SMART Clinical Trial Designs for Developing Dynamic Treatment Regimes

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SMART Clinical Trial Designs for Developing Dynamic Treatment Regimes

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The effective management of many health disorders often requires individualized, sequential decision making whereby treatment is dynamically adapted and re-adapted over time based on a patient characteristics and on response to treatment. Dynamic Treatment Regimes (DTRs) operationalize this sequential decision making via a sequence of decision rules that specify whether, how, for whom and when to alter the intensity, type, or delivery of pharmacological, behavioral and/or psychosocial treatment at critical decision points. In this talk a novel, clinical trial design (namely, sequential multiple assignment randomized trials, or SMARTs) is proposed for the purpose of developing
and optimizing dynamic treatment regimes. Principles that guide the design of the SMART and potential primary analyses are discussed along with examples of SMARTs.

In this talk we discuss how a data analysis method developed for solving multi-stage decision problems in computer science, Q-learning, can be used with SMART study data to construct proposals for high quality dynamic treatment regimes. In this talk we discuss and illustrate the use of Q-Learning and provide a bootstrap based method for constructing asymptotically valid confidence sets.
Outline

- Dynamic Treatment Regimes
- SMART experimental designs
- Trial Design Principles and Analysis
- Exploring Individualization using the “Adaptive Interventions for Children with ADHD” study (W. Pelham, PI).

Other names are adaptive treatment strategies, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols.
Dynamic Treatment Regimes are individually tailored sequences of interventions, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

• Brooner et al. (2002, 2007) Treatment of Opioid Addiction

• McKay (2009) Treatment of Substance Use Disorders

• Marlowe et al. (2008, 2011) 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 dynamic txt regime, 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

Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR.

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 Dynamic Treatment Regimes?

- 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 (and relapse is common)
- 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

These are all reasons why we need to plan ahead because we are likely to need to use a sequence of treatments
Adaptive Interventions in Drug Court: A Pilot Experiment

Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR.

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

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
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
Some Critical Decisions

• 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 intervention is a multi-stage decision problem.

Also how to combine therapies?
Other names are adaptive treatment strategies, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols.
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.
An Dynamic Treatment Regime is indicated in blue
Alternate Approach I to Constructing a Dynamic Treatment Regime

- Why not use data from multiple trials to construct the dynamic treatment regime?
- 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 Dynamic Treatment Regime
Delayed Therapeutic Effects

Why not use data from multiple trials to construct the dynamic treatment regime?

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 a maintenance therapy and comparing more distal 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 Dynamic Treatment Regimes, 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 dynamic treatment regime?

**Negative synergies:** Treatment A may produce a higher proportion of responders but also result in side effects that reduce effectiveness of some 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 dynamic treatment regime?

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 adherence support than tx B, then patients who require the adherence 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 an adherence support during the maintenance or aftercare phase.
Sample Selection Effects

Why not use data from multiple trials to construct the Dynamic Treatment Regime?

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 high 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. 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.

Consider the issue of motivation. Nonresponder trials recruit individuals who are not responding to their present treatment, say Med A. An important consideration is whether these nonresponders represent the population of individuals who do not respond to Med A or whether the nonresponders recruited into the trial are more motivated. Such selection bias will prevent us from realizing that we might need a behavioral intervention to encourage nonresponders to start again with treatment.
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 a dynamic txt regime.

We “control” for the effects of secondary txts by experimental design as opposed to analysis methods.
Alternate Approach II to Constructing an Dynamic Treatment Regime

Why not use theory, clinical experience and expert opinion to construct the Dynamic Treatment Regime and then compare this strategy against an appropriate alternative in a confirmatory randomized two group trial?

Don’t know why your treatment strategy worked or did not work. Did not open black box. Should we wait until patient has had 5 heavy drinking days before giving up on this medication or should we give up on this medication after only 2 heavy drinking days?
Why constructing an Dynamic Treatment Regime and then comparing the strategy against a standard alternative is not always the answer.

- Don’t know why your dynamic treatment regime worked or did not work. Did not open black box.
- Dynamic treatment regimes are multi-component treatments
  - We need to address: when to start treatment?, when to alter treatment?, which treatment alteration?, what information to use to make each of the above decisions?
These are intervention development trials. These trials are not confirmatory in the sense of confirming that one adaptive intervention is best.

The primary analyses are being conducted with the second two other trials in cancer.
Other names are adaptive treatment strategies, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols.

Outline

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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.
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 dynamic treatment regime.
  • Power trial to address these hypotheses.

