Developing Evidence-Based Adaptive Treatment Strategies

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1 hour Other names are dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive treatment strategies, treatment protocols. Structured treatment interruptions in the treatment of AIDS are a form of adaptive strategy

Individualized interventions
Outline

- Why Adaptive Treatment Strategies?
  - “new” treatment design
- Why SMART experimental designs?
  - “new” clinical trial design
- Trial Design Principles and Analysis
- Examples of SMART Studies
- Discussion

Other names are dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive treatment strategies, treatment protocols. Structured treatment interruptions in the treatment of AIDS are a form of adaptive strategy.

Individualized interventions
Adaptive Treatment Strategies are individually tailored treatments, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008) Drug Court
- Rush et al. (2003) Treatment of Depression

Provide a paradigm whereby we can seek to improve clinical practice which by its nature is adaptive.

Tailoring is achieved by use of a decision rules. Takes ongoing info (past response, adherence, burden, etc) and outputs txt level type.

Most clinical scientists develop the decision rules using trial and error, developmental and behavioral theories; clinical experience.

Brooner uses a two component adaptive txt strategy, one component has to do with txt and the other with encouragement to adhere.

One steps up/down intensity and type of counseling sessions based on negative urines and adherence.

One steps up/down behavioral contingencies based on adherence to counseling sessions.

Rules are explicit.

McKay has a book on this topic—see Treating Substance Use Disorders With Adaptive Continuing Care (Hardcover) by James R. McKay.

Criminal Justice Review 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M. Benasutti, Jason R. Croft and James R. McKay

Adaptive Interventions in Drug Court: A Pilot Experiment

The decision rules used by Brooner et al, Marlowe et al., and McKay are quite detailed, and based on explicit actions by patient, whereas in contrast the Rush et al study (Texas Medication Algorithm Project) appears to be more loosely structured; the clinician uses clinical judgment to decide if depression levels are clinically significant and thus an augmentation or switch in treatment intensity is needed. The particular secondary treatment is chosen out of a set of specified alternatives and depends on clinical judgment/patient preference.
Why Adaptive Treatment Strategies?

- High heterogeneity in response to any one treatment
  - What works for one person may not work for another
  - What works now for a person may not work later
- 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

Many patients do not initially respond to therapy. For example about 50% of all nonpsychotic patients with major depression respond to an initial treatment (Depression Guideline Panel, volumes 1 and 2, 1993) and only 50% to 65% of these initial responders do not experience residual symptoms of depression (Frank et al., 1991). In the ‘‘Clinical Antipsychotic Trials of Intervention Effectiveness in Patients with Alzheimer’s Disease,’’ (CATIE-Ad) trial, 75% of the patients did not respond well to their first treatment (Schneider, personal communication). In a prospective general clinic study of HIV infected patients placed on HAART therapy, Mocroft et al. (2000) report that approximately 30% of the patients did not achieve viral control ($< 400$ copies/ml) by 12 months. And in a clinical trial of 4 psychosocial treatments for cocaine dependence (Crits-Christoph et al., 1999) 35 to 60% of patients were continuing to use cocaine at the end of the 6 month treatment.

Even once a patient has responded to therapy it is not unusual for patients to relapse at a later date. In a prospective study of 318 subjects by Solomon et al. (2000) with unipolar major depressive disorder, 25% relapsed with one year and by 5 years 60% had relapsed. Finney et al., (1996) find that 40 to 70% of patients resume drinking within a year following treatment. Mocroft et al. (2000) report that approximately 12% of the HIV infected patients had relapsed by 6 months following initial achievement of viral control while on HAART therapy.

In a prospective study of opiate dependent individuals in Philadelphia, Metzger et al. (1993) found that initially 10%-20% of the opiate dependent individuals were infected with HIV and by end of 7 years 20-50% of the opiate dependent individuals had HIV. Furthermore as many as 7 to 10 million persons are dually diagnosed with mood and substance use disorders (SAMHSA National Advisory Council, 1998). Kessler et al., (2003) finds that 1 out of 4 persons with major depression also have a substance use disorder.

