Adaptive designs as enabler for personalized medicine

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Thanks to Donald A Berry
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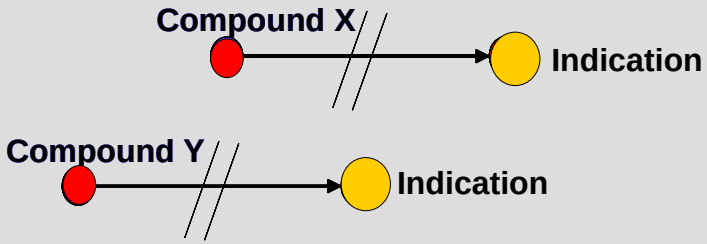
Borrowing information across compounds

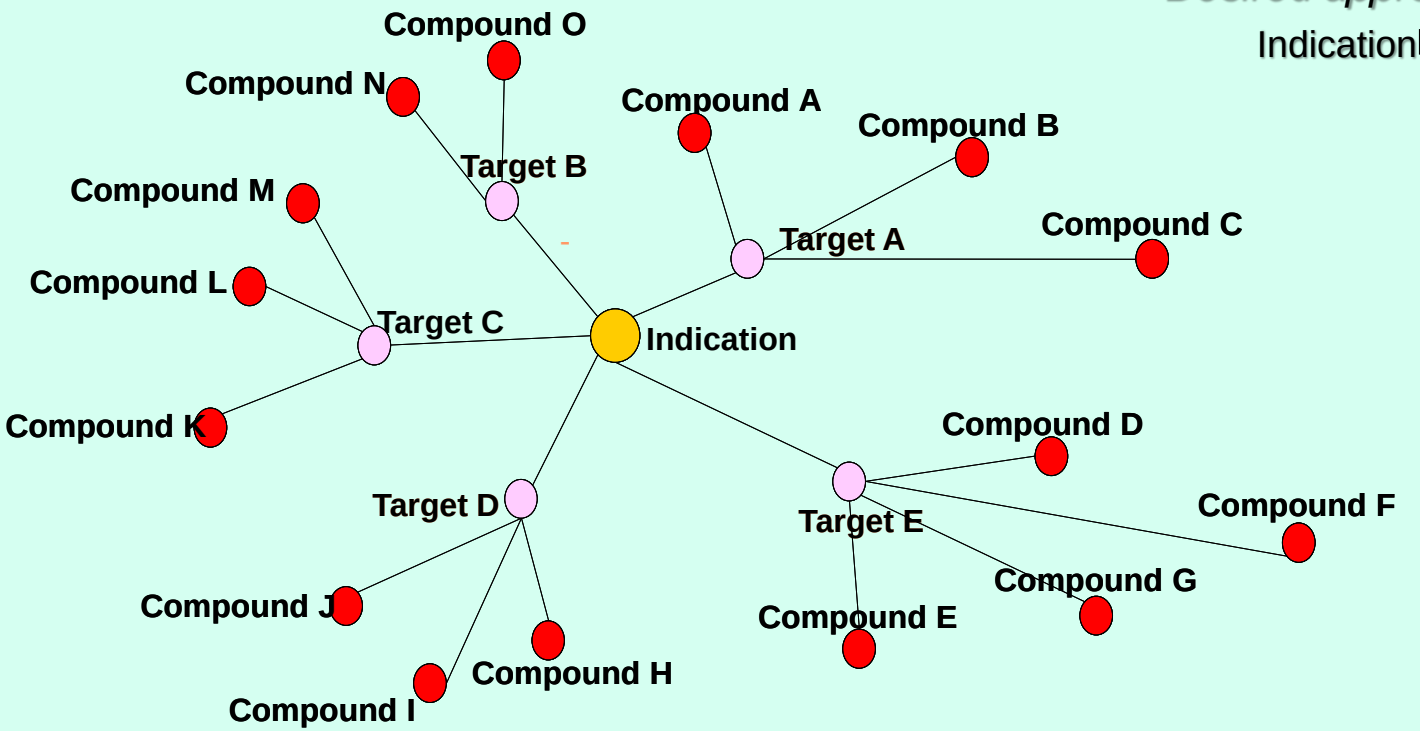


Traditional “mapping” is one-dimensional

Compound ⇨ Indication

Desired approach is multi-dimensional

Indication ⇨ Target ⇨ Compounds



Adaptive design - definition

- uses accumulating data to decide on how to modify aspects of the study
- without undermining the *validity* and *integrity* of the trial

Validity means

- providing correct statistical inference (such as adjusted p-values, estimates and confidence intervals)
- assuring consistency between different stages of the study
- minimizing operational bias

