SMART Case Studies

Module 3

Experimental Design and Analysis Methods for Developing Adaptive Interventions: Getting SMART

Inbal (Billie) Nahum-Shani, Daniel Almirall

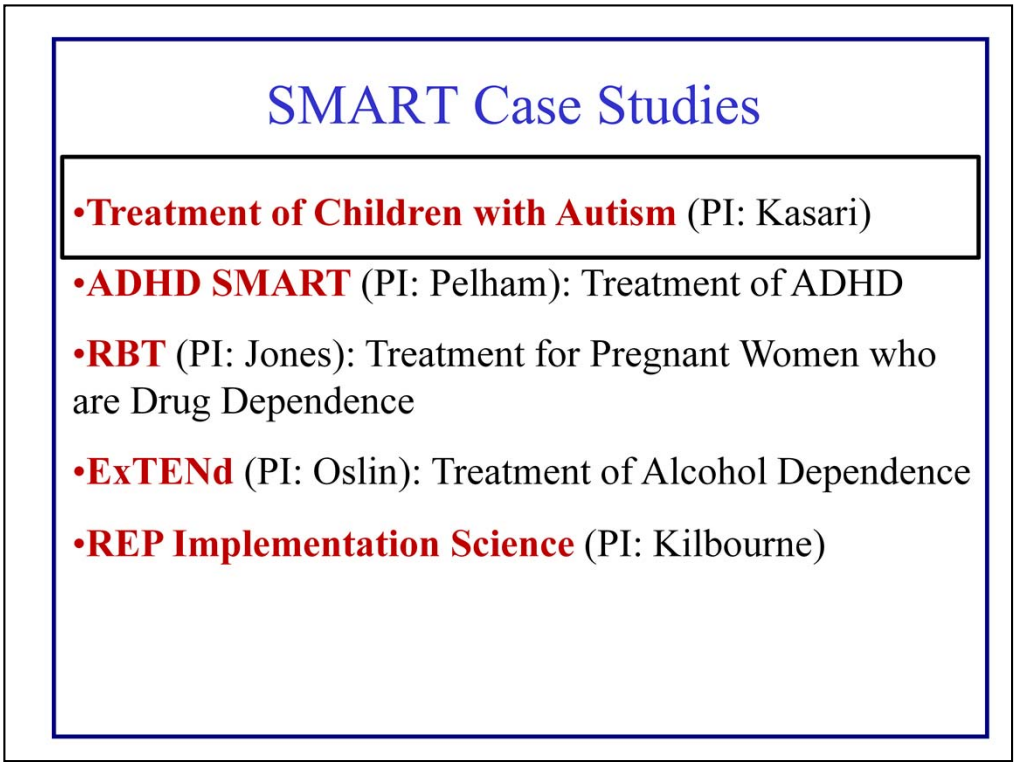
60 minutes

- Give examples of six SMARTs that are completed or in the field
- 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

- **Treatment of Children with Autism** (PI: Kasari)
- **ADHD SMART** (PI: Pelham): Treatment of ADHD
- **RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependence
- **ExTENd** (PI: Oslin): Treatment of Alcohol Dependence
- **REP Implementation Science** (PI: Kilbourne)
- Summary Comparison of the five SMARTs

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.



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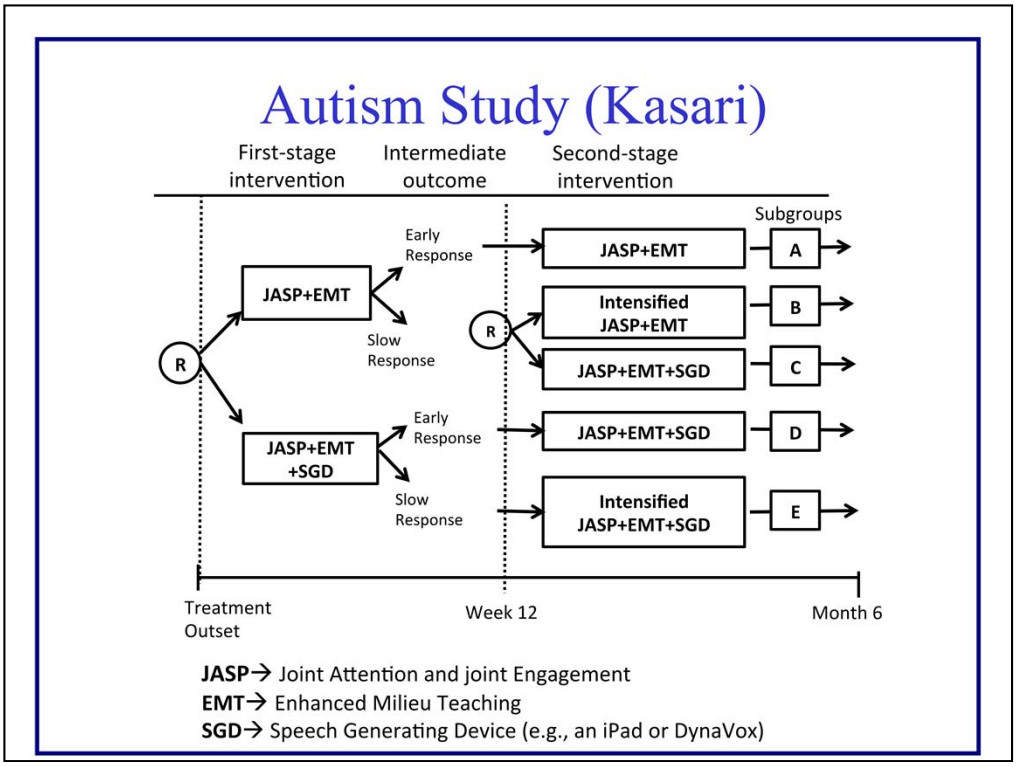

Population: Children with autism spectrum disorders who are nonverbal (not using spoken language) by age 5 despite involvement in traditional intervention programs

N=90 was the planned sample size; but this N was not achieved due to recruitment difficulties. The final study had only N=61.

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Primary outcome: Total spontaneous communicative utterances

JASP (Joint Attention Symbolic Play Engagement and Regulation) focuses on early social-communication skills, including coordinated joint attention gestures known to be associated with the development of later spoken language of children with autism. Includes the creation of contextually relevant and meaningful learning opportunities during interactions with adult partners (therapists, parents) who are responsive to child interests and actions, who model and expand play and gesture use and maintain joint engagement.

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Autism Study (Kasari)

- Population:
  - Non-verbal children with ASD who have not made progress by age 5 even though they have received traditional intensive behavioral language interventions

ASD: ASD spectrum disorder

6 month study

Autism Study (Kasari)

- Rationale:
  - 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.
  - Speech generating devices (eg, iPads) are costly and no rigourous research, depsite all the rave!
  - Can SGDs improve outcomes in the context of promising behavioral language interventions?

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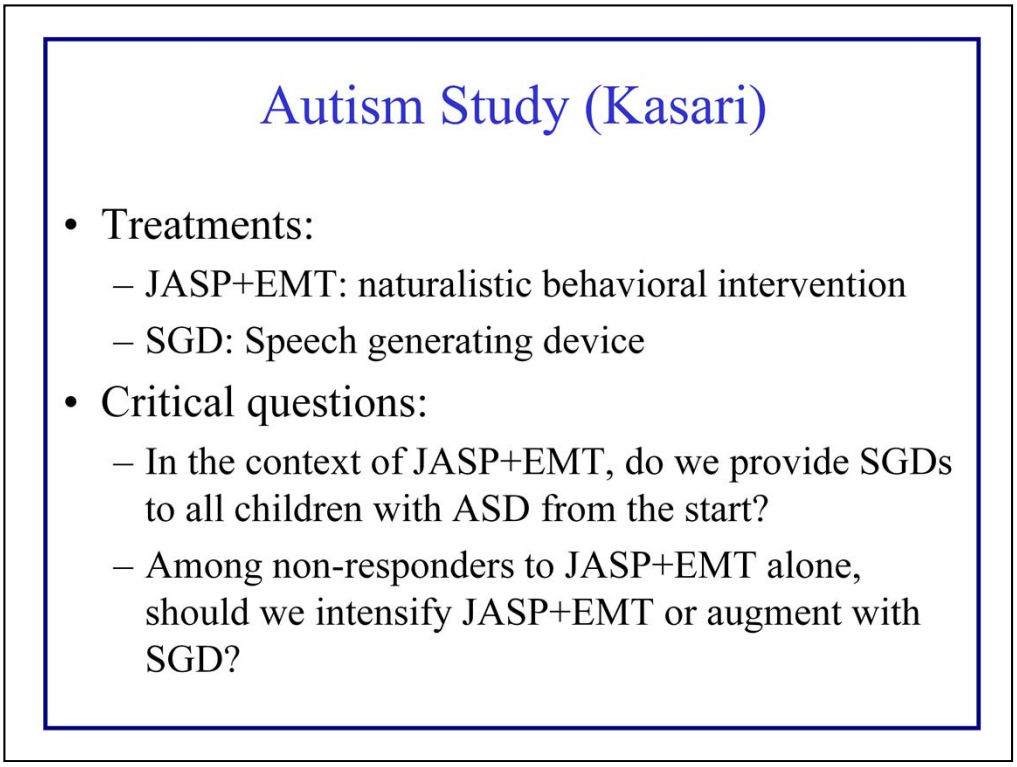

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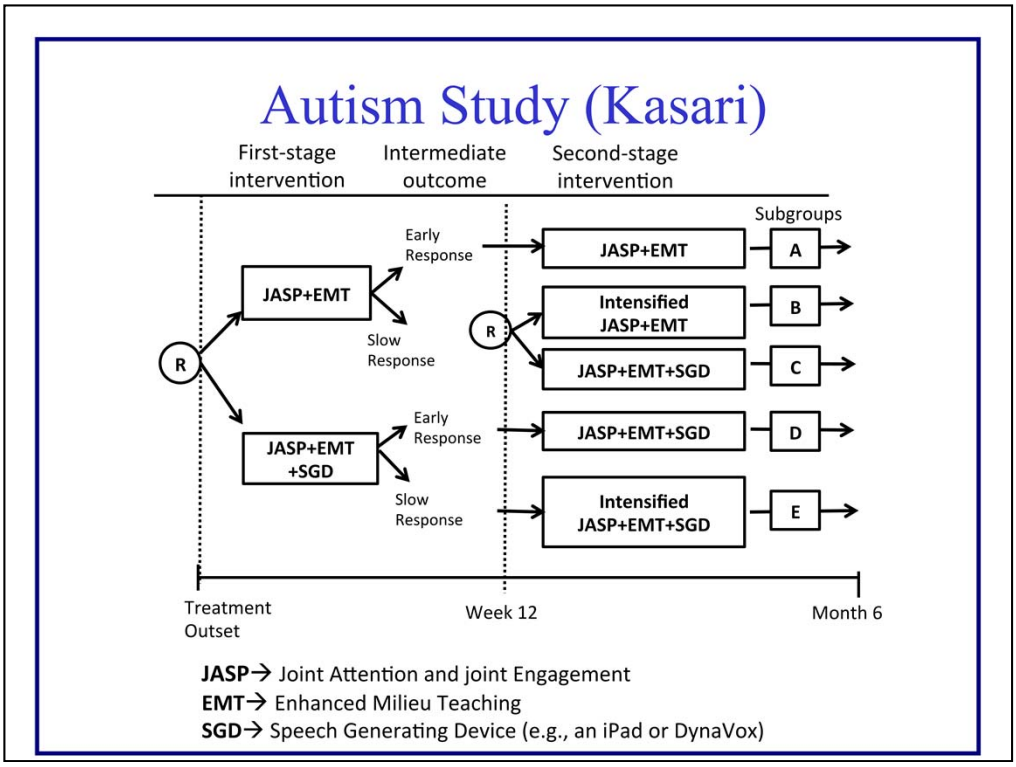