In drug dependence treatment nonadherence is common (Hser et al., 1997). For example, in D. Oslin's study, ‘‘Naltrexone Treatment of Alcohol Dependence,’’ 40 to 60% of the patients were nonadherent by 6 months (Oslin, personal communication). As many as 70% of depressed elderly patients take only 50% to 75% of their prescribed dose (NIH, 1992). In a prospective 12 month study of 46 HIV infected patients on antiretroviral therapy, Singh et al. (1996) find that approximately 40% complied with 80% or more of their therapy.
Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

• Treatment incurs side effects and substantial burden, particularly over longer time periods.
• Problems with adherence:
  • Variations of treatment or different delivery mechanisms may increase adherence
  • Excessive treatment may lead to non-adherence
• Treatment is costly (Would like to devote additional resources to patients with more severe problems)

  More is not always better!

Why not give a universal intervention to all for a sufficiently long time??

More is not always better.

These are all reasons why you should not provide MORE treatment than is needed.

Only provide MI to people who need motivation to adhere.

That is a multi-component fixed treatment is not practical or is too costly or would not result in good adherence

A principle of adaptive tx strategies is to provide no more than needed to accomplish desired result!
Example of an Adaptive Treatment Strategy

• Adaptive Drug Court Program for drug abusing offenders.
• Goal is to minimize recidivism and drug use.
• Marlowe et al. (2008)

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minimize recidivism and drug use is operationalized by graduating from the drug court program.

High risk: ASPD or history of drug treatment otherwise low risk

Noncompliance: is(1) falls below threshold for attendance in counseling sessions or status hearings, (2) fails to provide scheduled urine specimens, or (3) commits a new crime or serious rule infraction

Nonresponsive = (1) is attending sessions and completing program requirements, and (2) is not committing new infractions, but (3) continues to provide drug-positive urine specimens.

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee
Adaptive Drug Court Program

All movement between steps or stages is operationalized.
High risk: ASPD or history of drug treatment otherwise low risk

These are assessed monthly:::

Noncompliance: is (1) falls below threshold for attendance in counseling sessions or (2) fails to provide 2 or more scheduled urine specimens

Nonresponsive = (1) is attending sessions and completing program requirements, and (2) is not committing new infractions, but (3) provides 2 or more drug-positive urine specimens.

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee
The Big Questions

• What is the best sequencing of treatments?
• What is the best timings of alterations in treatments?
• What information do we use to make these decisions? (how do we individualize the sequence of treatments?)

This is really related to clinical management of chronic disorders.

Take a broad view of what constitutes therapies: changing intensity, switching medication, augmenting medication, behavioral contingencies, monitoring schedules, motivational therapy, support networks.

The design of the adaptive treatment strategy is a multi-stage decision problem. In general the component treatments/therapies have been shown to be efficacious and “safe”; they require explication for appropriate implementation.

Also how to combine therapies?
Outline

• Why Adaptive Treatment Strategies?
  – “new” treatment design
• Why SMART experimental designs?
  – “new” clinical trial design
• Trial Design Principles and Analysis
• Examples of SMART Studies
• Discussion
Why SMART Trials?

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

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

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

In stat. people may call these multistage trials (the randomization at each stage is assumed)
Hypothetical trial: Outcome is not shown but is on far right. The second randomization can take place up front (if you do not want to stratify or block by stage 1 outcomes such as adherence).

Equal randomization

Usual reaction is (1) I’m worried about sample size and
(2) This looks awfully complicated.
In reality, both of these problems are less worrisome than one might think—see following slides.
Alternate Approach to Constructing an Adaptive Treatment Strategy

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

• Choose the best initial treatment on the basis of a randomized trial of initial treatments and choose the best secondary treatment on the basis of a randomized trial of secondary treatments.

Particularly attractive since potential initial treatment may have been evaluated in prior trials. So you propose a responder study or you propose a nonresponder study.

Or, why choosing the best initial treatment on the basis of a randomized trial of initial treatments and choosing the best secondary treatment on the basis of a randomized trial of secondary treatments is not the best way to construct an adaptive treatment strategy.
Delayed Therapeutic Effects

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

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.

counseling and then if respond, monitoring with low level telephone counseling.

A consequence is that comparing two initial therapies based on a proximal outcome may produce different results from the comparison of two initial therapies when followed by one of several maintenance therapies based on longer term outcomes. Additionally, restricting comparisons to longer term outcomes, a comparison of two initial therapies followed by usual care or no therapy may yield different results from the comparison of two initial therapies when followed by one of several maintenance therapies.

