# Discussion

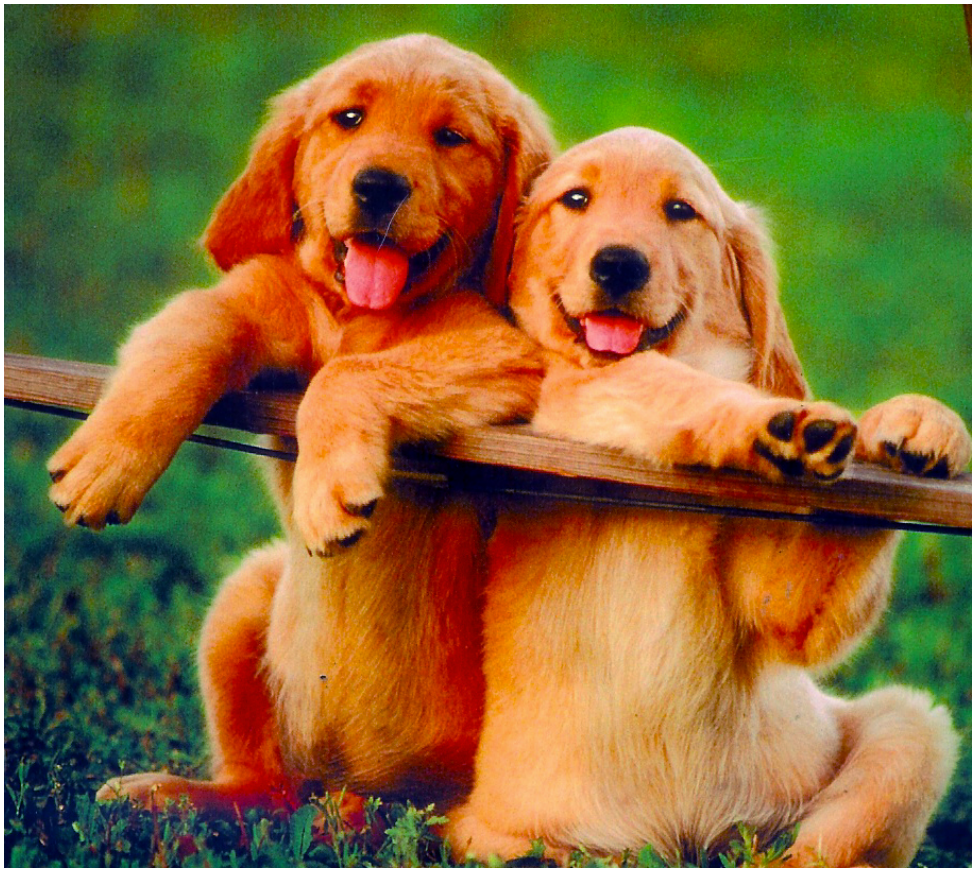
Peter Thall
Department of Biostatistics
M.D. Anderson Cancer Center

*Workshop P6: Clinical Trials for Adaptive Intervention Designs: Design and Conduct of Sequential Multiple Assignment Randomized Trials*

*Society for Clinical Trials, Annual Meeting*
*Philadelphia, PA*
*Sunday, May 18, 2014*

# Disclaimer

No cute puppies were harmed in preparing this discussion.



# OPINIONS

## The two main reasons to do SMARTs

1. They reflect actual medical practice: a multi-stage outcome-adaptive process, or "dynamic treatment regime" (DTR).
2. If you want data for unbiased comparisons, randomize.

Together, these imply **the scientific ideal is to be SMART**

→ account for multiple stages of therapy

→ randomize at each stage, if it is ethical/practical

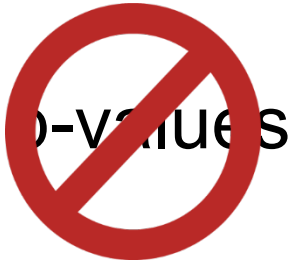
## Important Caveats

1. Actual implementation is hard!
2. Only viable DTRs should be included, not mathematical fantasies that a physician would never use.