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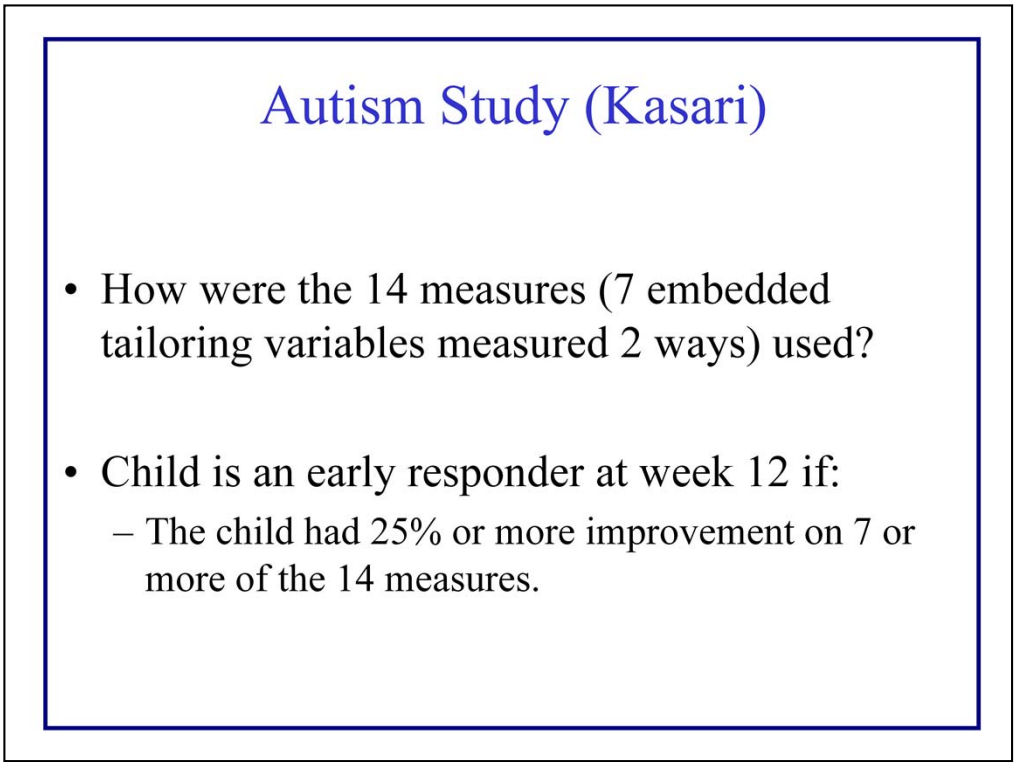
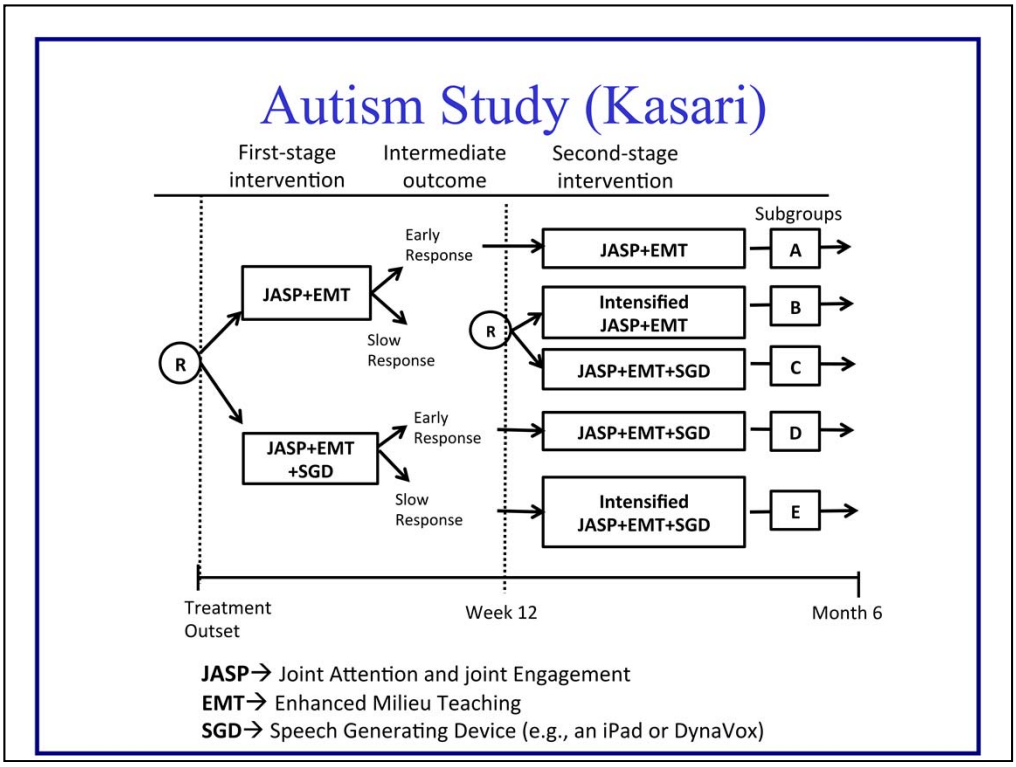
Autism Study (Kasari)

- Seven 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,
  - (*f*) words per minute, and
  - (*g*) unique word combinations
- Measured two ways at the end of week 12: therapist measured & blinded evaluator



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



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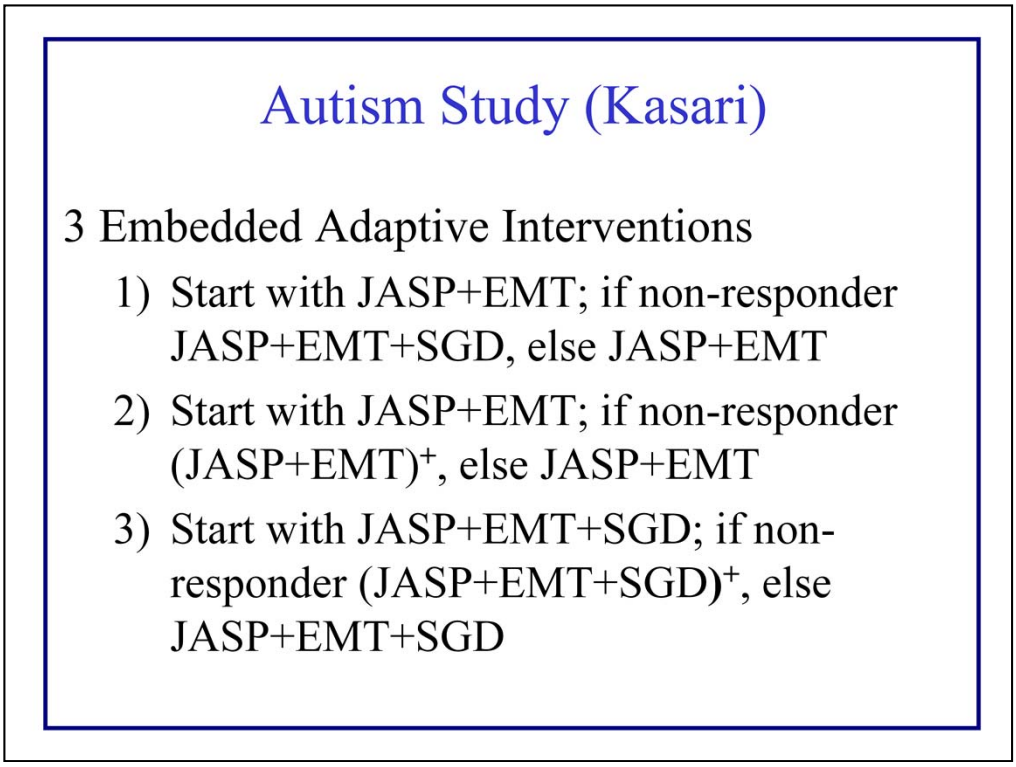

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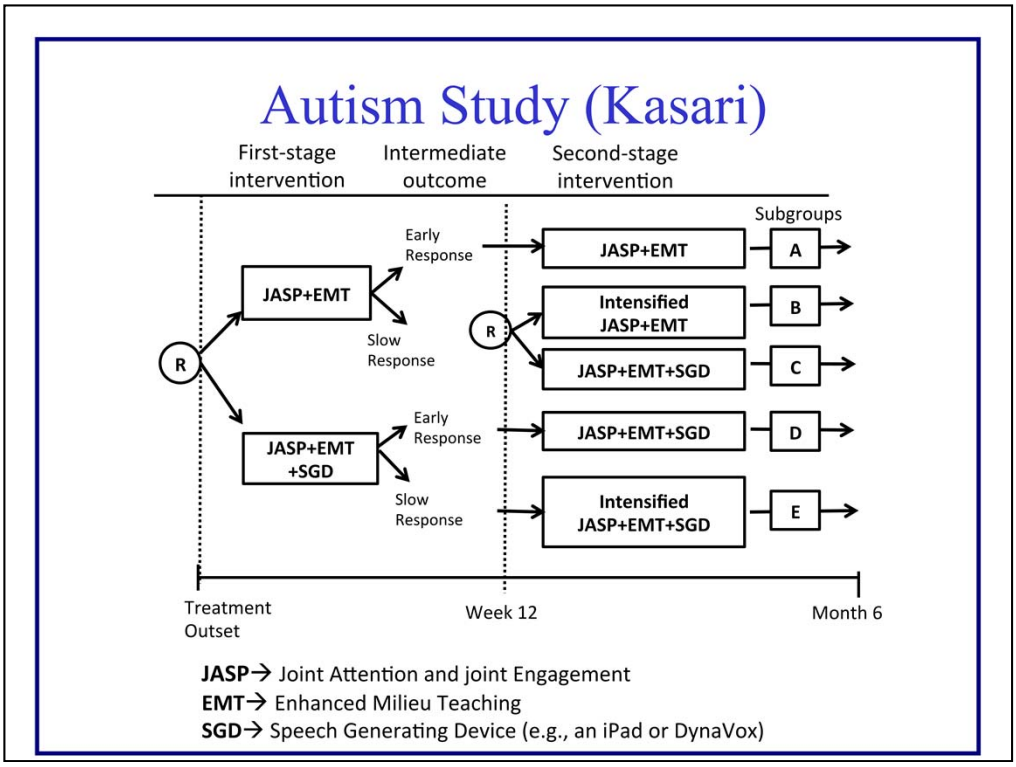

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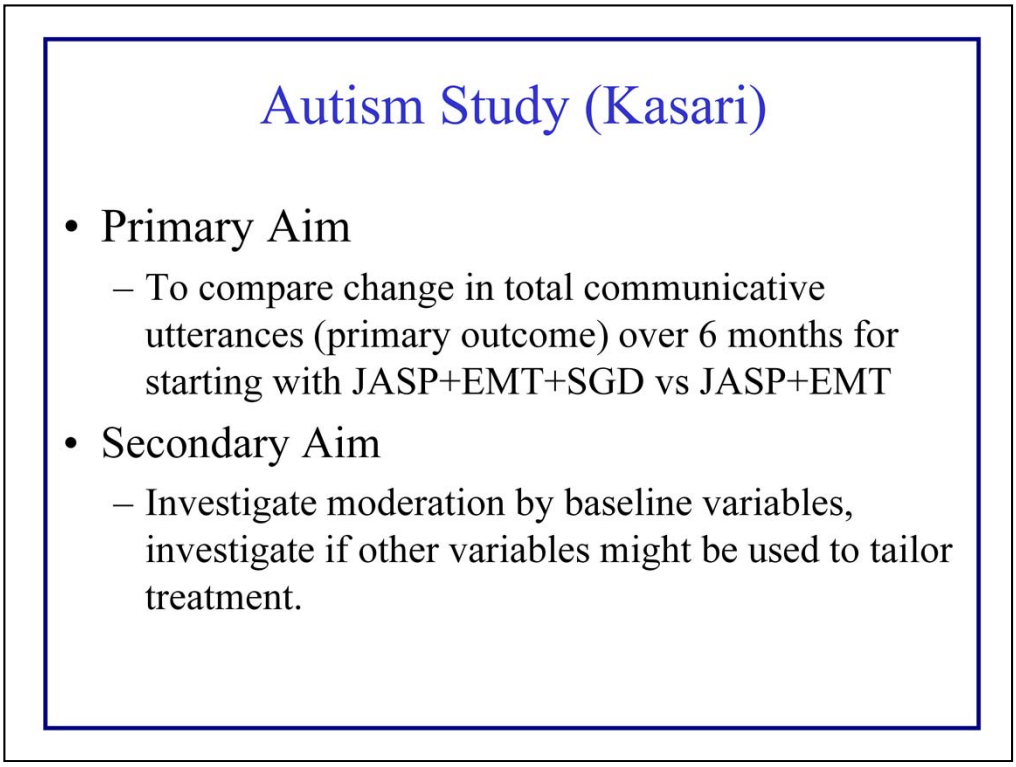
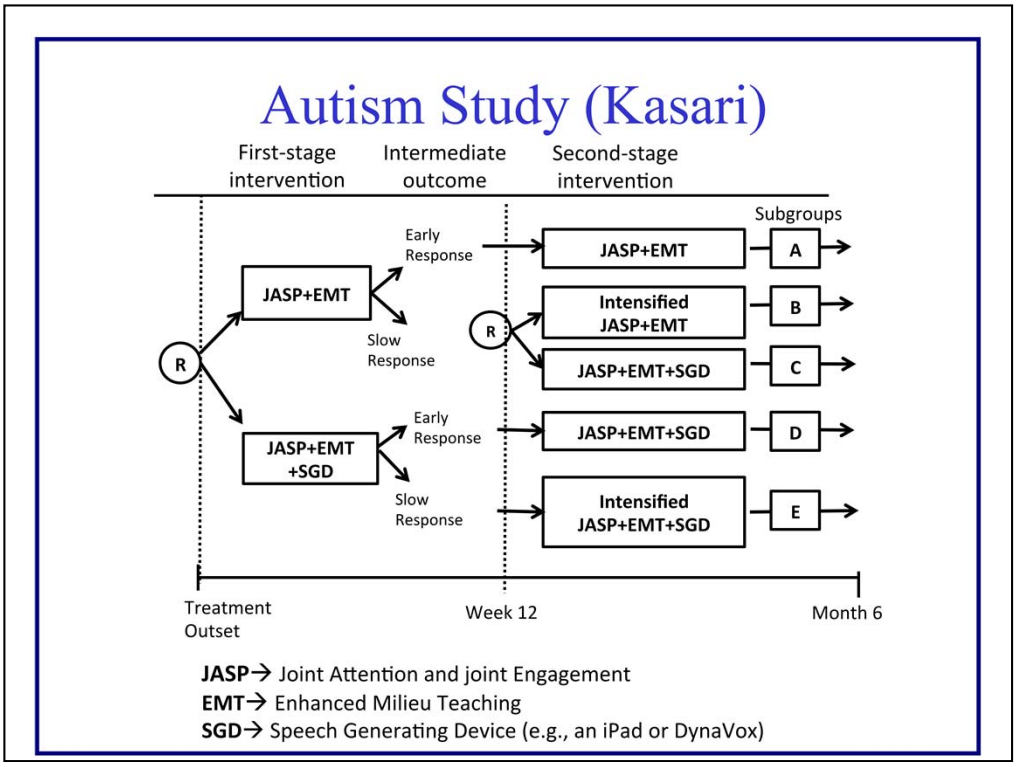


Primary Analyses involve:

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.



