CESSATION: WHAT WORKS? PHARMACOTHERAPIES

Drug	Comparison	# Trials	N	RR (95% CI)
NRT	Placebo/no treatment	111	40,000	1.58 (1.50-1.66)
Varenicline (Chantix)	Placebo	10	4,443	2.13 (2.01-2.66)
Bupropion (Zyban)	Placebo/no treatment	36	11,140	1.69 (1.53-1.85)
Varenicline	Bupropion	3	1,622	1.52 (1.22-1.88)