Randy Millikan: "The future is combinations and sequences."

## Actual Goals of SMARTs

1. Estimate overall outcome means (expected survival or DFS in oncology, probability of, or mean time to, disease worsening in a study to treat alcoholism, schizophrenia, etc.) for all DTRs in an unbiased fashion. Then rank and select.
2. Use the estimates and ranks to refine the DTRs, or possibly modify physician/professional behavior
3. Don't try to test hypotheses. There are usually far too many DTRs, and hypothesis testing is silly anyway.

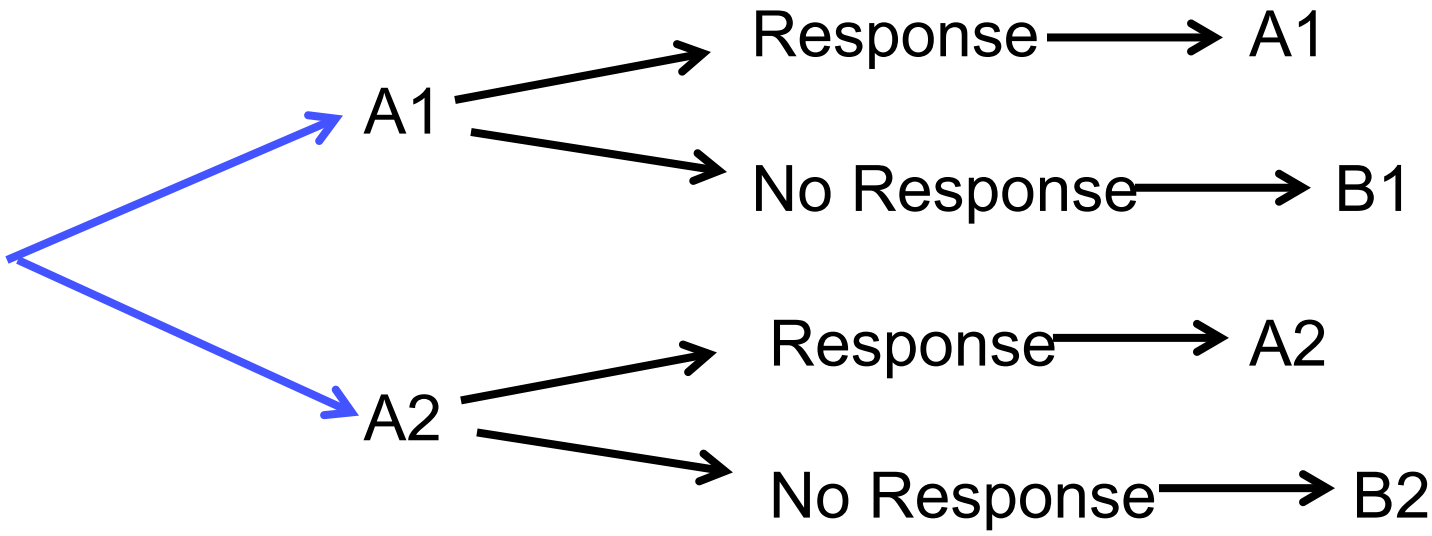



Data Analysis:

Things almost never go as designed (dropouts, missed appointments, deviation from study design, etc.) →

Methods for analyzing observational data typically are needed - IPTW, G-estimation, matching, imputation, etc.