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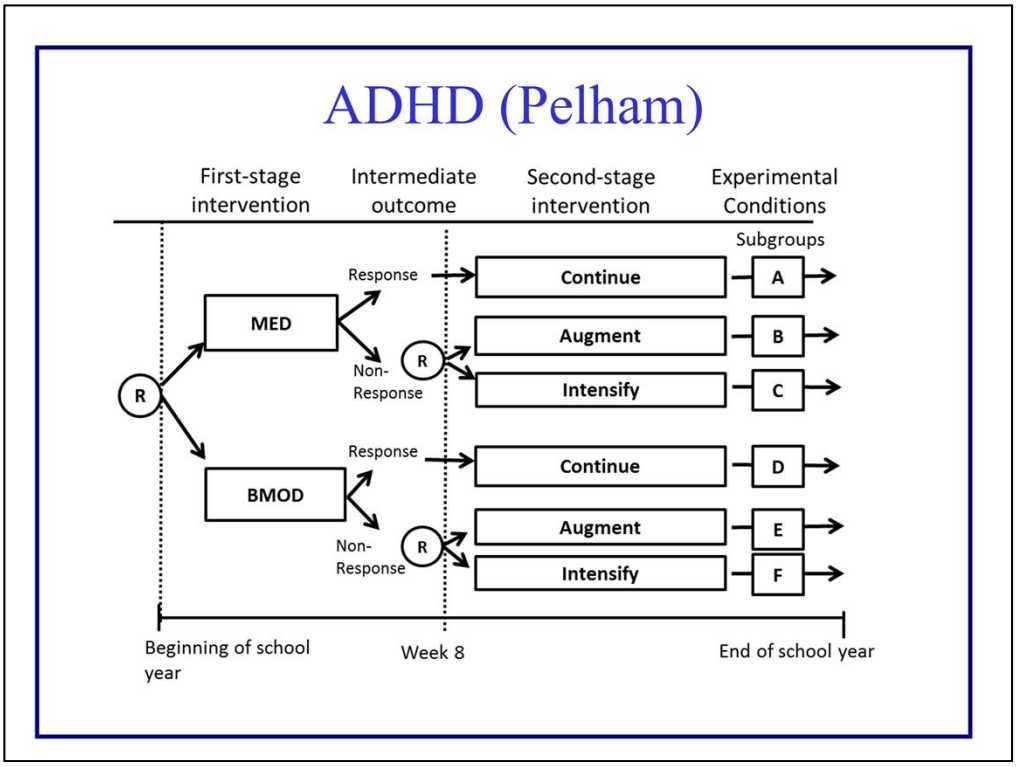

MED is Ritalin.

BMOD is behavioral modification, itself a multi-component behavioral intervention.

The interventions include differing doses of MED methylphenidate (a psychostimulant drug) and differing intensities of behavioral modification BMOD (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).

Intensified MED: The higher-dose option for methylphenidate includes late-afternoon doses, if needed.

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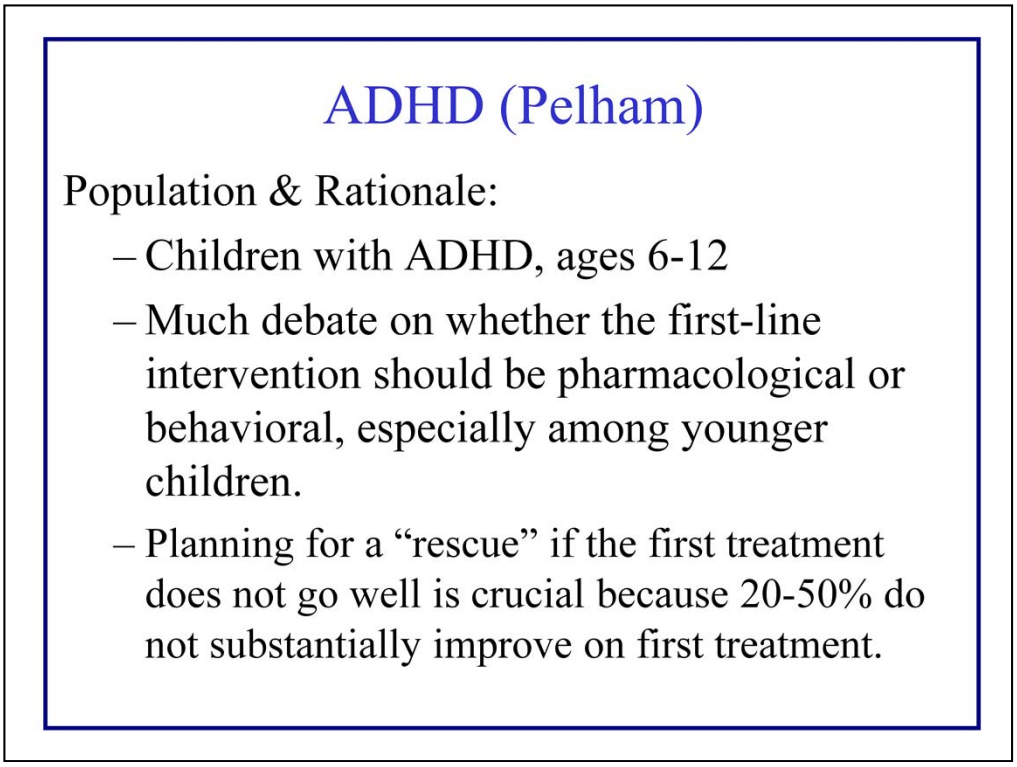
> (1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND
> (2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

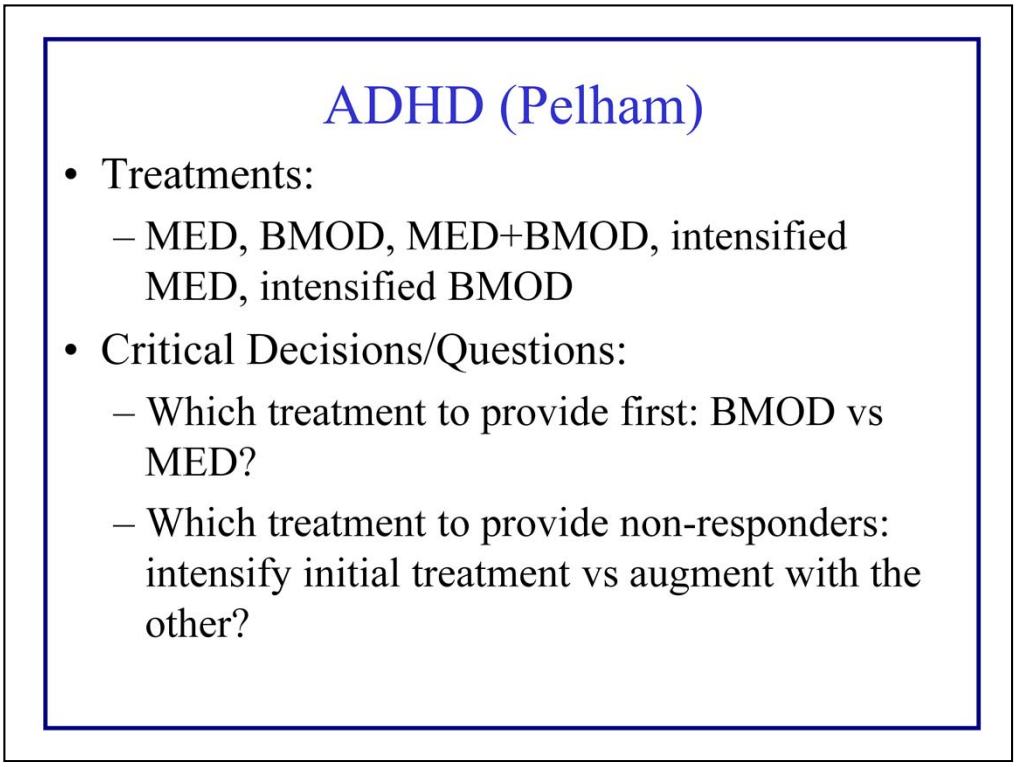
N=153

Primary outcome is measure of child behavior at 8 months, end of school year.

Sized for the primary comparison of initial treatments (MED vs. BMOD). That is, sized for the main effect of initial treatment.



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.



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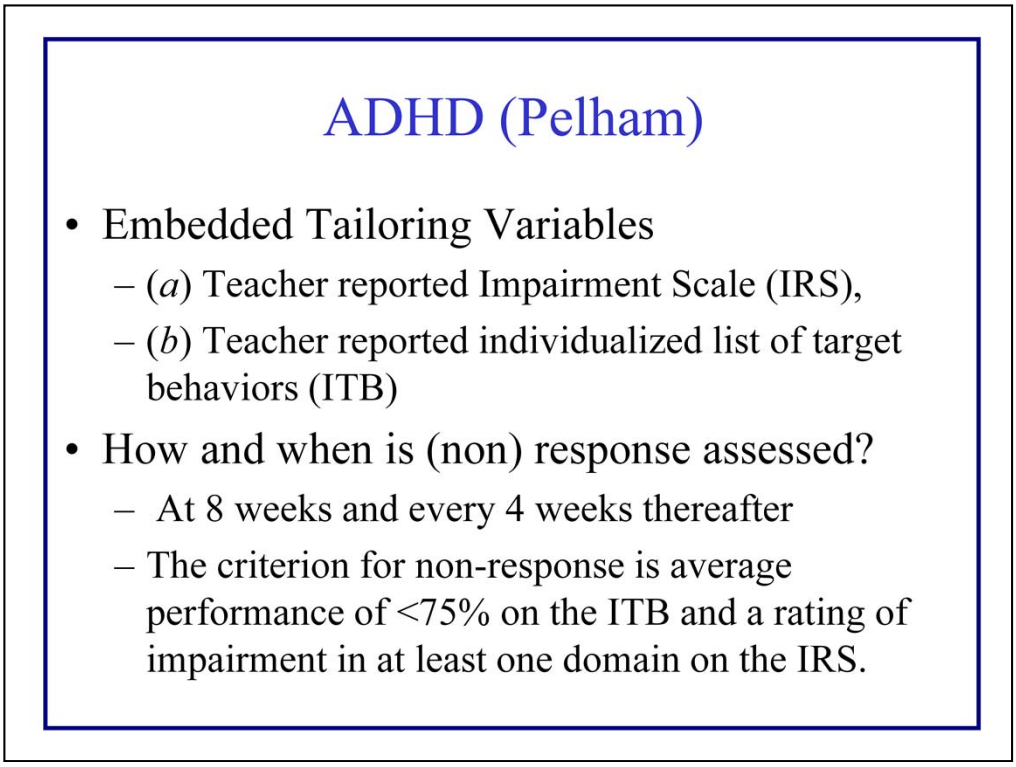
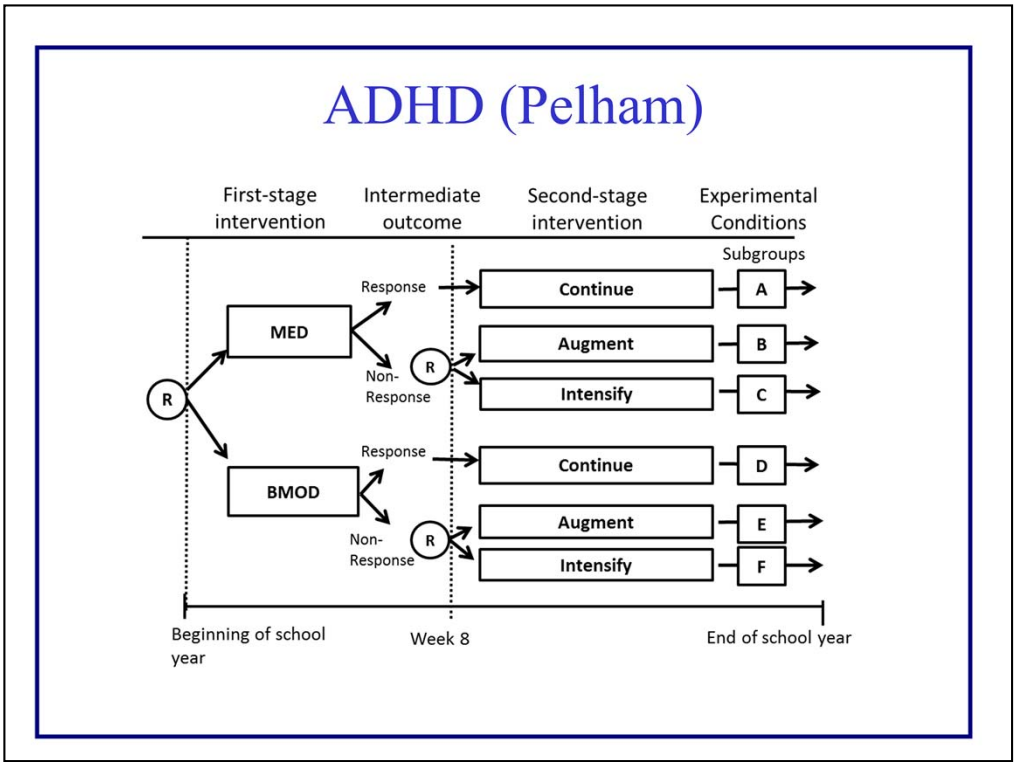