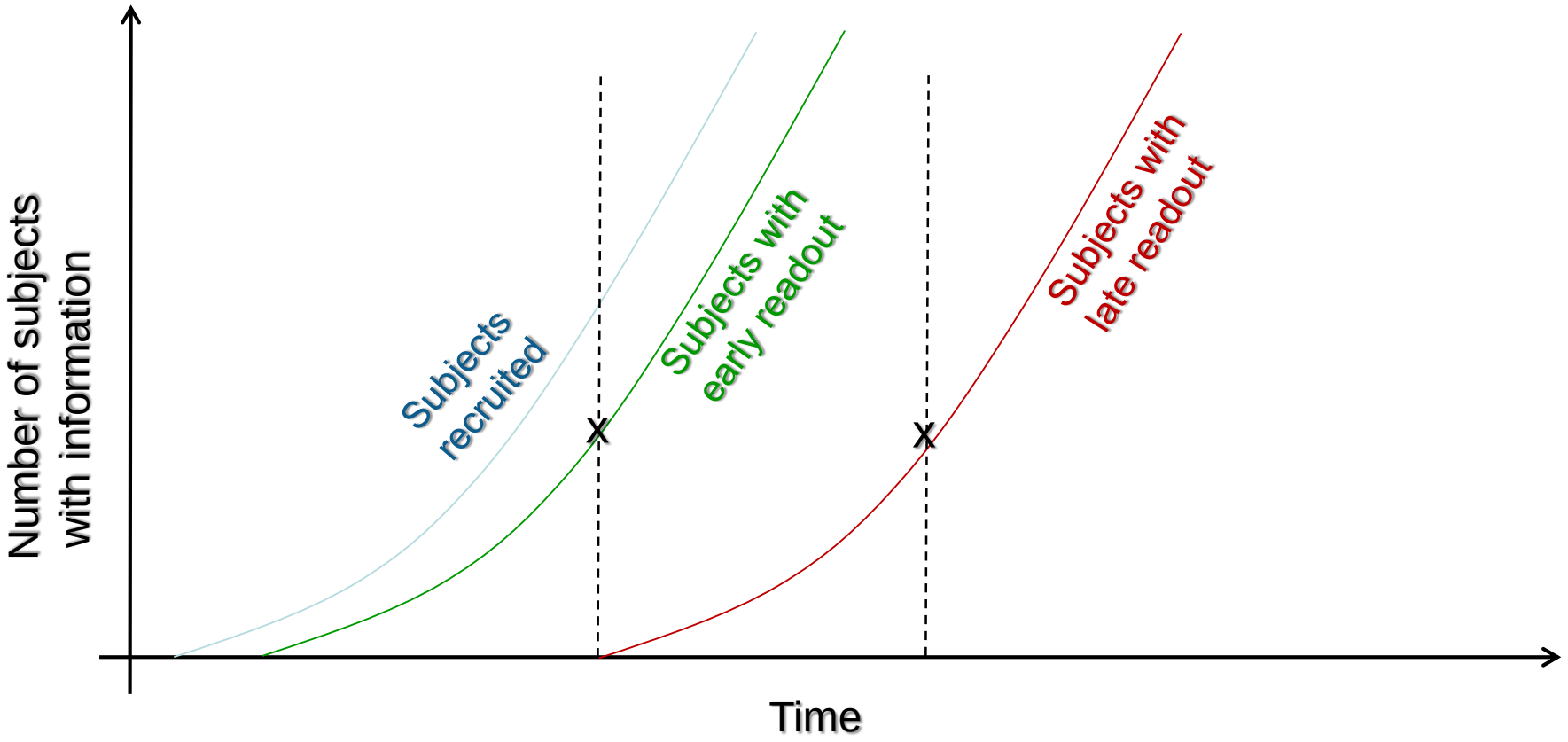
Integrity means

- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data

Biomarkers Are Critical

to enable efficient decision making within clinical trials

- Biomarkers as “necessary condition” with early readout
  - Can be used to adapt treatment allocation (drop a dose or stop for futility)