Identifying the DTRs (blue → for randomization)



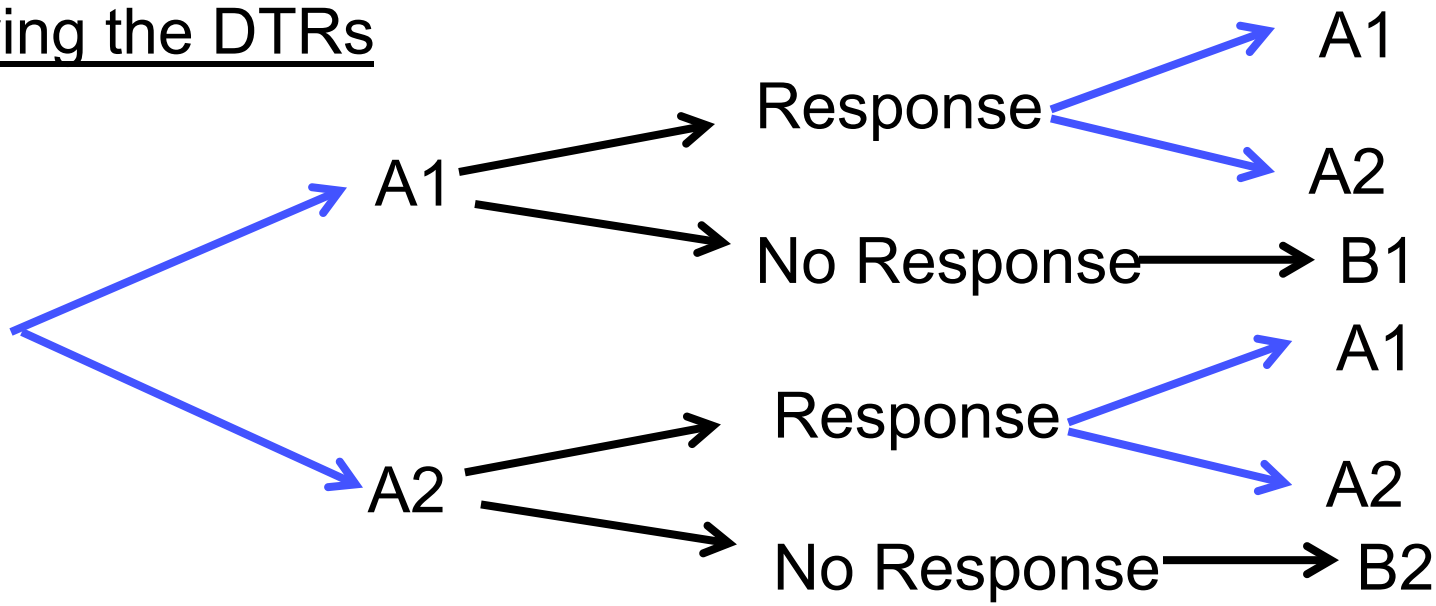

The Regimes:

(A1, A1, B1) = Give A1, repeat it if you get a response, switch to B1 if you don't

(A2, A2, B2) = Give A2, repeat it if you get a response, switch to B2 if you don't

**There is no re-randomization** - - but they still are adaptive.

Identifying the DTRs




The Regimes:

(A1, A1, B1)
(A2, A2, B2)
(A1, A2, B1) : Even if A1 gets a response, try A2
(A2, A1, B2) : Even if A2 gets a response, try A1

Note: One could easily get 4 more DTRs by switching B1 and B2.

The SPARC SMART in Metastatic Renal Cancer

DFS = approx 9 months → Try 3 targeted agents :