The Impairment Rating Scale (IRS) (Fabiano et al. 2006) and an individualized list of target behaviors (ITB) (e.g., Pelham et al. 1992). The IRS provides a comprehensive index of a child's impairment in various domains such as peer relationships, classroom behavior, family functioning, and academic achievement. 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



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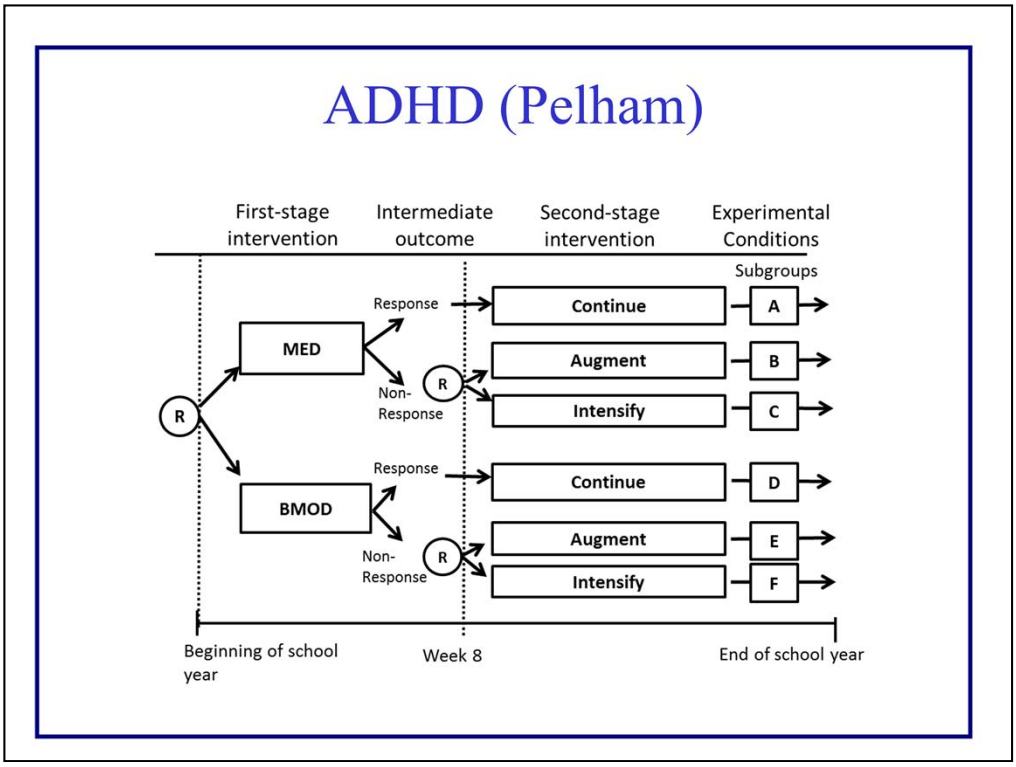
ADHD (Pelham)

4 Embedded Adaptive Interventions

1) Start with BMOD; if non-responder intensify BMOD, else continue BMOD
2) Start with BMOD; if non-responder BMOD +MED, else continue BMOD
3) Start with low-dose MED; if non-responder Intensify MED, else continue low-dose Med
4) Start with low-dose MED; if non-responder BMOD+MED, else continue low-dose Med.

You can also conceptualize the second-stage treatments in these embedded adaptive interventions as tactics rather than treatments.



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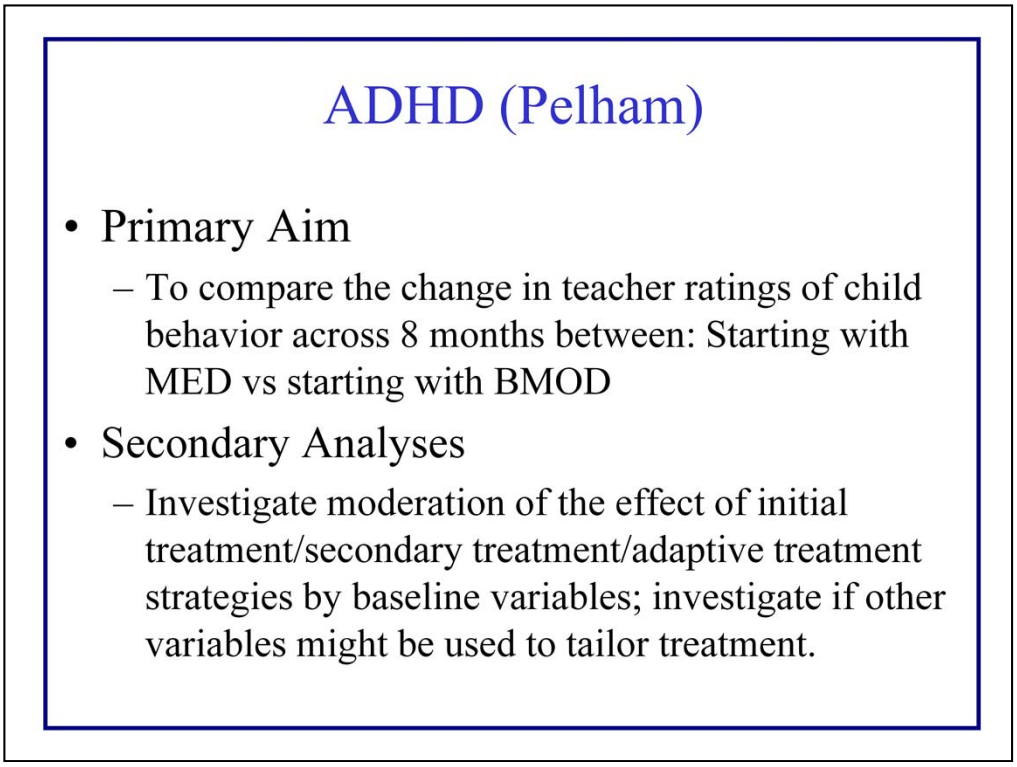
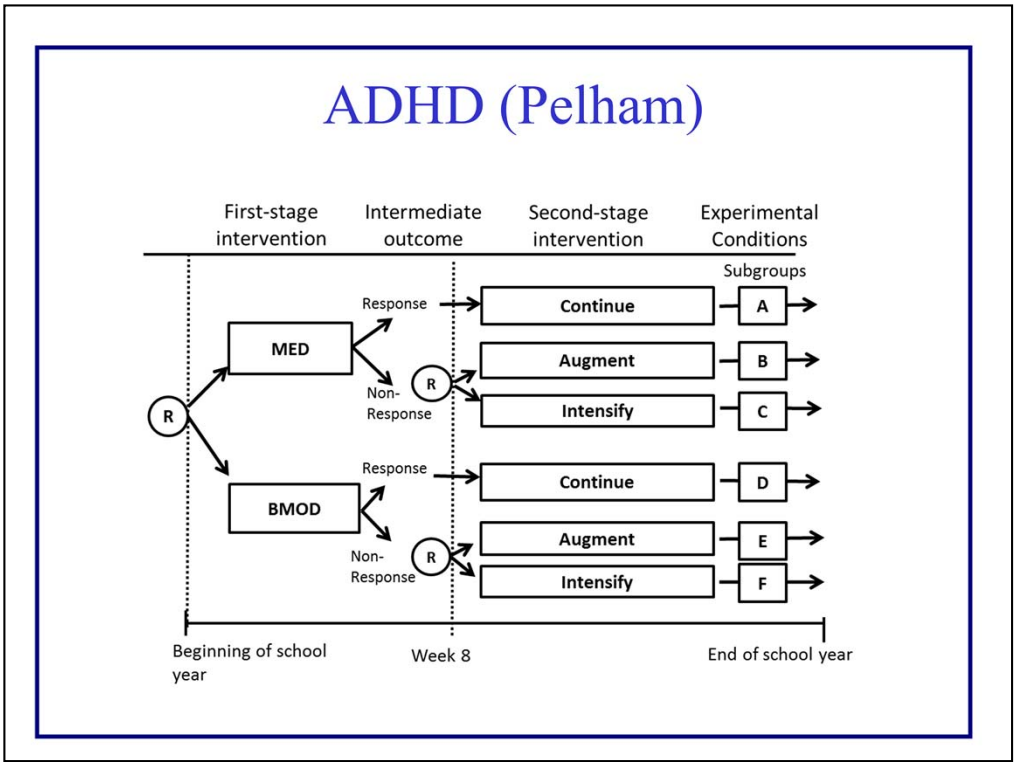


Potential baseline moderator was whether the child had received medication for ADHD in prior year.



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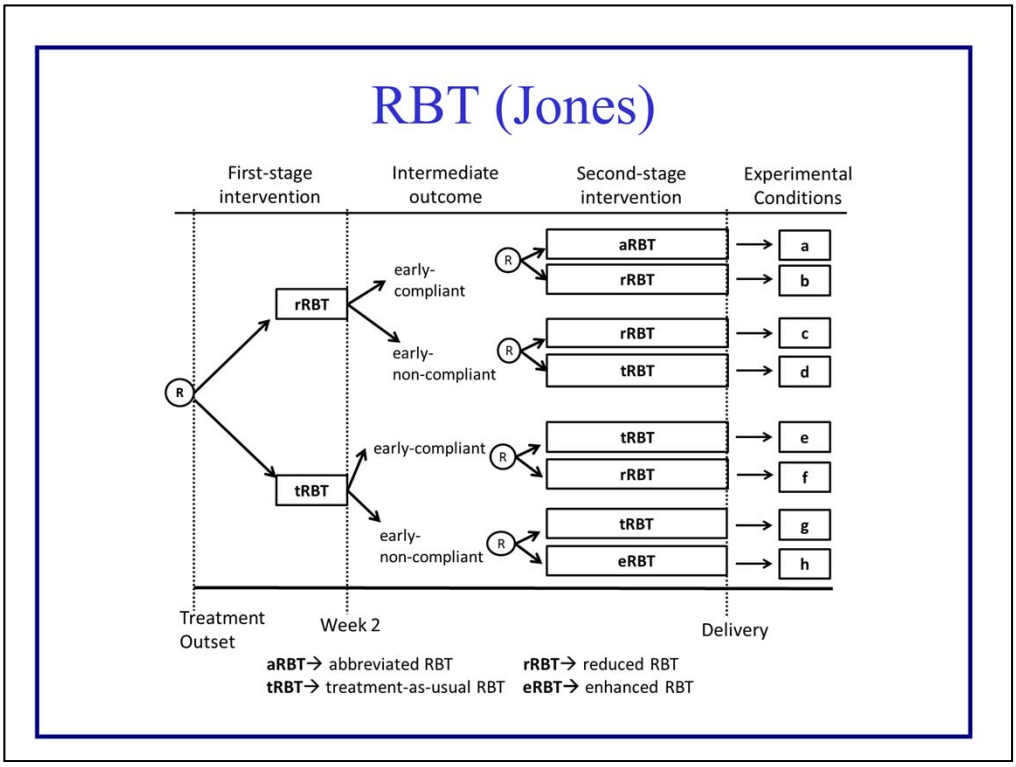
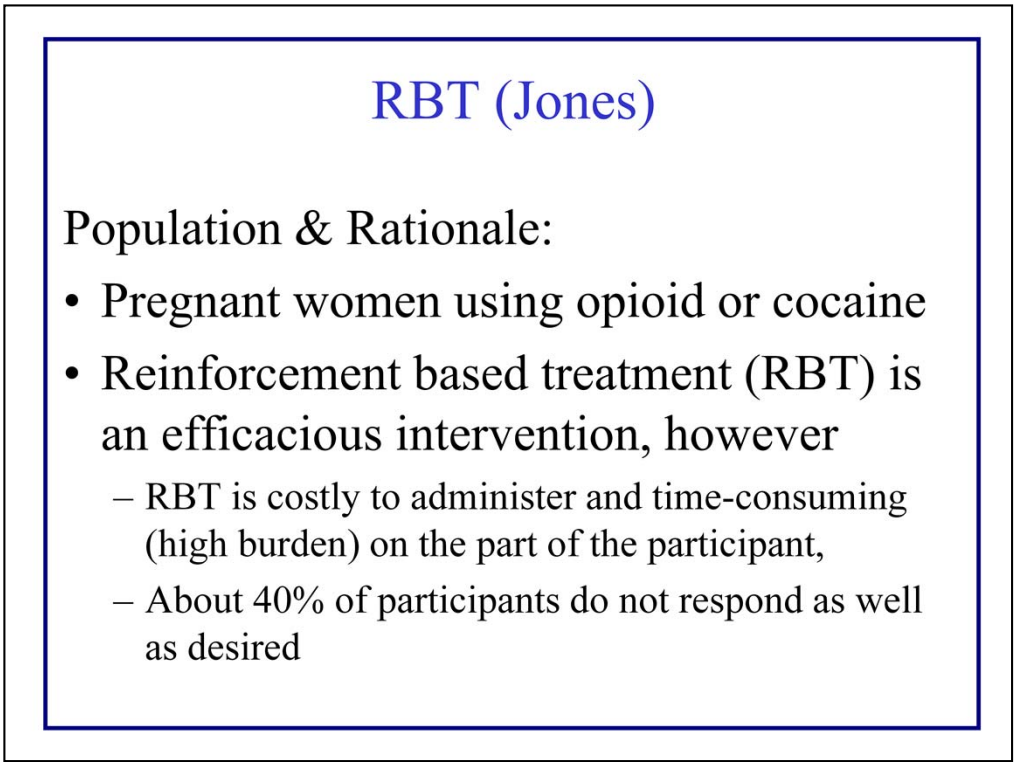


