SMART Case Studies

Module 3—Day 1

Getting SMART About Developing Individualized Adaptive Health Interventions

Methods Work, Chicago, Illinois, June 11-12
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60 minutes

• Give examples of SMARTs that are completed or in the field
  o ASD, child ADHD, women who are pregnant and abuse substances, adult alcohol use, depression
• Discuss the variety of rationales underlying the SMARTs, types of critical decisions; range of treatment modalities, differences in primary aims
• Compare balanced versus unbalanced SMART designs
Outline

- Adaptive ASD Developmental and Augmented Intervention (Kasari, PI)
- Adaptive Pharmacological and Behavioral Treatments for Children with ADHD Trial (Pelham, PI)
- Adaptive Reinforcement-Based Treatment for Pregnant Drug Abusers (Jones, PI)
- Extending Treatment Effectiveness of Naltrexone (Oslin, PI)
- Comparison of SMARTs

ASD=autism spectrum disorder
This trial is in the field
See
http://www.semel.ucla.edu/ASD/research/project/ccnia-developmental-augmented-intervention-facilitating-expressive-language

CCNIA=characterizing cognition in nonverbal individuals with ASD

N=96 6 month trial
Kasari ASD SMART

• Population & Rationale:
  – Non-verbal children with ASD who have not made satisfactory progress by age 5 even though they have received traditional intensive interventions
  – These children experience poor outcomes yet represent 25-30% of children with ASD.
  – Planning for a “rescue” if the first treatment does not go well is crucial.

ASD: ASD spectrum disorder
6 month study
The joint attention/joint engagement (JAE) intervention was combined with two interventions, enhanced milieu teaching (EMT) and augmentative and alternative communication (AAC). JAE (Adamson et al. 2004; Kasari et al. 2006, 2008) was developed to facilitate a state of supported or coordinated joint engagement between the child and a social partner. Both EMT and AAC were developed to facilitate expressive language in young children with developmental disabilities. EMT (Hancock & Kaiser 2006) is a naturalistic language intervention that promotes functional use of new language forms in the context of everyday interactions with parents and other social partners. The AAC intervention utilizes a developmentally chosen augmentative communication device (Cafiero 2005) to facilitate communicative exchanges within play routines and daily activities. Both EMT and AAC were adapted for 5- to 8-year-old children and integrated with JAE to form two interventions, JAE + EMT and JAE + AAC. More intensive versions of both JAE + EMT and JAE + AAC included additional sessions provided by a skilled child therapist and additional training with the parent to promote parent and child generalization. Overall, four intervention options are considered: JAE + EMT, JAE + AAC, intensified JAE + EMT, and intensified JAE + AAC.

Kasari ASD SMART

- Critical Decisions:
  - Which treatment to provide first? Which treatment to provide non-responders?

- Treatments:
  - JAE, EMT, AAC, (JAE+EMT), (JAE+AAC)
Kasari ASD SMART

- Embedded Tailoring Variables: (a) total social communicative utterances, (b) percentage communicative utterances, (c) number different word roots, (d) mean length of utterance in words, (e) number of utterances where the function is to comment (rather than request), (f) words per minute, and (g) unique word combinations (included only if the child’s target talk consists of more than two words).
for each assessment, the first variable was calculated as the difference in the average assessment between the first two intervention sessions and the last two intervention sessions during the first stage of the intervention; the second variable was calculated as the difference between the assessment at the screening visit and the month-three visit. The above measures are collected via videotapes of the child and therapist sessions.