• Conduct secondary analyses that further develop the dynamic treatment regime and that use the randomization to eliminate confounding.
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 by 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></th>
<th>Example 1</th>
<th>Example 2</th>
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<tbody>
<tr>
<td>( \Delta \mu/\sigma = .3 )</td>
<td>N = 402</td>
<td>N = 402/initial nonresponse rate</td>
</tr>
<tr>
<td>( \Delta \mu/\sigma = .5 )</td>
<td>N = 146</td>
<td>N = 146/initial nonresponse rate</td>
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\( \alpha = .05, \quad \text{power} = 1 - \beta = .85 \)

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
Exploring Greater Individualization using the “Adaptive Interventions for Children with ADHD” study (W. Pelham, PI)

Q-Learning
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
2 Stages

**Goal:** Construct decision rules that input information available at each stage and output a recommended decision; these decision rules should lead to a maximal mean \( Y \) where \( Y \) is a function of

\[
X_1, \ a_1, \ X_2, \ a_2, \ X_3
\]

The *dynamic treatment regime* is the sequence of two decision rules:

\[
d_1(X_1), \ d_2(X_1, a_2, X_2)
\]

\( Y \) might be a measure of symptoms or functionality or a composite

Note that mean \( Y \) is maximized if the decision rule selects each person’s maximal potential (counterfactual) \( Y \)
Data for Constructing the Dynamic Treatment Regime:

One subject’s data from a SMART.

\[ X_1, \ A_1, \ X_2, \ A_2, \ X_3 \]

\( A_j \) is a randomized action with known randomization probability.

binary actions with \( P[A_j=1]=P[A_j=-1]=.5 \)
Q-Learning

*Q-Learning is an extension of regression to sequential treatments.*

- This regression results in a proposal for an optimal dynamic treatment regime.
- A subsequent trial would evaluate the proposed dynamic treatment regime.
A Simple Version of Q-Learning – \( A_j \in \{-1, 1\} \)

There is a regression for each stage.

- Stage 2 regression: Regress \( Y \) on \( S'_2, S_2A_2 \) to obtain \( \hat{\alpha}_2 S'_2 + \hat{\beta}_2 S_2A_2 \)

- Stage 1 regression: Regress \( \hat{Y} \) on \( S'_1, S_1A_1 \) to obtain \( \hat{\alpha}_1 S'_1 + \hat{\beta}_1 S_1A_1 \)

\( S'_2 \) and \( S_2 \) are summaries of \( X_1, A_1, X_2 \)
\( S'_1 \) and \( S_1 \) are summaries of \( X_1 \)

Stage 2 only involves data from individuals who enter stage 2!
\( S_1, S'_1, S_2, S'_2 \) include a constant indicator to pick up the intercept (or main effect of \( A_1, A_2 \)).
Patients who remain responding get a $\hat{Y} = Y$

Patients who do not respond as some time after 2 months get a $\hat{Y}$.

You could pool over time, use more flexible models and use penalization etc…… one could use log linear regression.

$\hat{Y}$ is a pseudo-outcome
Because because $S2'$ contains all covariates for the step 1 regression this is a good $\hat{Y}$. Otherwise you would want to use a $\hat{Y}$ as in Murphy (2003) or Robins (2004). This $\hat{Y}$ is

$\hat{Y} = \hat{Y} - \beta_2 S_2 A_2 + \max_{a_2} \beta_2 S_2 a_2$

This latter $\hat{Y}$ might be better in terms of maintaining near homogeneous residual variance for the stage 1 regression.
If $S_2'$ contains $(S_1A_1, S_1')$ and actions are centered to have mean zero then Q-learning = opt. nested structural mean model (not doubly robust version of robins).

You could pool over time, use more flexible models and use penalization etc……

Yhat is a pseudo-outcome

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<td>• Stage 2 regression, (using $Y$ as dependent variable) yields</td>
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<td>$\hat{\alpha}_2^T S_2' + \hat{\beta}_2^T S_2 a_2$</td>
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<td>• Stage 1 regression, (using $\hat{Y}$ as dependent variable) yields</td>
</tr>
<tr>
<td>$\hat{\alpha}_1^T S_1' + \hat{\beta}_1^T S_1 a_1$</td>
</tr>
</tbody>
</table>
The $\hat{\beta}_2^T S_2$ is like a decision boundary.

Decision Rules:

$$\tilde{d}_2(x_1, a_1, x_2) = \begin{cases} 
1 & \text{for } \beta_2^T s_2 > 0 \\
-1 & \text{for } \beta_2^T s_2 \leq 0
\end{cases}$$

and

$$\tilde{d}_1(x_1) = \begin{cases} 
1 & \text{for } \beta_1^T s_1 > 0 \\
-1 & \text{for } \beta_1^T s_1 \leq 0
\end{cases}$$

where $s_j$ is a vector summary of the observations ($x$'s, $a$'s) available at stage $j$. 
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.