We can expect that in an optimized adaptive treatment strategies, the best subsequent therapy will build on the gains achieved by prior therapies and thus these delayed effects should be common.

We want big positive delayed effects. We want profound positive cross-over effects!!!
Delayed Therapeutic Effects

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

**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.

treatment of psychosis: a medication may result in many immediate responders but Some patients are not helped and/or experience abnormal movements of the voluntary muscles (TDs). The class of subsequent medications is greatly reduced.

Or the kind of response produced may not be sufficiently strong so that patients can take advantage of maintenance care.

A negative delayed effect would occur if the initial treatment overburdens an individual, resulting decreased responsivity to future treatment; see Thall et al. (2007), Bembom and van der Laan (2007) for an example of the latter in cancer research.
Prescriptive Effects

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

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.

Consider the issue of motivation as expressed via adherence; if tx A has provides less social support than tx B, then patients who require the social support will exhibit adherence problems during tx with A but not during tx with B. This is useful information as we then know that these patients, even if they respond will potentially need an enhancement of social support during the maintenance or aftercare phase.
Selection Effects

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

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.

Consider the issue of adherence; in many historical trials subjects were assigned a fixed treatment, that is, there were no options besides non-adherence for subjects who were not improving. This often leads to higher than expected drop-out or non-adherence. This is particularly the case in longer studies where continuing treatments that are ineffective is likely associated with high non-adherence especially if the subject doesn’t know if they are receiving treatment such as in a double bind study. As a result the subjects who remained in the historical trial may be quite different from the subjects that remain in a SMART trial, which by design provides alternates for non-improving subjects. David Oslin made this point to me.
Summary:

- When evaluating and comparing initial treatments, *in a sequence of treatments*, we need to take into account, e.g. control, the effects of the secondary treatments thus SMART.
- Standard one-stage randomized trials may yield information about different populations from SMART trials.

Just because an initial txt looks best when looking at intermediate outcomes does not mean that it is best in an adaptive txt strategy.
Hypothetical trial: Outcome is not shown but is on far right. The second randomization can take place up front (if you do not want to stratify or block by stage 1 outcomes such as adherence).

Equal randomization

Usual reaction is (1) I’m worried about sample size and
(2) This looks awfully complicated.
In reality both of these problems are less worrisome than one might think—see following slides.
Examples of “SMART” designs:

• CATIE (2001) Treatment of Psychosis in Schizophrenia
• STAR*D (2003) Treatment of Depression
• Pelham (primary analysis) Treatment of ADHD
• Oslin (primary analysis) Treatment of Alcohol Dependence
• Jones (in field) Treatment for Pregnant Women who are Drug Dependent
• Kasari (in field) Treatment of Children with Autism

The first two studies are actually precursors to SMART (they do not possess all the characteristics of a smart trial as they do not collect the same info from responders as they do from non-responders) These are primarily hypothesis generating or strategy developing trials. These trials are not confirmatory in the sense of confirming that one dynamic regime is best.

The primary analyses are being conducted with the second two

J. McKay has 2 SMART studies in the field as well.
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Individualized interventions
SMART Design Principles

• **KEEP IT SIMPLE**: At each stage (critical decision point), restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

• Collect intermediate outcomes that might be useful in ascertaining for whom each treatment works best (adherence, etc.); information that might be used to individualize treatment.

Note we considered different txt’s for the responders as compared to the nonresponders.
In mental illness studies feasibility considerations may force us to use preference in this low dimensional summary.
SMART Design Principles

• Choose primary hypotheses that are both scientifically important and aid in developing the adaptive treatment strategy.
  • Power trial to address these hypotheses.

• Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.
  • Trial is not necessarily powered to address these hypotheses.
SMART Designing Principles: Primary Hypothesis

• EXAMPLE 1: (sample size is highly constrained): Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

• EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.