b = bevacizumab,  s = sunitinib,  t = temsirolimus

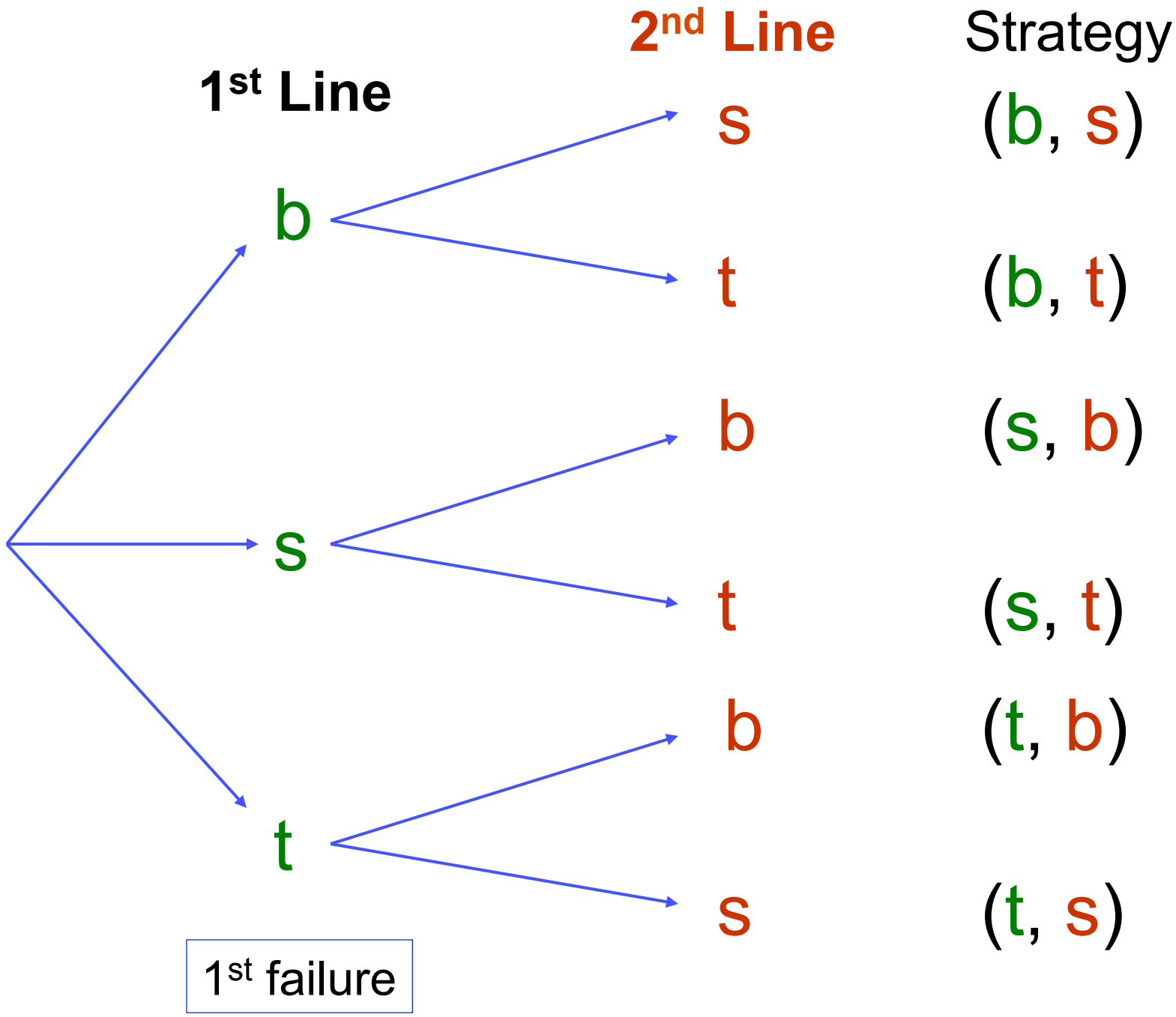
Stage1 of Therapy

At entry, randomize the patient among { b, s, t }

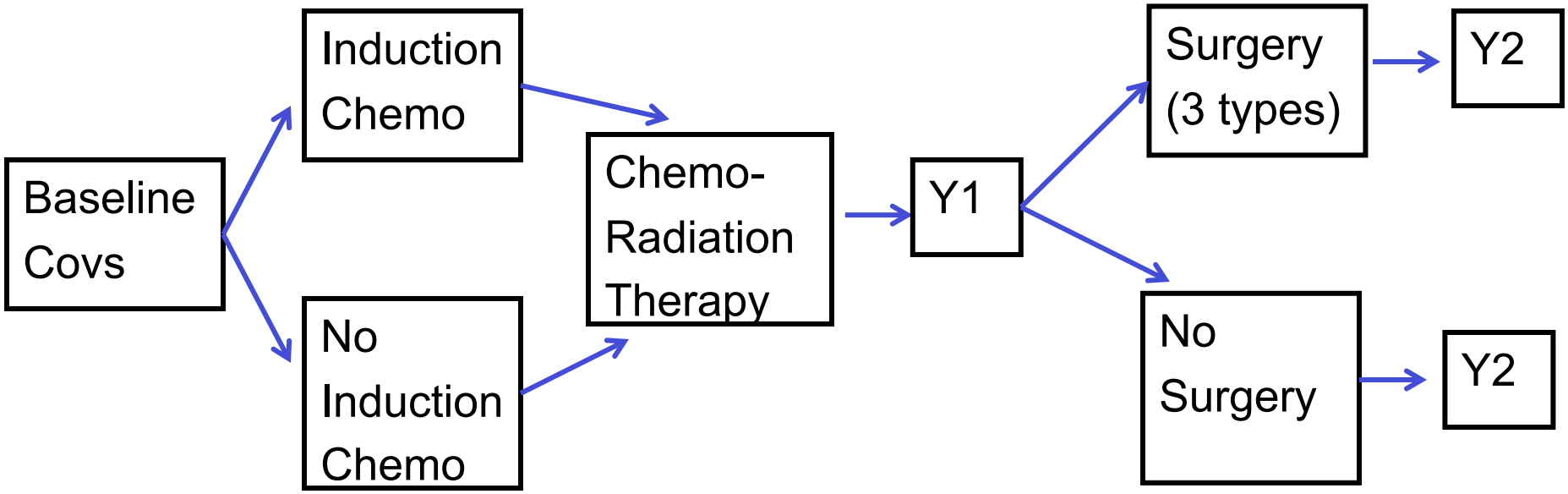
Stage 2 of Therapy

If the 1st failure is disease progression (not discontinuation)
at time of progression re-randomize the patient
between the two treatments not received initially

"Try something. If it fails, try something else"


1st Line
2nd Line
Strategy
b
s
t
s
b
t
b
t
s
(b, s)
(b, t)
(s, b)
(s, t)
(t, b)
(t, s)
1st failure

## *Data Mining* DTRs for Esophageal Cancer: No Randomization




- Induction chemo is given to de-bulk the disease
- Y1 = Chemo-Rad Outcome, Y2 = disease-free survival time
- CRT: 3 chemo types x 3 RT types x 2 RT fields = 18 CRTs
- [2 Ind Chemo = Y/N] x [18 CRTs] x [4 surg. cats.] → 144 DTRs

*But only 81 with n> 0 in our dataset . . .*

Inbal (Billie) Nahum-Shani:
Intro to Adaptive Interventions and SMARTs

The 'Adaptive Drug Court Program' is an example of an adaptive intervention. It is not a SMART ( no randomization ).
Q: (in the figure) What happens if they are compliant or responsive?

The ADHD SMARTer MED,BMOD study (pay attention!!) the one second stage rule is "Repeat a treatment that works; if not, Enhance (give more of the same trt)." The other second stage rule Augments (add a 2nd other type of trt)"