N=300 drug-abusing pregnant women

Outcomes included treatment completion through to the end of pregnancy (primary), repeated weekly and bi-weekly assessments of drug-use and session attendance

Early non-compliance: a missed unexcused treatment day, a positive opioid or cocaine urine specimen, or self-reported drug use.

Sized to detect a difference between rRBT throughput and tRBT throughout.



The women must have first completed a eight-day residential detoxification stay.

Inner-city Baltimore.

RBT (Jones)

Critical Questions:

- (a) whether the traditional 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.

RBT (Jones)

- Treatments:
  - aRBT < rRBT < tRBT < eRBT (increasing order in intensity/scope or RBT)
- Embedded Tailoring Variables:
  - a) self-reported drug use,
  - b) results of urine tests, and
  - c) attendance on intervention days

aRBT = abbreviated RBT

rRBT = reduced RBT

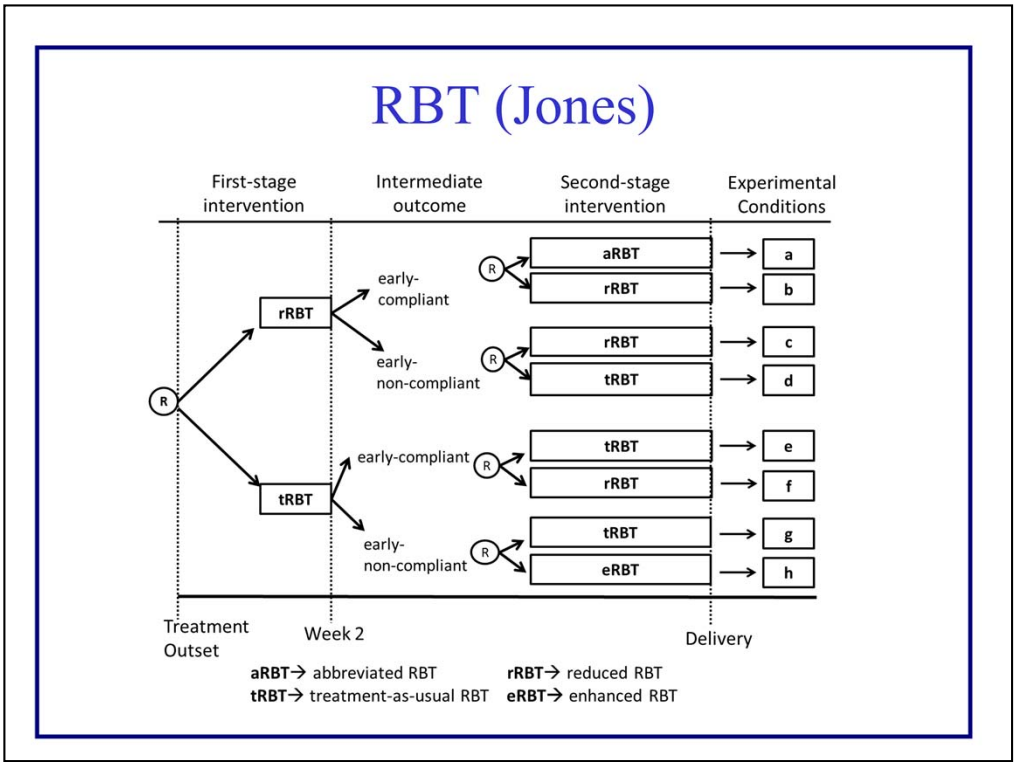
tRBT = traditional RBT (or treatment as usual RBT)

eRBT = enhanced RBT

RBT (Jones)

- How and when is non-compliance assessed at week 2?
- The criterion for non-compliance is
  - missing an intervention day with no excuse, or
  - a positive opioid or cocaine urine specimen, or
  - self-report use of either drug.
- It is a combination of non-compliance and non-response

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



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RBT (Jones)

8 Embedded Interventions (6 are Adaptive)

1) Always tRBT (not adaptive)
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

RBT (Jones)

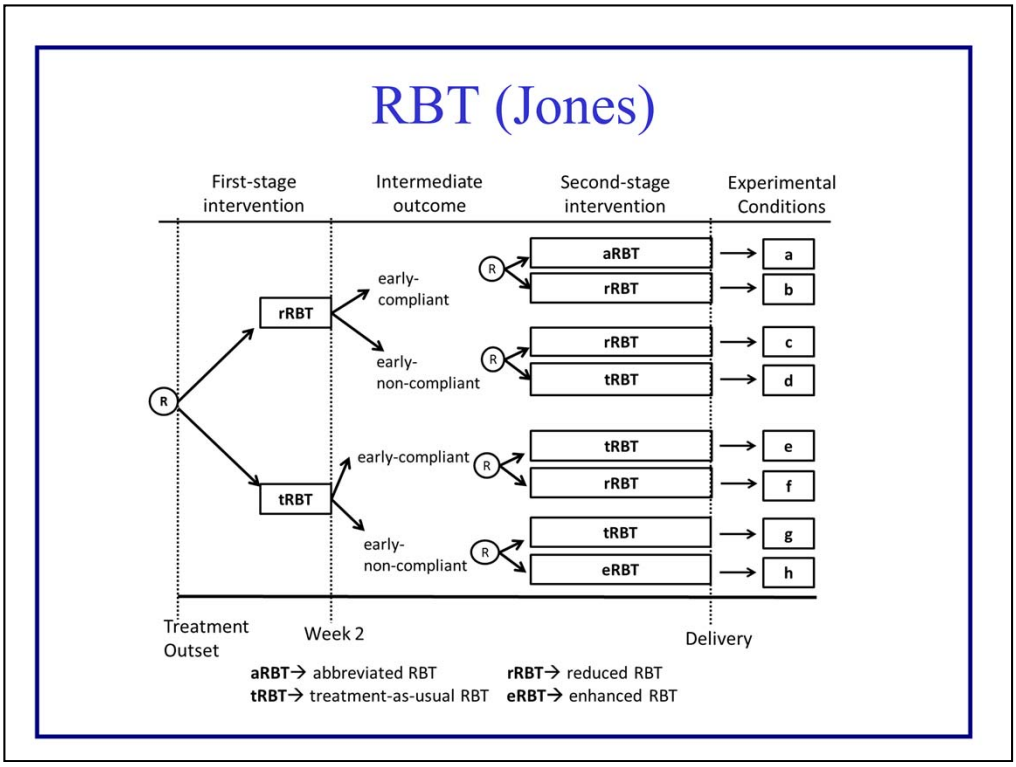
8 Embedded Interventions (6 are Adaptive)

5) Always rRBT (not adaptive)
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

RBT (Jones)

- Primary Aim
  - To compare program completion (delivery of child while in treatment) of the always tRBT arm versus the always rRBT arm (two non-adaptive interventions!)
- Secondary Aim
  - 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).



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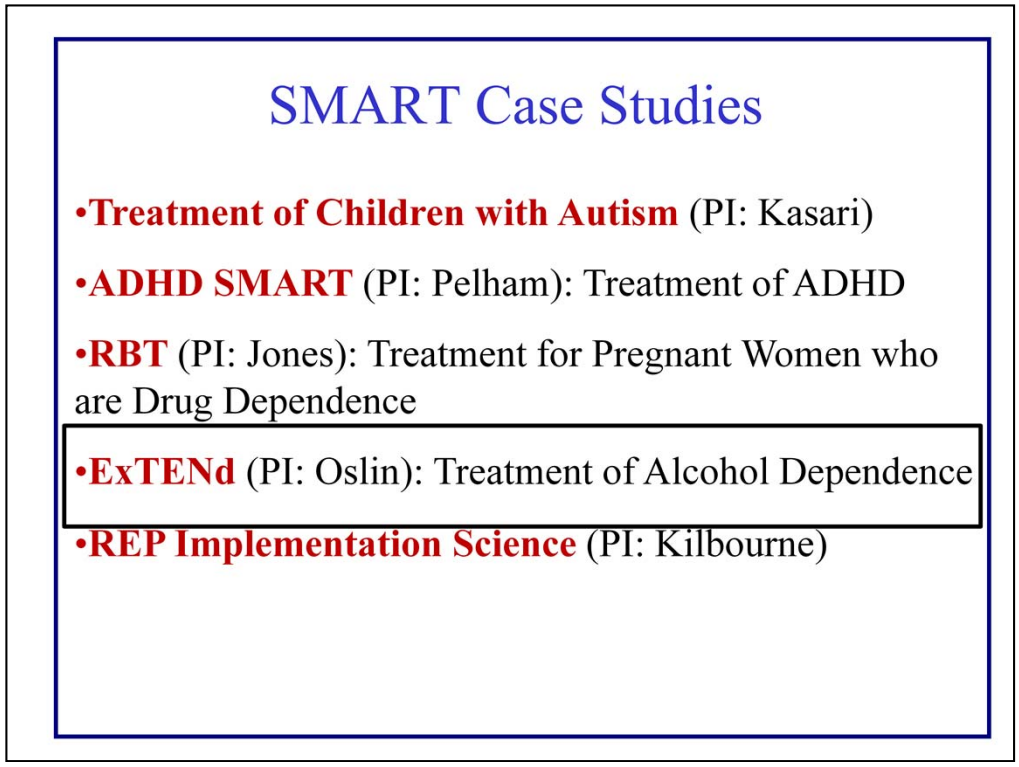

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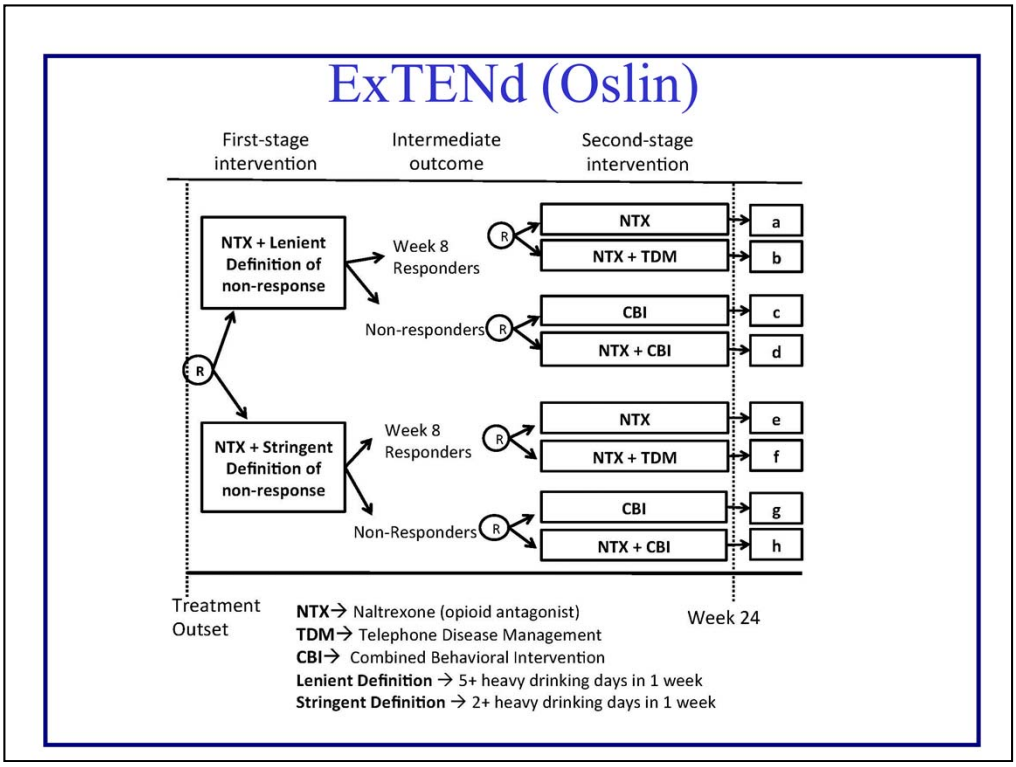


Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist (that blocks the euphoric effects of drinking) then in ensuing two months are monitored for heavy drinking

N=302

Study was sized to detect the contrast between two alternatives for non-responders: CBI vs CBI + Naltrexone

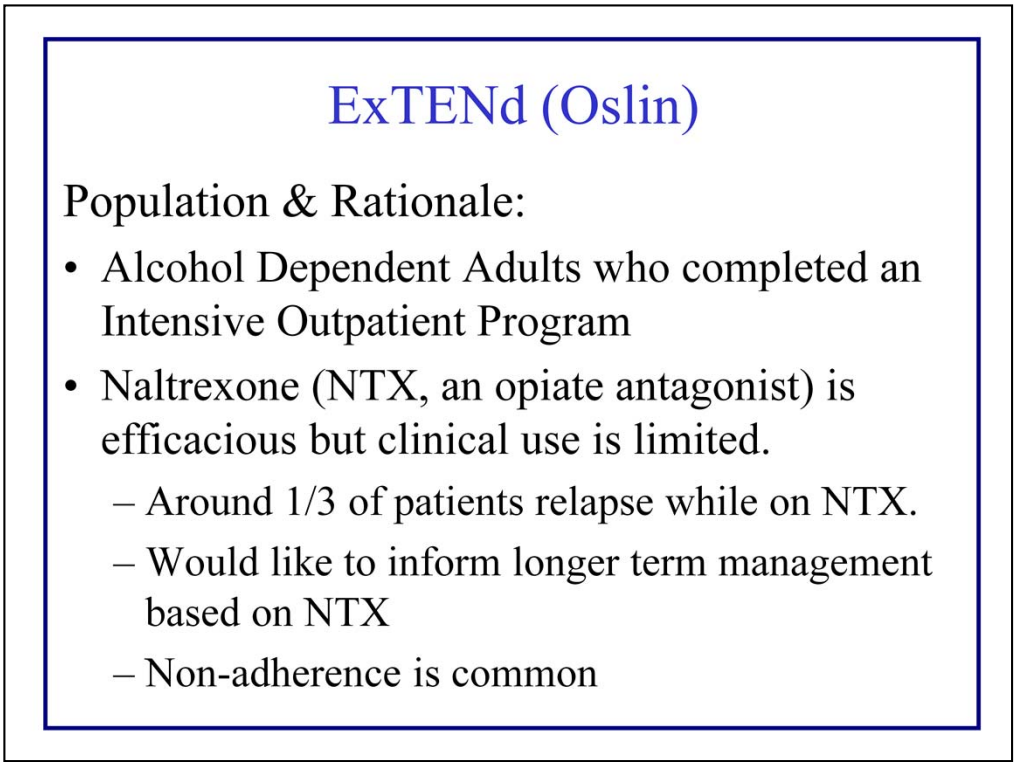
Primary outcome (drinking behavior from the TLFB)

TDM: Telephone Disease Management: phone-based basic, minimal clinical support for the use of effective pharmacotherapy and reduction in drinking.

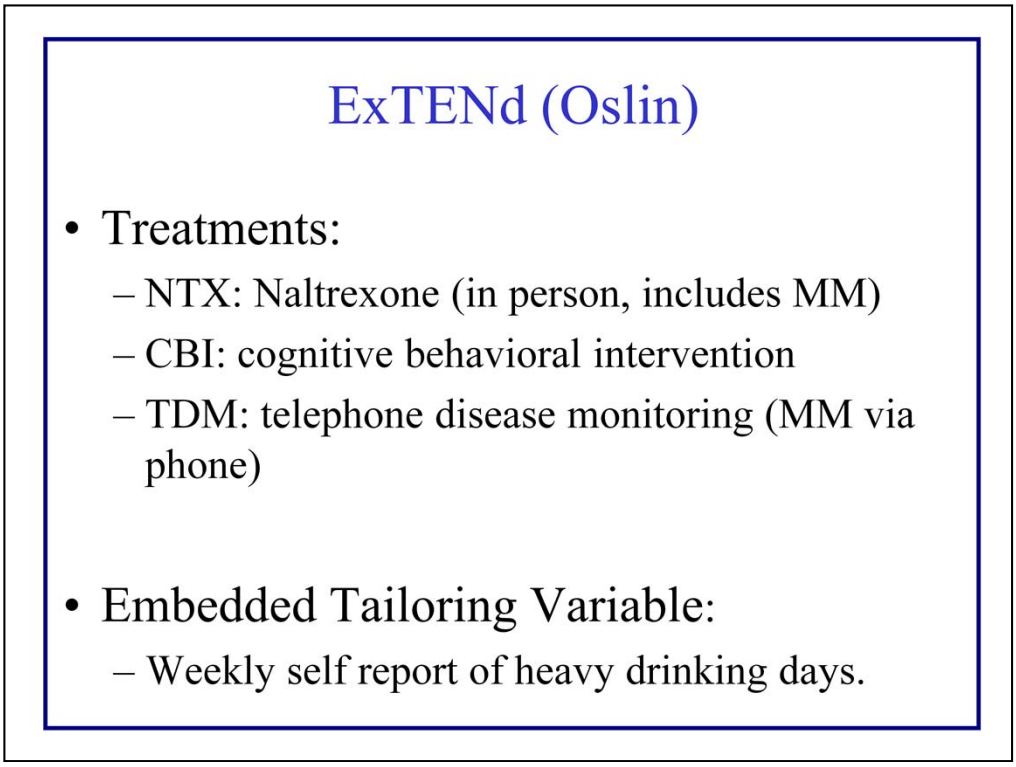
MM is a face-to-face, basic, minimal clinical support for the use of effective pharmacotherapy and reduction in drinking (Pettinati et al. 2004, 2005).

CBI: multicomponent intervention that includes components targeting adherence and motivation for change + family/community involvement when possible. It 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)



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.



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).

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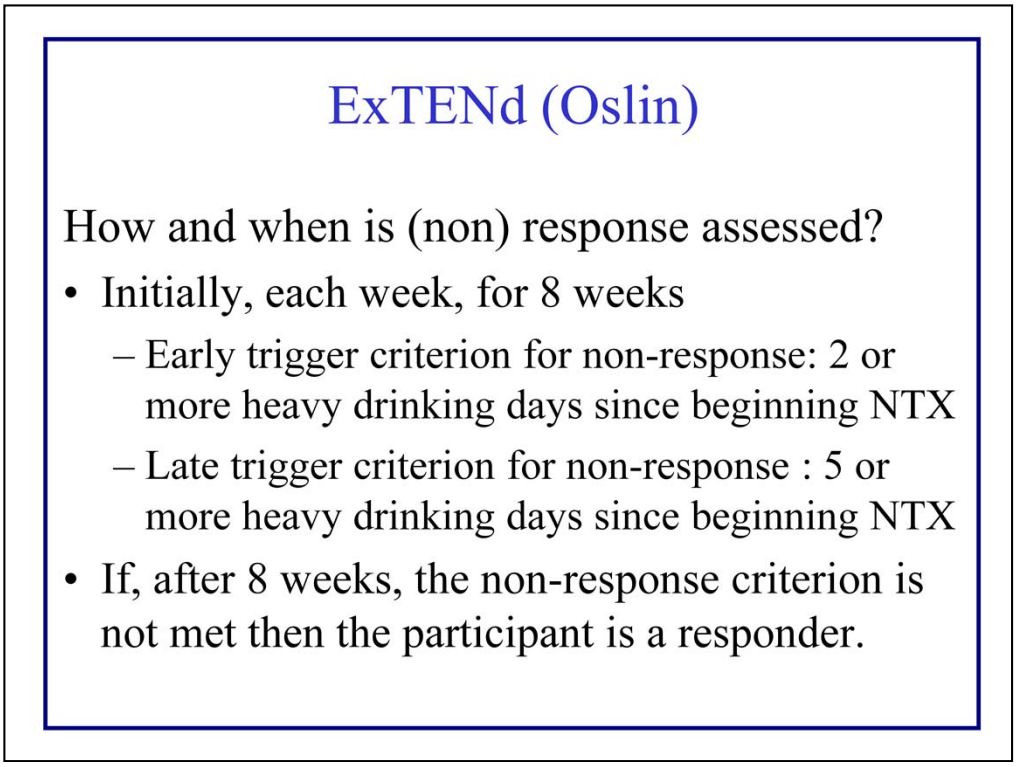
ExTENd (Oslin)

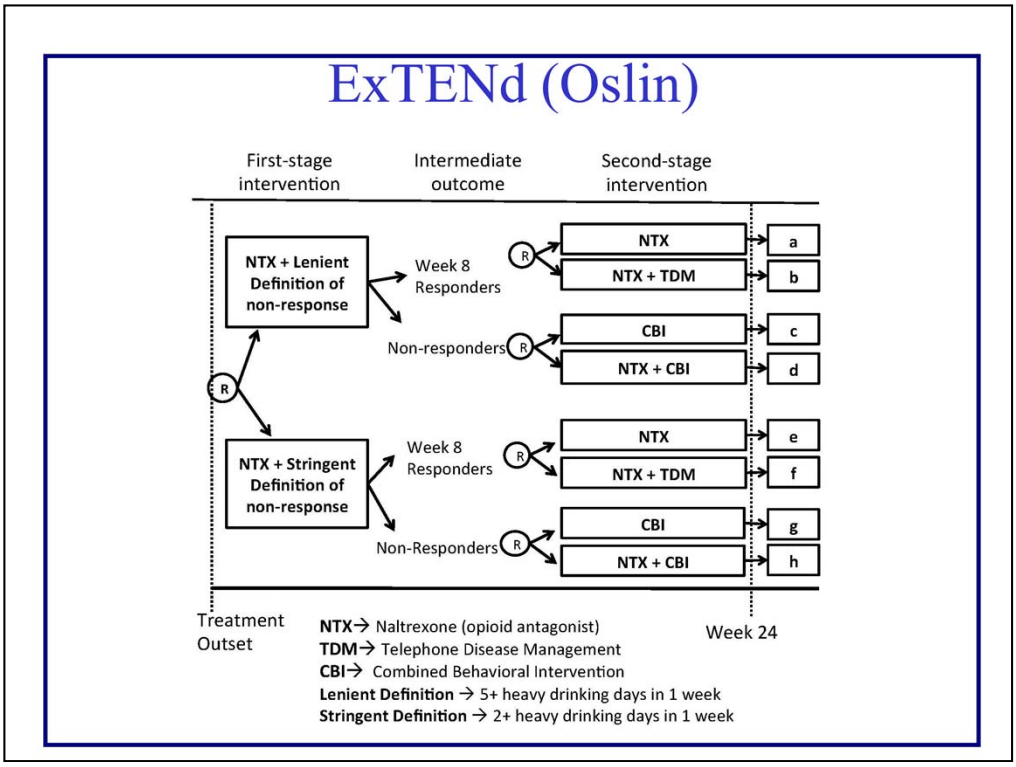
Critical Questions:

- (a) What extent of drinking behavior best reflects non-response to NTX?
- (*b*) What type of treatment would be useful among participants who do not respond adequately to NTX?
- (*c*) What type of treatment would be useful among participants who respond adequately to NTX?



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.