These are main effects a la’ ANOVA
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

Example 1: Effects of secondary treatments are controlled by experimental design – not be statistical analysis
A study of initial tx’s in which subsequent tx’s are controlled. Here you can use a variety of analyses, growth curve models, survival analysis, etc.
A study of nonresponders in which one controls the tx’s to which people don’t respond to.
SMART Designing Principles: Sample Size Formula

• EXAMPLE 1: (sample size is highly constrained): Hypothesize that given the secondary treatments provided, the initial treatment A results in lower symptoms than the initial treatment B. *Sample size formula is same as for a two group comparison.*

• EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D. *Sample size formula is same as a two group comparison of non-responders.*

These are main effects a la’ ANOVA
### Sample Sizes

N = trial size

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta \mu / \sigma = .3$</td>
<td>N = 402</td>
</tr>
<tr>
<td>$\Delta \mu / \sigma = .5$</td>
<td>N = 146</td>
</tr>
</tbody>
</table>

N = 402/initial nonresponse rate

N = 146/initial nonresponse rate

$\alpha = .05$, power = $1 - \beta = .85$

Sigma for example 1 is the std of primary outcome of patients initially assigned tx A (or B)

Sigma for example 2 is the std of primary outcome of non-responding patients who are assigned a switch (or augment)

Throughout working assumptions are equal variances and normality

Sample sizes calculated on the website:

http://hedwig.mgh.harvard.edu/sample_size/quan_measur/para_quant.html
An analysis that is less useful in the development of adaptive treatment strategies:

Decide whether treatment A is better than treatment B by comparing intermediate outcomes (proportion of early responders).

works if all secondary txt’s are equally effective.
SMART Designing Principles

• Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.

• EXAMPLE: Hypothesize that non-adhering non-responders will exhibit lower symptoms if their treatment is augmented with D as compared to a switch to treatment C (e.g. augment D includes motivational interviewing).

Confounding::: alternative explanations other than txt effect for the observed comparisons

Use analysis of covariance or regression.
A study of nonresponders in which one controls the tx’s to which people don’t respond to.
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Individualized interventions
Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist then in ensuing two months are monitored for heavy drinking

Trigger for nonresponse is heavy drinking days
Early trigger 2 or more hdd
Late trigger 5 or more hdd
The medication is Ritalin

Adaptive Pharmacological and Behavioral Treatments for Children with ADHD: Sequencing, Combining, and Escalating Doses

(1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND
(2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

Our outcome will be a teacher rated classroom performance recorded at 8 months. N=149
This study is going into the field

Nonresponse == missed unexcused tx day or positive urine for opioid or cocaine use or self report of opioid/cocaine use

RBT == reinforcement based tx

aRBT is abbreviated RBT

rRBT is reduced RBT
tRBT is traditional
eRBT is enhanced
Discussion

- Secondary analyses can use pretreatment variables and outcomes to provide evidence for a more sophisticated adaptive treatment strategy are coming out soon. (when and for whom?)

- We have a sample size formula that specifies the sample size necessary to detect an adaptive treatment strategy that results in a mean outcome $\delta$ standard deviations better than the other strategies with 90% probability (A. Oetting, J. Levy & R. Weiss are collaborators)

- Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.

Alter delivery mechanism, or improve motivation or form of treatment

Adherence is not a statistical nuisance; adherence indicates need to tailor treatment.
Another Secondary Analysis

Regression for SMART Studies
- This regression results in a proposal for an optimal adaptive treatment strategy.
- A subsequent trial would evaluate the proposed adaptive treatment strategy.
The medication is Ritalin

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Adaptive Treatments for Children with ADHD

• Stage 1 data: \((X_I, A_I, R_I)\)
  \(- R_I = 1\) if responder; \(= 0\) if non-responder
  \(- A_I = 1\) if BMOD, \(A_I = -1\) if MED
  \(- X_I\) includes baseline school performance, \((Y_0)\) and a measure of acceptability of medication \((S_I)\)
    \- \(S_I = 1\) if medication known to be acceptable; \(= 0\), if this is unknown.

• Stage 1 involves all children

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of \(Y, S_1, S_2\).

\[A_1 = 1\] if BMOD, \(-1\) if MED
\[A_2 = 1\] if enhance, \(-1\) if augment
Adaptive Treatments for Children with ADHD

• Stage 2 data: \((X_2, A_2, Y)\)
  – \(Y\) = end of year school performance
  – \(A_2 = 1\) if Enhance, \(A_2 = -1\) if Augment
  – \(X_2\) includes the month of non-response, \((M_2)\)
    and a measure of adherence in stage 1 \((S_2)\)
  • \(S_2 = 1\) if adherent in stage 1; =0, if non-adherent

• Stage 2 involves only children who do not respond in Stage 1 \((R_1=0)\).