Q: Why not also include "Switch to something else" for non-responders, instead of just "augment"?

Page 11: Nice "If-then-else" computer program!! This will help people think about adaptive interventions as well-operationalized treatment regimes which is what they are.

# James McKay : 2-Stage SMARTs for SUDs

## Acronyms

SUD = Substance Use Disorder, e.g. drinking too much beer because you like your SUDs (or cocaine: SNORTs)
TX = treatment (not the state where I live)
IOP = Intensive Outpatient Program

## Goal

**Prevent relapse** for alcoholics (or snorters) who graduate from residential programs and get clean

Questions: Can a 2nd (adaptive) try with a different TX improve outcomes for SUD patients who

- do not want standard TX
- go to TX but leave (“drop out”)
- rejected a first offer of TX

Standard SUD TXs

Behavioral intervention, grp counseling, 12-step program

Translations

- Drop Out : The attempt at TX failed
- Tailoring : Base actions on IOP attendance
- Participant : Middle-aged African-American man
- SMART : Repeatedly phone people who drop out until they come back to IOP, randomize if 'disengaged'
- Outcome : How much alcohol or coke they say they are using, or an actual urine sample

Conclusions:

1) If you leave it up to the subject, they are more likely to keep drinking / snorting - - - **Relapse is a problem in SUD!**

2) "Compliance" is the actual outcome that treatment should target.