Preliminary studies indicated that these interventions should show changes within a 3 month period; this time frame is consistent with recommendations by the National Research Council.
6 month trial
Kasari ASD SMART

3 Embedded Adaptive Treatment Strategies

1) Start with JAE+EMT; if non-responder JAE+AAC, else JAE+EMT
2) Start with JAE+EMT; if non-responder (JAE+EMT)$^+$, else JAE+EMT
3) Start with JAE+AAC; if non-responder (JAE+AAC)$^+$, else JAE+AAC
Identify some of the embedded adaptive txt strategies
Primary Analyses involve:

Outcomes such as Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4) (given at 0, 6, 9 months): This test for receptive vocabulary development and is appropriate for children aged 2.6 years and older. and Verbal Motor Production Assessment for Children (VMPAC) (given at 0, 6, 9 months) The VMPAC is designed to examine oral and speech-motor control in children. The items are arranged from basic to complex and assess three main areas: Global motor control, focal oromotor control and sequencing.

Secondary Analyses involve:

The baseline variables included severity of repetitive compulsive behaviors, degree of apraxia, and developmental variables (based on cognitive and language test results). In particular, the research team hypothesized that children with greater severity of apraxia would do better on beginning with JAE + AAC than beginning with JAE + EMT because the communication device would better provide a means to communicate.
Other potential tailoring variables that might be investigated in secondary analyses?
Other secondary analyses?
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1-school year study (approx. 8 months) N=153

Note non-response is assessed monthly beginning at month 2 (8 weeks)
for example, a task force of the American Psychological Association recommends psychosocial first (Brown et al. 2007), whereas the guidelines of the American Academy of Child and Adolescent Psychiatry (2007) recommend using medication first.
Med is ritalin

The interventions include differing doses of methylphenidate (a psychostimulant drug) and differing intensities of behavioral modification (consisting of a school-based component with the teacher, a Saturday treatment component involving social skills development, and a parent-training component targeted at helping parents to identify problematic behaviors with the relevant child-functioning domains). The higher-dose option for methylphenidate includes late-afternoon doses, if needed. The higher-intensity option for the behavioral modification includes more intensive training in social skills in the school-based component and, if needed, both additional individual parent training sessions that target specific behavior management issues and practice sessions with children.
The Impairment Rating Scale (IRS) (Fabiano et al. 2006) and an individualized list of target behaviors (ITB) (e.g., Pelham et al. 1992). The IRS provides a comprehensive index of a child’s impairment in various domains such as peer relationships, classroom behavior, family functioning, and academic achievement. The ITB was used to assess improvement on child-specific behavior goals.

Investigators felt that 8 weeks was needed in order to obtain a reasonable assessment of children’s response to treatment and to give clinicians time to implement the school-based interventions and conduct parent training.
Pelham ADHD Study

Begin low-intensity BMOD

8 weeks
Assess Adequate response?
Yes 
Random assignment

No
BMOD + Med

Random assignment

Begin low dose Med

8 weeks
Assess Adequate response?
Yes 
Random assignment

No
BMOD**

Continue, reassess monthly; randomize if deteriorate

Random assignment

Continue, reassess monthly; randomize if deteriorate

BMOD + Med

Random assignment

Med**
Pelham ADHD SMART

4 Embedded Adaptive Treatment Strategies

1) Start with BMOD; if non-responder BMOD++, else BMOD
2) Start with BMOD; if non-responder BMOD +Med, else BMOD
3) Start with Med; if non-responder Med++, else Med
4) Start with Med; if non-responder BMOD+Med, else Med.
### Pelham ADHD SMART

4 Embedded Adaptive Treatment Strategies

**conceptualized in terms of tactics**

1) Start with BMOD; if non-responder intensify, else continue same
2) Start with BMOD; if non-responder augment with other treatment, else continue same
3) Start with Med; if non-responder intensify, else continue same
4) Start with Med; if non-responder augment with other treatment, else continue same.