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N=302

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Heavy drinking days (≥5 drinks/day for males; ≥4 for females)

ExTENd (Oslin)

8 Embedded Adaptive Interventions

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

HDD: heavy drinking days ($\geq$5 drinks/day for males; $\geq$4 for females)

ExTENd (Oslin)

8 Embedded Adaptive Interventions

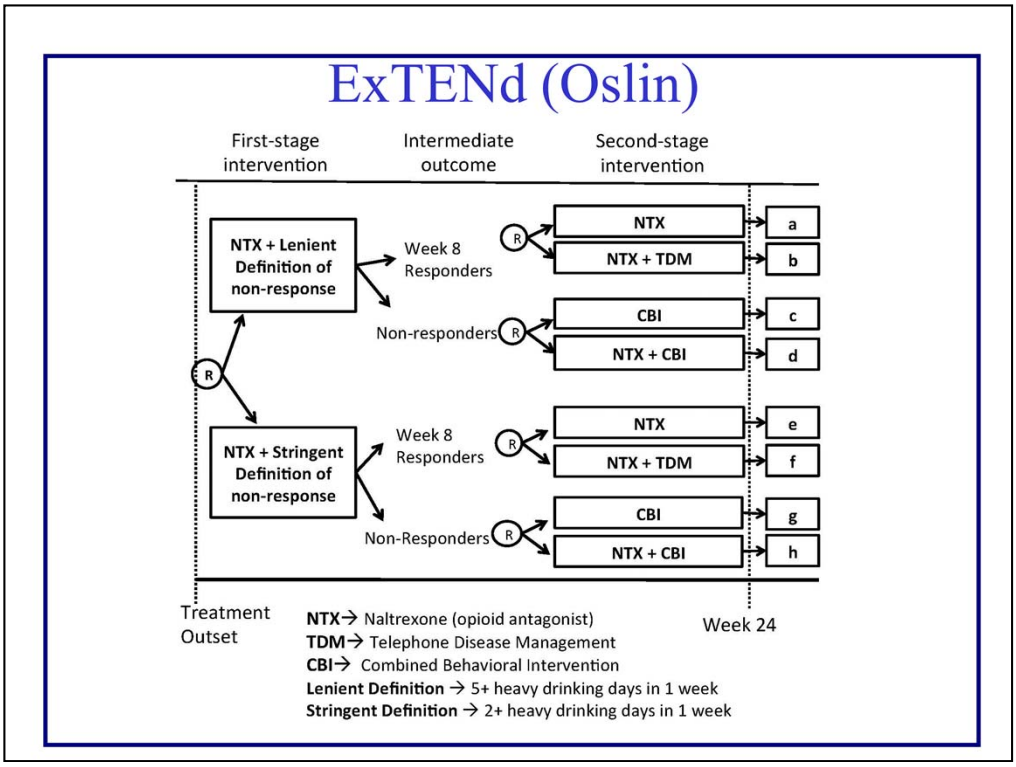
4) Start with NTX; if 2 HDD occurs prior to 8 weeks, switch to CBI, else at 8 weeks continue on NTX+TDM
5) …if 5 HDD then CBI+NTX; else NTX…
6) …if 5 HDD then CBI; else NTX…
7) …if 5 HDD then CBI+NTX; else NTX+TDM…
8) …if 5 HDD then CBI; else NTX+TDM…

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

ExTENd (Oslin)

- Primary Aim
  - Focus is on non-responders to NTX
  - Compare percent days abstinent on CBI+NTX versus to CBI alone.
- Secondary Aim
  - 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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SMART Case Studies

- **Treatment of Children with Autism** (PI: Kasari)
- **ADHD SMART** (PI: Pelham): Treatment of ADHD
- **RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependence
- **ExTENd** (PI: Oslin): Treatment of Alcohol Dependence
- **REP Implementation Science** (PI: Kilbourne)

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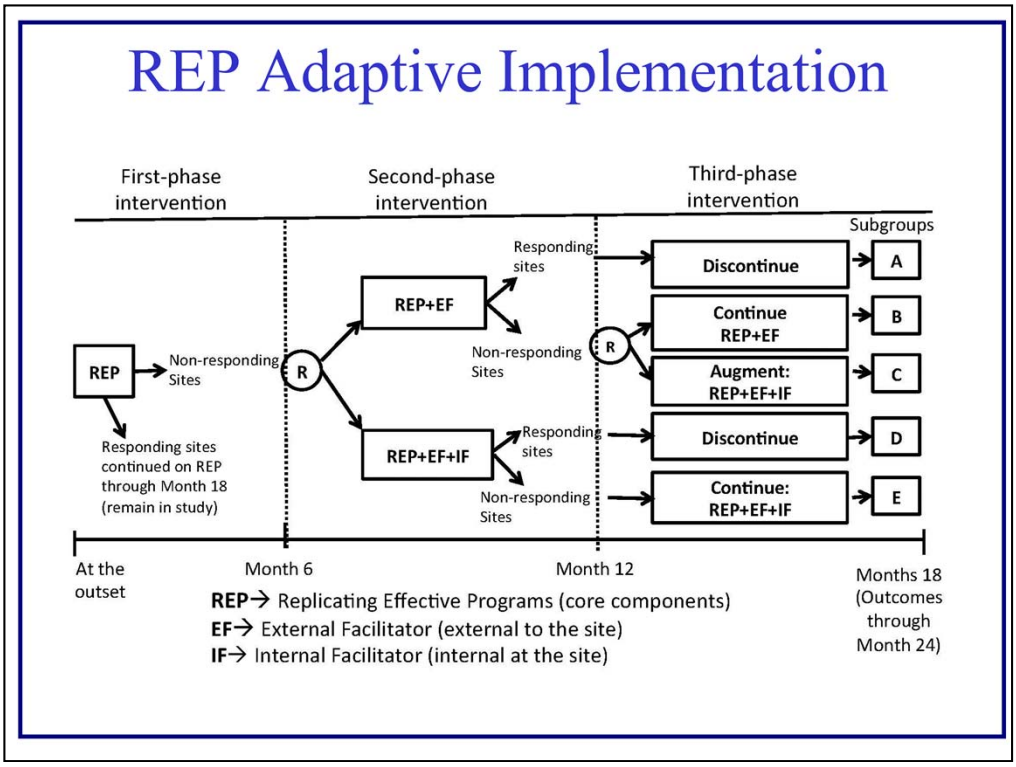


Total sites in first-phase: k=80. (Expect k=60 to not-respond at month 6.)

Total sites in second-phase: k=60

Patients per site: n=20

Total patients: N=1200

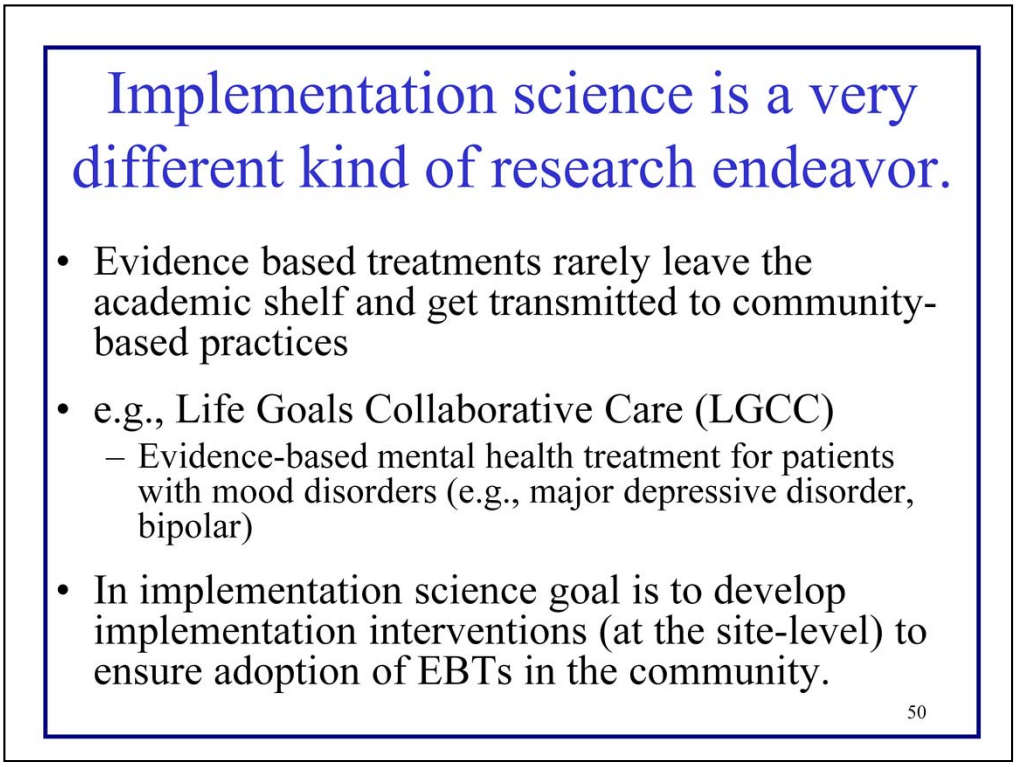
Non-responsive site: <10 patients receiving LG and the enrolled patients (<10) received <75% group sessions

The treatment they are trying to implement at sites is called Life Goals, a collaborative care model for improving outcomes in patients with mood disorders.

REP: Disseminate LG package, identify patients for LG, train site providers in LG, monitor LG and provide feedback via monthly report sheets.

REP+EF: External Facilitators (EFs) are part of the study team and reside outside the clinic and provide technical expertise to providers in adapting EBPs to address organizational and financial barriers. The EF's core functions through the technical assistance calls include dissemination of additional information and materials on LG implementation based on site-specific needs. The EFs will initially contact the LG provider and set measurable objectives in implementing LG (e.g., number of patients completing at least one group session), and review progress based on these measures via monthly calls for six months. Monthly calls will last one hour and primarily include discussion of barriers to LG implementation.

REP+EF/IF: In contrast to EFs, Internal Facilitators (IFs) reside within each site and have an internal working knowledge of the site. In contrast to the site LG provider ("champion") IFs act as third parties and are responsible for enhancing the uptake of LG, notably by incorporating input to support the adoption of the EBP from frontline providers and aligning the EBP with organizational priorities via a direct reporting line with leadership. Using their knowledge of the local site's culture and needs, the IFs will identify the site's priorities, align the goals of implementing LG with these priorities, and identify other provider champions to assist in implementing LG. About $5500 in costs.



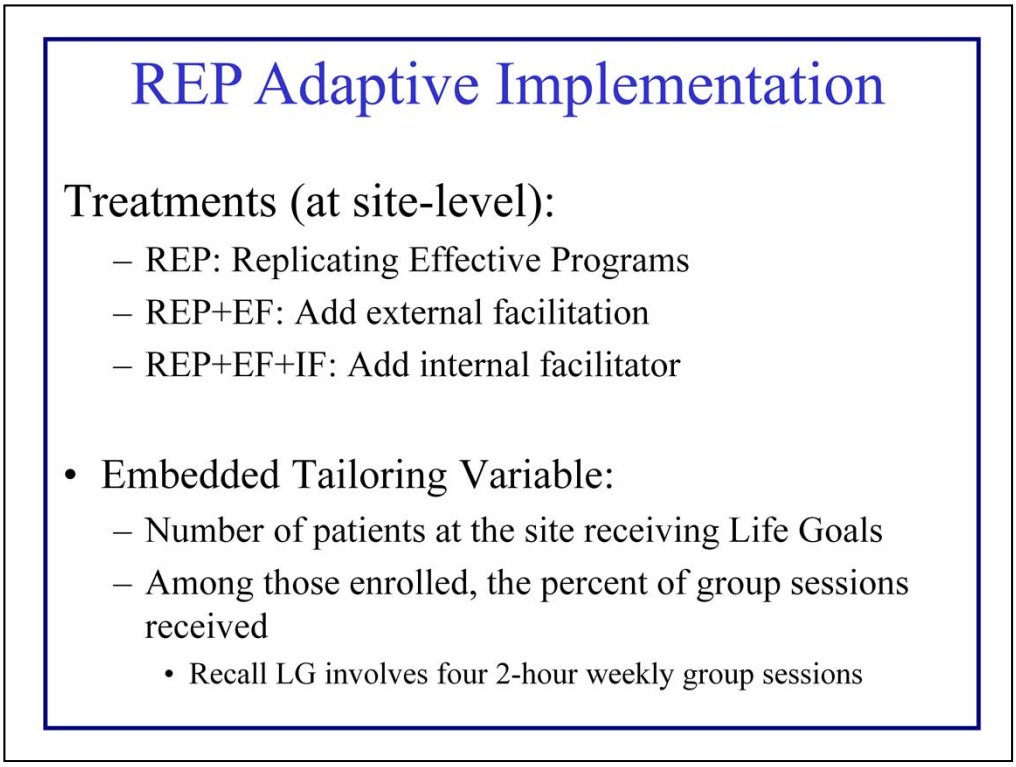
As described by Professor Amy Kilbourne, PhD, Univ of Michigan:

LG is an evidence-based psychosocial treatment based on the collaborative care model that has been shown in six randomized controlled trials across mental health and primary care settings to improve medical and psychiatric outcomes in patients with mood disorders (including bipolar disorder or depression). LG was also cited as an EBP in a recent meta-analysis and systematic review of collaborative care models. LG is based on social cognitive theory and delivered in four two-hour weekly group sessions and at least six tailored care management contacts that encourage active discussions focused on individuals' personal goals that are aligned with healthy behavior change and symptom management strategies.