Amy Kilbourne: Mental Health Implementation Science

Focus on the "Research-to-Practice" gap by getting sites to adopt evidence based practices - - I could not agree more!!!

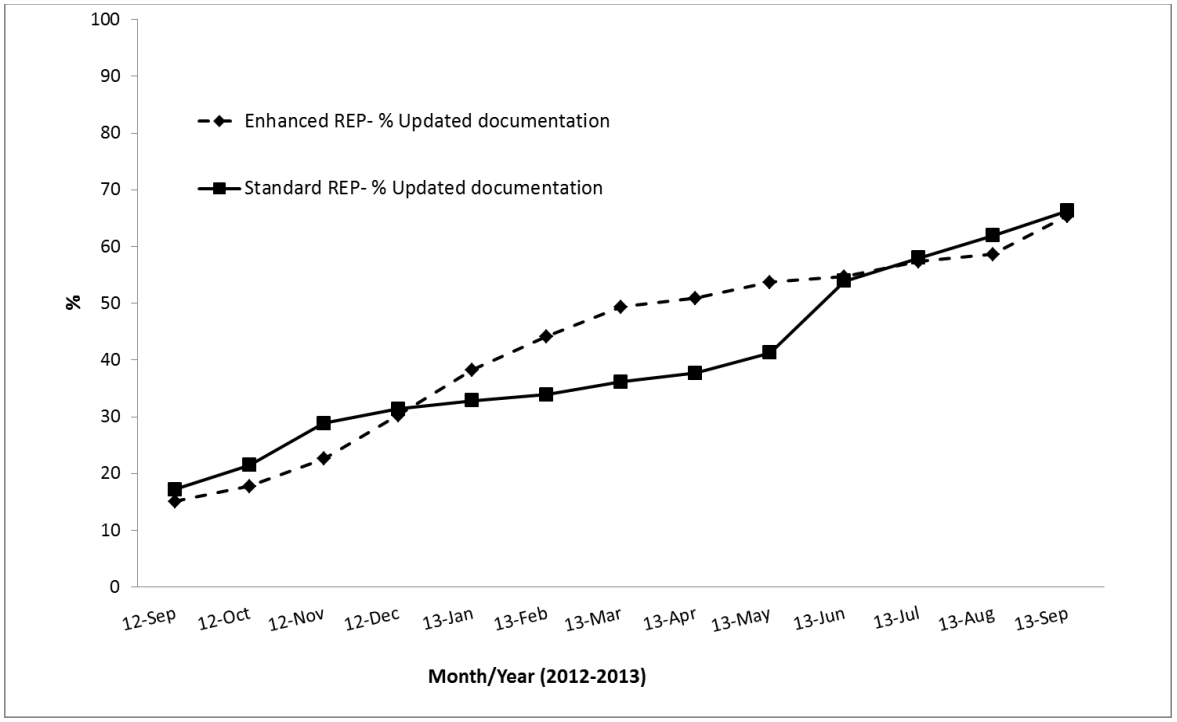
**Major Caveat** - - Make sure your conclusions are very likely to be true before you make a recommendation.
Q: What is the intervention you are trying to get sites to adopt in your SMART (Study #3)? Is there strong evidence for it?

Excellent use of acronyms:
EBQI, PARiHS, REP, GTO (also a great muscle car from the 60's), TA, ROCC, QOL, SMI, VHA, VA NPCD, CSI

REP was developed by the CDC to improve adoption of HIV prevention and treatment interventions.
Q: Is this goal of REP the same as enhancing treatment fidelity, buy in, or compliance?