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\(A_1 = 1\) if BMOD, -1 if MED  
\(A_2 = 1\) if enhance, -1 if augment
Regression for SMART Studies

• Conduct the regressions in backwards order! E.g. Stage 2 first, then Stage 1.
• Why?
  – Stage 1 dependent variable must control for Stage 2 treatment.
  – Stage 1 dependent variable is a predictor of $Y$ under optimal treatment in stage 2. (This permits delayed and diagnostic effects.)
  – Stage 2 analysis is used to construct $\hat{Y}$

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y$, $S1$,$S2$, $Y$.

A1=1 if BMOD, -1 if MED
A2=1 if enhance, -1 if augment
Stage 2 Regression for Non-responding Children

- Dependent Variable: $Y$ (end of school year performance)
- Treatment: $A_2 = 1$ if Enhance, $A_2 = -1$ if Augment
- Interactions with Treatment, $A_2$: stage 1 treatment ($A_1$) and adherence ($S_2$)
- Controls: baseline school performance, ($Y_0$) and acceptability of medication ($S_1$), month of non-response ($M_2$), stage 1 treatment ($A_1$)

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$A_1 = 1$ if BMOD, -1 if MED
$A_2 = 1$ if enhance, -1 if augment
Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y$, $S1$, $S2 Y$.

$A1=1$ if BMOD, -1 if MED

$A2=1$ if enhance, -1 if augment
Stage 1 Regression for All Children

- Dependent Variable: $\hat{Y}$ (predicted end of school year performance under optimal stage 2 treatment)
- Treatment: $A_1 = 1$ if BEMOD, $A_1 = -1$ if MED
- Interactions with Treatment, $A_1$: acceptability of medication ($S_1$)
- Control: baseline school performance, ($Y_0$)

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y$, $S_1$, $S_2$. $Y$.

A1=1 if BMOD, -1 if MED
A2=1 if enhance, -1 if augment
Stage 1 Regression for All Children

- S1=Acceptability of medication
  Difference = 0.40,
  Adaptive 95% CI: (-1.1314, 0.2724)

- S1= No knowledge re Acceptability of Medication
  Difference = 0.49,
  Adaptive 95% CI: (0.0746, 0.8978)
Adaptive Treatments for Children with ADHD

Adaptive Treatment Strategy Proposal:

- If there is no evidence that medication is highly acceptable begin with BMOD; otherwise select either BMOD or MED.
- If the child is nonresponsive and was non-adherent, augment present treatment; if the child is nonresponse and was adherent, select intensification of current treatment.

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y, S_1, S_2, Y$

$S_1 = 1$ if med is highly acceptable, $=0$ otherwise
Discussion

• Secondary analyses can use pretreatment variables and outcomes to provide evidence for a more sophisticated adaptive treatment strategy are coming out soon. (when and for whom?)

• We have a sample size formula that specifies the sample size necessary to detect an adaptive treatment strategy that results in a mean outcome $\delta$ standard deviations better than the other strategies with 90% probability (A. Oetting, J. Levy & R. Weiss are collaborators)

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This seminar can be found at:
http://www.stat.lsa.umich.edu/~samurphy/
seminars/UCLA_ISAP.01.28.10.pdf

This seminar is based on work with many collaborators some of which are: L. Collins, K. Lynch, J. McKay, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham. Email me with questions or if you would like a copy:

samurphy@umich.edu
Adaptive Treatments for Children with ADHD

- Stage 2 regression for $Y$:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_2\beta_{23})$$

- Stage 1 outcome: $R_1 Y + (1 - R_1)\hat{Y}$

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y, S1, S2$. 

Adaptive Treatments for Children with ADHD

• Stage 1 regression for $\hat{Y}$:

$$(1, Y_0, S_1) \alpha_1 + A_1(\beta_{11} + S_1\beta_{12})$$

• Interesting stage 1 contrast: should the knowledge that medication is highly acceptable, determine the best initial treatment in the sequence?

Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of $Y$, $S1$, $S2$.

$S1=1$ if med is highly acceptable, $=0$ otherwise