REP Adaptive Implementation

Population & Rationale:

- Research-to-practice gap in psychosocial EBTs such as Life Goals (LG). Organizational barriers!
- Implementation interventions exist to improve adoption of EBTs; however, approximately 75% sites do not adopting EBTs by month 6
- Goal is to develop an adaptive implementation intervention to improve adoption of LG at 80 small, low-resourced, community-based sites/practices across CO, AR, MI



Recall LG involves four two-hour weekly group sessions and at least six tailored care management contacts

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REP Adaptive Implementation

Critical questions:

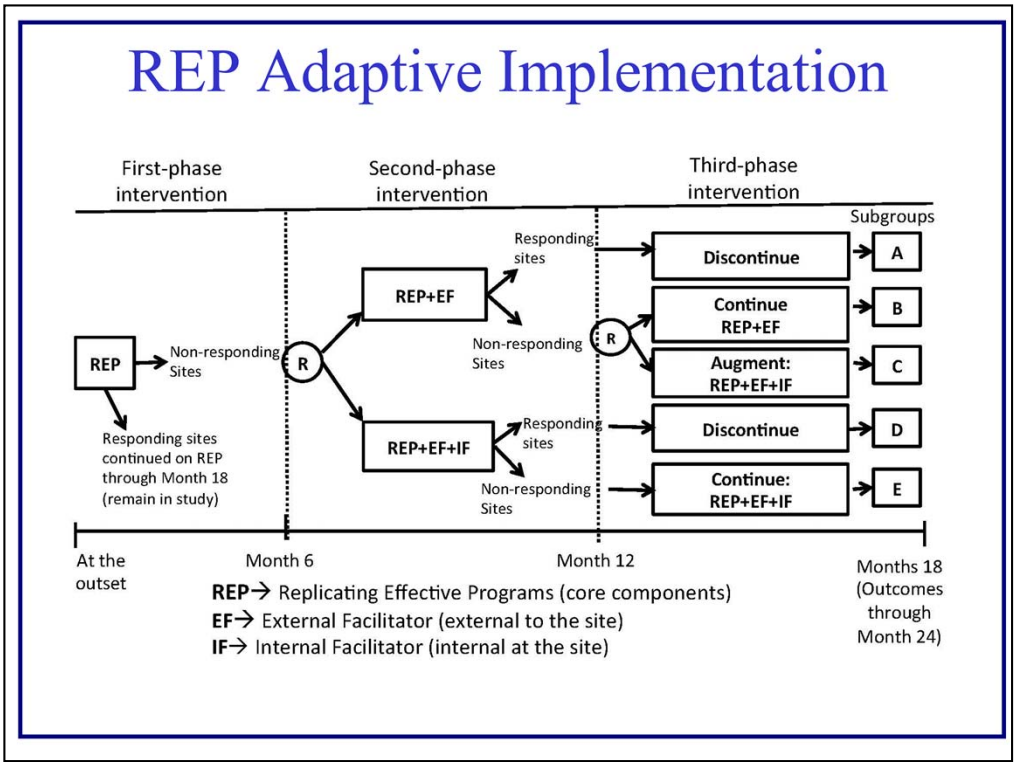
- Among sites not-responsive to REP at month 6, do we augment with REP+EF vs REP+EF+IF?
- Among sites not-responsive to REP+EF at month 12, do we augment with REP+EF+IF or continue?

REP Adaptive Implementation

How and when is non-response defined? A site/practice is non-responsive if

- <10 of the identified patients at the site receiving LG within 6 months, and
- Enrolled patients received <75% of group sessions
  - Recall LG involves four 2-hour weekly group sessions

- May appears to be a low bar; however, based on prior data 75% sites do not meet this criteria!
  - And those that do not meet at month 6, are highly likely not to meet it even 6 additional months later



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REP Adaptive Implementation

3 embedded adaptive implementation interven.

All begin with REP; if respond, continue REP for 12mo; else if non-responsive at 6mo…

1. REP+EF for 6mo; if response at 12mo, discontinue; else, continue REP+EF
2. REP+EF for 6mo; if response at 12mo, discontinue; else, continue REP+EF+IF
3. REP+EF+IF for 6mo; if response at 12mo, discontinue; else, continue REP+EF+IF

REP Adaptive Implementation

- Aims focus on non-responders to 6mo REP
- Primary Aim
  - Compare MH-QOL (primary), functioning, psychiatric sx, #LG encounters (secondary) between sites REP+EF vs REP+EF+IF.
- Secondary Aim
  - Compare REP+EF vs REP+EF+IF among sites still not responding at 12mo
  - Cost-effectiveness comparison of 3 embedded adaptive interventions

Note the primary aim. Quite different from other case studies.

Quickly Compare the Five SMART Case Studies

We will compare along these 4 dimensions:

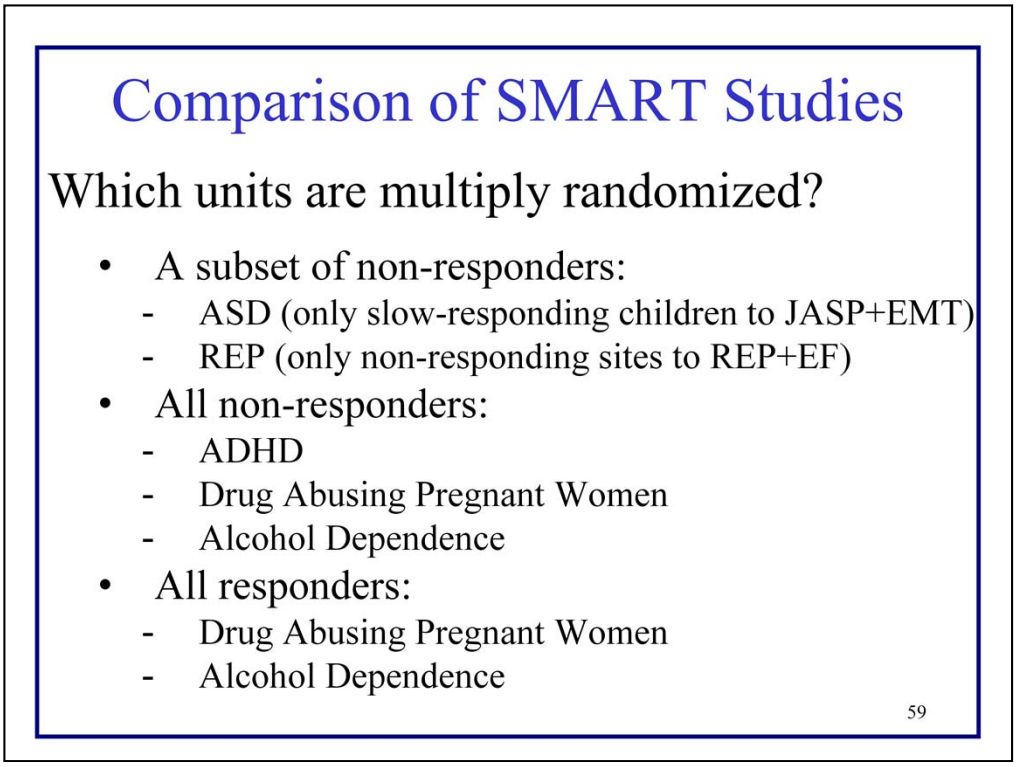
1) Which units are multiply randomized?

1) When does the re-randomization occur?

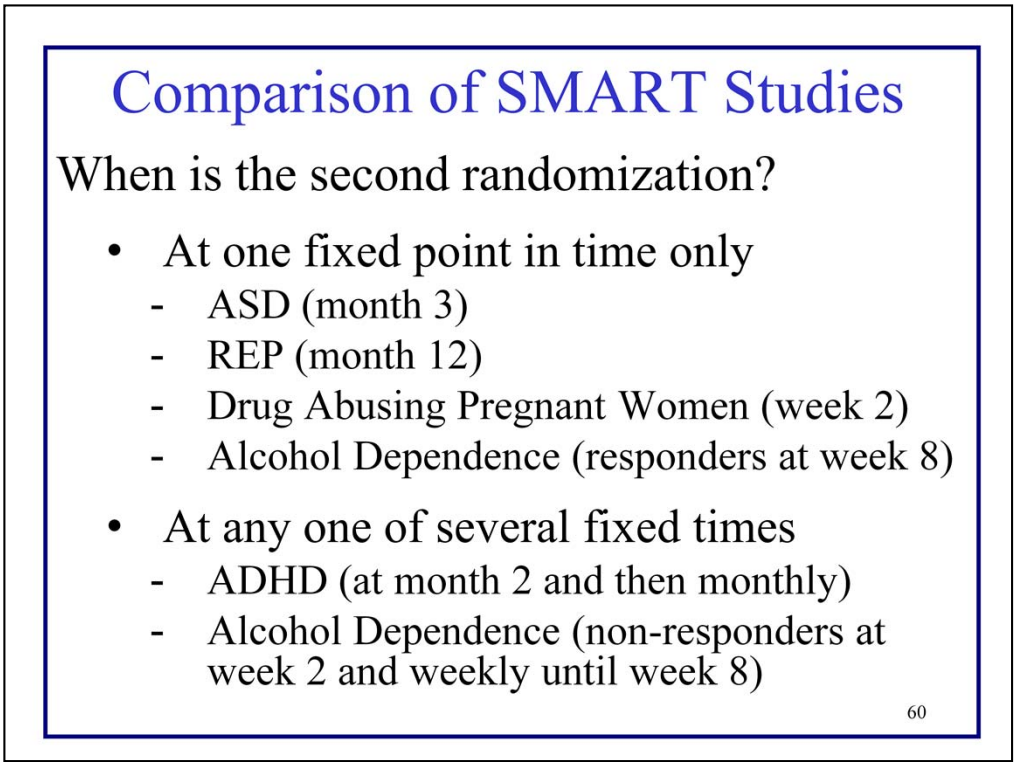
2) Types of the critical questions

3) Primary aims (=> study sizing)

58



The larger the number of categories of people re-randomized, the larger the number of embedded adaptive treatment strategies.



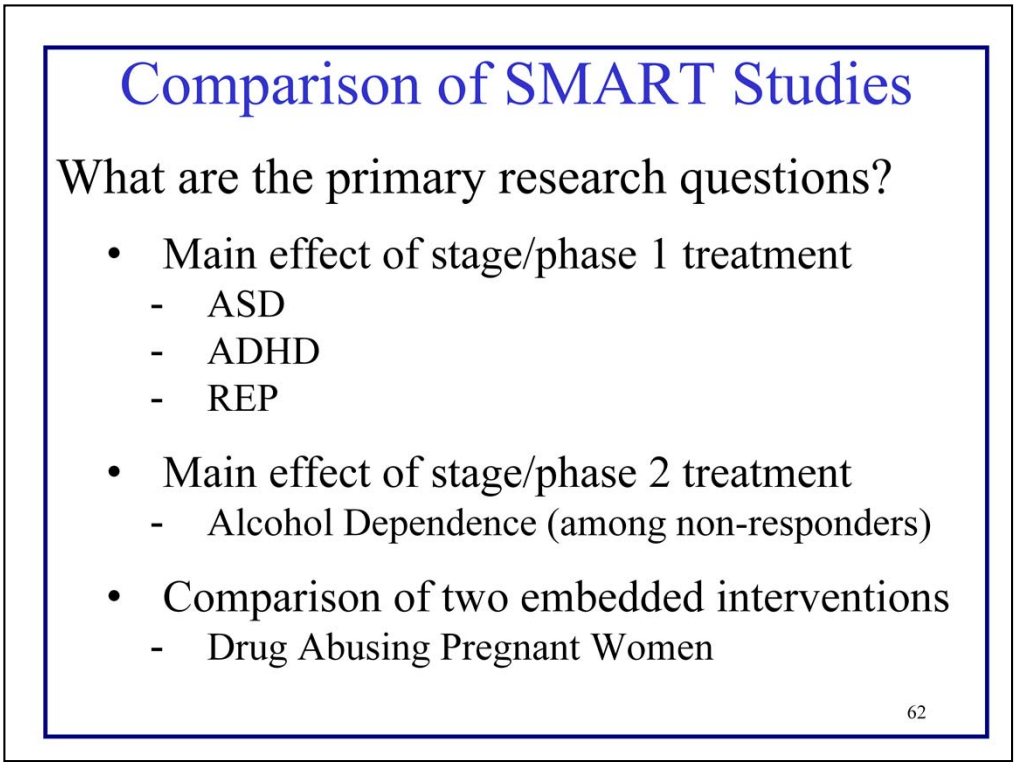
Also in both the ADHD and the Alcohol Dependence SMARTS as soon as non-response detected, the participant is re-randomized.

Comparison of SMART Studies

What kinds of critical questions?

- 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 next?
  - Alcohol Dependence
- Which treatment second and which third?
  - REP

61



These are the comparisons that are used to size the SMART

Primary Reference

H. Lei, I. Nahum-Shani, K. Lynch, D. Oslin and S.A. Murphy. A SMART Design for Building Individualized Treatment Sequences, *The Annual Review of Clinical Psychology (2012),* Vol. 8: 21-48

Practicum

(a)Review your critical questions once more

(b)Sketch/revise a SMART design to address these critical questions.

(b) Outline/sketch the argument/rationale for your SMART design.