Conceptualize second stage in terms of tactics as opposed to the treatments….
Potential baseline moderator was whether the child had received medication for ADHD in prior year.
Pelham ADHD Study

Other secondary analyses?
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This study is in the field n=300
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
The women must have completed an eight-day residential detoxification stay.
Jones Drug Abuse SMART

Critical Decisions:

– (a) Whether the frontline version of RBT can be reduced in intensity and scope;
– (b) whether a woman who does not respond quickly should continue on the same version or be moved to a more-intensive, larger-scope version of RBT; and
– (c) whether the intensity and scope of RBT can be reduced if a woman responds quickly.
Jones Drug Abuse SMART

- Treatments:
  - aRBT < rRBT < tRBT < eRBT (increasing order in intensity/scope)

- Embedded Tailoring Variables:
  - a) self-reported drug use, b) results of urine tests, and c) attendance on intervention days
Prior studies documented that the most vulnerable period for treatment drop-out is during the first two weeks of outpatient care and that very early drug use lapse or relapse is a predictor of poor treatment response.
Jones Drug Abuse SMART

8 Embedded Adaptive Treatment Strategies

1) Always tRBT
2) Start with tRBT; if non-responder tRBT, if responder rRBT
3) Start with tRBT; if non-responder eRBT, if responder tRBT
4) Start with tRBT; if non-responder eRBT, if responder rRBT
Jones Drug Abuse SMART

8 Embedded Adaptive Treatment Strategies

5) Always rRBT
6) Start with rRBT; if non-responder tRBT, if responder rRBT
7) Start with rRBT; if non-responder rRBT, if responder aRBT
8) Start with rRBT; if non-responder tRBT, if responder aRBT
Primary Analysis
- To compare program completion (delivery of child while in treatment) of the always tRBT arm versus the always rRBT arm (two non-adaptive strategies!)

Secondary Analyses
- Investigate moderation by baseline variables, investigate if other variables might be used to tailor treatment.

Secondary aims involve assessing the usefulness of candidate tailoring variables, such as the amount of illegal activity (e.g., prostitution).
Other secondary analyses?
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All Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist + medical management (NTX+MM)

N=302
Oslin Alcoholism SMART

Population & Rationale:
- Alcohol Dependent Adults who completed an Intensive Outpatient Program
- Naltrexone (NTX, an opiate antagonist) is efficacious but clinical use is limited.
  - Around 1/3 of patients relapse while on NTX.
  - Would like to inform longer term management based on NTX
  - Non-adherence is common

Oslin wrote in his justification: Despite the efficacy of naltrexone (NTX) for prevention of relapse to alcoholism as established by the majority of randomized clinical trials, as many as a third of subjects relapse while taking NTX. These studies have raised a second generation of questions regarding the best long-term management of subjects who are non responders: do these subjects require some type of augmented therapy or stepped care approach (more intensive psychotherapy, a second medication, etc.), should they be switched to a different therapy altogether and if so is there any benefit to remaining on NTX, or do they need further exposure to NTX to demonstrate a response? In considering testable hypotheses for non-responders we relied on our existing data and experience with other common chronic diseases such as depression, hypertension and arthritis. For instance in depression management, after treatment non-response with one medication it is usually assumed that a second medication or psychotherapy will be tried. However, there is considerable debate over whether the first medication should be continued or discontinued, as there may have been partial response to the first medication or potential synergistic effects with the second treatment. We are proposing to mirror this type of design by testing the benefits of remaining on NTX after adding a combination of motivational enhancement therapy and cognitive behavioral therapy (Combined Behavioral Intervention -CBI) to Medical Management (MM). Given the economic costs related to long term NTX treatment, we see this question as critical in developing long term treatment strategies that involve the use of NTX. The economic impact of this issue was highlighted by Ilstrup in a commentary on ineffective treatments. Given that a significant proportion of non-response to NTX may be due to non-adherence, a secondary aim of this project is to examine the role of medication adherence as a mediating factor in treatment improvement among those randomized to NTX.
Oslin Alcoholism SMART

Critical Decisions:

– (a) What extent of drinking behavior best reflects nonresponse to NTX?

– (b) What type of treatment would be useful for participants who do not respond adequately to NTX?