# SMI Re-Engage Findings (Study#2)

Comparison of Enhanced REP (n=39) vs Standard REP (n=49) based on % of veterans with updated documentation




Q: Is the effect around March-April clinically significant or just statistically significant?

Q: The adaptive intervention (ie, Standard REP) appears to catch-up. What are the policy implications of this?

## SMART REP Trial on Facilitation

- EF+IF versus usual dissemination strategy
- 60+ community care clinics across 3 US states
- Applied to build cost-effective adaptive implementation strategy

## SMART REP Trial (60+ clinics, 1200+ patients)

- Goals: Among sites not initially responding to REP, estimate effect of adaptive implementation interventions in sites receiving REP+EF/IF vs REP+EF on 12-month outcomes
- SMART : Very complex, with run-in (all sites start with REP), re-randomization among continued non-responders, etc.

Q: Results likely to be very sensitive to definition of “response” at the site level. Is the definition based on data? Rationale?

Q: The study is complex. What challenges do you anticipate?

Sylvie Naar-King: Pilot Studies of Obesity

Nice pictures - - very Darwinian.

Comment: Actual SMARTs are almost all "pilot" studies, of varying sizes, since N / [number of DTRs] is seldom large (e.g., in cancer research).

Motivation: We now live in **Fat City**. People are fat, and getting fatter, **and being fat causes lots of terrible diseases**. Getting less fat → better overall health → **This is Very Important!!**

Strategy:

1) Get 'em while they're young, i.e. target adolescents.
2) Eat less, exercise more. But behavior change is difficult to get people to do!

## Pilot Studies of Obesity

In home-based treatments, very little success, very dependent on adherence and motivation →

Develop an adaptive intervention to enhance motivation using a SMART!!

Comment: In summary of "Intrinsic Motivation (IM vs. CO)" Study 2, there appears to be too much reliance on p-values. Could try using posterior probability summaries.

Q: Are the effect sizes clinically significant, actually meaningful?

Next Strategy: Use extrinsic motivation (CM)

Pilot Studies of Obesity

The “Home vs Office” SMART

**Q1: Why is 3% weight loss in 3 months a “response” ?**
**Specifically, what is the rationale for this definition?**
**Empirically-based?**

**Q2: What happened to changing diet and exercise ?**
Is changing diet and increasing exercise part of the skills training components in stage 1 of treatment?

**Q3: Your first question focuses on delivering the intervention at HOME vs in the OFFICE/CLINIC?**
Why is this such an important scientific question to address?

**Q4: Your second question focuses on effect of CM?**
Can you clarify what is CM? Is CM a feasible intervention in the real-world?

Dan ("The Man") Almirall: Adaptive Interventions for Childhood Autism: Two SMARTs

Motivation: Traditional interventions to develop language skills in autistic children are lousy → Need for improvement
Possibilities: JASP or AAC (acronyms are essential)

The DTR: If JASP works continue it; o/w augment w. AAC, in 12-week stages.
Outcome is 7-variate Y
Comment: The way that Y is reduced to 1-dim response is critical → M advice: Use additive elicited utility weight function $U(Y) = w(Y_1) + \ldots + w(Y_7)$

*→ The Kasari UCLA study rule becomes $U(Y) > u^*$ , or possibly with AR proportional to posterior mean $E\{U(Y)|\theta\}$*

Comparisons of Competing DTRs in the Kasari UCLA Autism Study

Comment: The data seem most useful to

*a) Rank (ACC, ACC+) > (JASP, ACC) > (JASP, JASP+)*

*b) Weed out inferior DTRs (JASP, JASP+), (JASP, ACC)*

*With n=61, as usual, the results are only suggestive.*

2nd Study On Social Play

Same design, different twist - - - human behavior is complex!

Thanks for listening.  Now it's time for lunch.

And eat a salad instead of french fries!!