A1=1 if BMOD, -1 if MED
A2=1 if enhance, -1 if augment
Since the primary analyses are being written up at this time we use altered data.

A1=1 if BMOD, -1 if MED
A2=1 if enhance, -1 if augment

Q-Learning using data on children with ADHD

• Stage 2 data: (X2, A2, Y)
  – Y = end of year school performance
  – A2=1 if Enhance, A2=-1 if Augment
  – X2 includes the month of non-response, (M2)
    and a measure of adherence in stage 1 (S2)
  • S2 =1 if adherent in stage 1; =0, if non-adherent
• Stage 2 involves only children who do not respond in Stage 1 (R1=0).
Q-Learning for SMART Studies

- Conduct the regressions in backwards order. E.g. Stage 2 first, then Stage 1.
- Why? Recall
  - 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.
  - Stage 2 analysis is used to construct the predictor of $Y$, $\hat{Y}$

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 baseline prior medication ($S_1$), month of non-response ($M_2$)

$A_1=1$ if BMOD, -1 if MED
$A_2=1$ if enhance, -1 if augment
Q-Learning using data on children with ADHD

- Stage 2 regression for $Y$:

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

- Interesting Stage 2 contrast: Does the best stage 2 tactic (enhance versus augment) for non-responding children differ by whether the child/family is adherent?

Only data from nonresponding children used in this analysis.
Since the primary analyses are being written up at this time we use altered data

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: prior medication \( (S_I) \)
- Control: baseline school performance, \( (Y_0) \)

Since the primary analyses are being written up at this time we use altered data
\( A_1 = 1 \) if BMOD, -1 if MED
\( A_2 = 1 \) if enhance, -1 if augment
Dependent Variable for Stage 1 Regression

- Recall the 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 dependent variable:

$$ R_1Y + (1 - R_1)\hat{Y} $$

$$ \hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\tilde{\alpha}_2 + |\tilde{\beta}_{21} + A_1\tilde{\beta}_{22} + S_2\tilde{\beta}_{23}| $$
Since the primary analyses are being written up at this time we use altered data
S1=1 if on med in prior year, =0 otherwise
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)
Dynamic Treatment Regime Proposal

IF medication has not been used in the prior year
    THEN begin with BMOD;
ELSE select either BMOD or MED.

IF the child is nonresponsive and was non-adherent, THEN augment present treatment;
ELSE IF the child is nonresponse and was adherent, THEN select intensification of current treatment.
Discussion

• Confidence Intervals have been developed.

• Software in R for Q-Learning out and, in SAS, is coming out soon.
  
  https://methodology.psu.edu/ra/adap-treat-strat/qlearning

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

Adherence is not a statistical nuisance; adherence indicates need to tailor treatment.
This seminar can be found at:
http://www.stat.lsa.umich.edu/~samurphy/
seminars/ASA_CT.03.21.12.pdf

This seminar is based on work with many collaborators, some of which are: L. Collins, E. Laber, M. Qian, D. Almirall, 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
Pop’n: children who are nonverbal (not using spoken language) by 5 years of age despite involvement in traditional intervention programs

N=90 6 month trial

cutoff for nonresponse at 12 weeks (three measures of communication to yield our *response/non-response indicator*: number of words used spontaneously during parent-child interaction, number of communicative functions used for each word during parent-child interactions, and generalization of spontaneous *words to express multiple communication functions*.) Responder status—increase of 25% over baseline in at least half of 14 assessment measures

**JAE Joint attention and joint engagement**

Enhanced Milieu Teaching (EMT) is a naturalistic language intervention that promotes functional use of new language forms in the context of every
day interactions with parents and teachers. EMT uses environmental arrangement, responsive interaction, language modeling, and systematic prompting procedures to teach functional language.

augmentative and alternative communication interventions (AAC)

Primary Aim:
1) To compare the slopes in outcome measures of communication and language across three time periods (times 0, 3 months and 6 months) for the two treatments: JAE +AAC strategy vs enhanced JAE strategy
This study is in the field  n=300  primary hypothesis compared always traditional RBT vs always reduce RBT

Primary outcome is “in treatment when child born”

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

These differ in intensity and scope (in increasing order below)
aRBT is abbreviated RBT
rRBT is reduced RBT
tRBT is traditional
eRBT is enhanced
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