– (c) What type of treatment would be useful in reducing the chance of relapse among participants who respond adequately to NTX?
These are NTX, medical management (MM), combined behavioral intervention (CBI), and telephone disease management (TDM). MM is a face-to-face, basic, minimal clinical support for the use of effective pharmacotherapy and reduction in drinking (Pettinati et al. 2004, 2005). CBI is a multicomponent intervention that includes components targeting adherence to pharmacotherapy and enhancement of participant motivation for change. This intervention includes family involvement when possible and emphasizes the utilization of the participant’s social/community context to reinforce abstinence (Longabaugh et al. 2005, Miller et al. 2003). TDM includes the same content as MM, but it is delivered via telephone.

Heavy drinking days (≥5 drinks/day for males; ≥4 for females)
This criterion was supported by preliminary data generated from a prior NTX study conducted. This study gave alcohol dependent subjects for 100mg/day or placebo with a less structured form of medical monitoring called BRENDA for 32 weeks. Results indicated that subjects who had taken the NTX (not placebo) and had 2 to 5 days of heavy drinking in the first 60 days were not likely to reduce their drinking if they just continued NTX and medical management.
All Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist + medical management (NTX+MM)
N=302
Oslin Alcoholism SMART

8 Embedded Adaptive Treatment Strategies

1) Start with NTX+MM; if 2 HDD occurs prior to 8 weeks, augment to CBI+NTX+MM, else at 8 weeks continue on NTX

2) Start with NTX+MM; if 2 HDD occurs prior to 8 weeks, switch to CBI +MM, else at 8 weeks continue on NTX

3) Start with NTX+MM; if 2 HDD occurs prior to 8 weeks, augment to CBI+NTX+MM, else at 8 weeks continue on NTX and add TDM

HDD: heavy drinking days (≥5 drinks/day for males; ≥4 for females)
Osln Alcoholism SMART

8 Embedded Adaptive Treatment Strategies

4) Start with NTX+MM; if 2 HDD occurs prior to 8 weeks, switch to CBI+MM, else at 8 weeks continue on NTX and add TDM

5) ..

6) ..

7) ..

8) ..

HDD: heavy drinking days (≥5 drinks/day for males; ≥4 for females)
Oslin Alcoholism SMART

- Primary Analysis
  - Focus on non-responders to NTX+MM.
  - Compare drinking outcomes (e.g. percent days abstinent) on CBI+NTX+MM versus to CBI+MM.

- Secondary Analyses
  - Test effectiveness of TDM for responders; test two criteria for non-response; assess moderation (psychosocial distress, severity of alcohol dependence, adherence in first stage)

Note the primary aim. Quite different from other case studies.
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Comparison of SMART Studies

Dimensions
1) Which participants are multiply randomized?
2) When are participants re-randomized?
3) The types of the critical decisions
4) What are the primary research questions?
The larger the number of categories of people re-randomized, the larger the number of embedded adaptive treatment strategies.
## Comparison of SMART Studies

When are participants randomized for the second time?

- At one fixed point in time only
  - ASD (month 3), Drug Abusing Pregnant Women (week 2), Alcohol Dependence (responders at week 8)
- At any one of several fixed times
  - ADHD (at month 2 and each month thereafter), Alcohol Dependence (non-responders at week 2 and weekly until week 8)

Also in both the ADHD and the Alcohol Dependence SMARTS as soon as non-response detected, the participant is re-randomized.
Comparison of SMART Studies

What kinds of critical decisions are investigated?

- Which treatment first and which second?
- ASD, ADHD, Drug Abusing Pregnant Women
- How soon to give up on initial treatment and which treatment to provide second?
- Alcohol Dependence
Comparison of SMART Studies

What are the primary research questions?
- Comparison of stage 1 treatments, controlling, by design, for stage 2 treatments.
- ASD, ADHD
- Comparison of stage 2 treatments, controlling, by design, for stage 1 treatment
  - Alcohol Dependence (non-responders)
  - Comparison of two embedded treatment strategies.
- Drug Abusing Pregnant Women

These are the comparisons that are used to size the SMART
Questions?

More information:

Practice Exercise

Exercise: Using your 2-3 simple ATSs, (a) construct a draft SMART design and (b) identify your primary scientific aim!