I-SPY2:
Adaptive Design to Identify Treatments for Biomarker Subtypes

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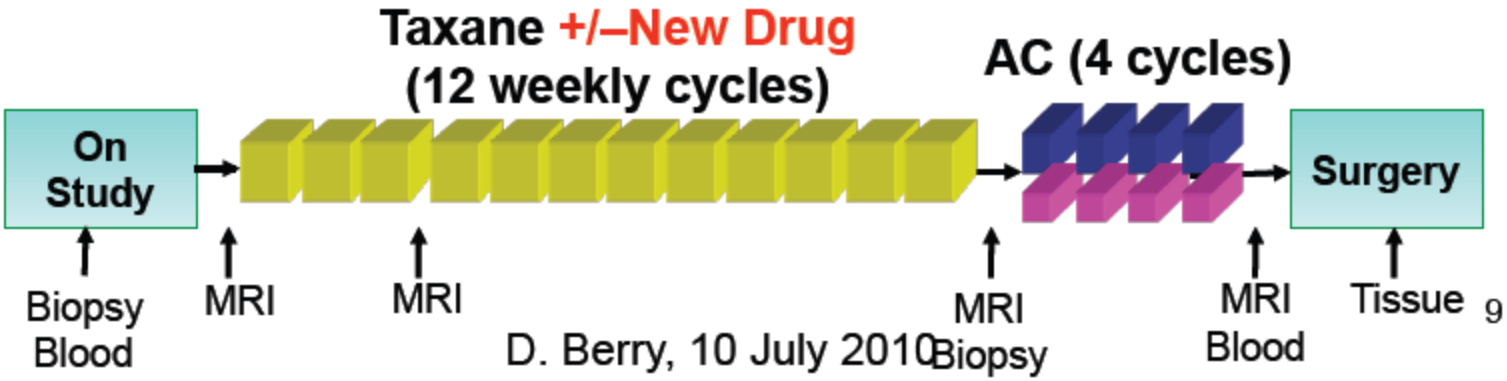
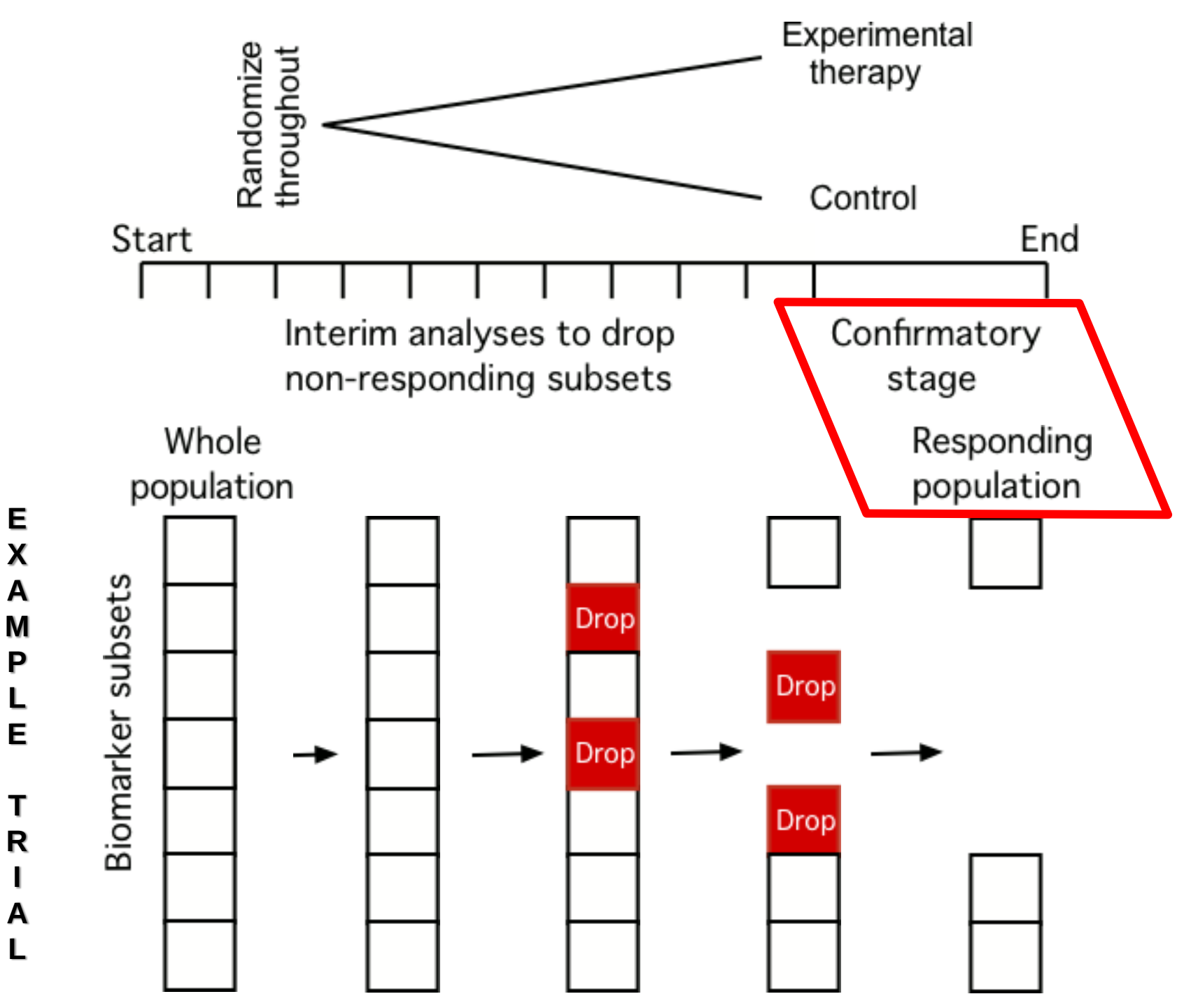
THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

I-SPY2: Adaptive Phase II Neoadjuvant Breast Cancer (Laura Esserman, UCSF, PI)

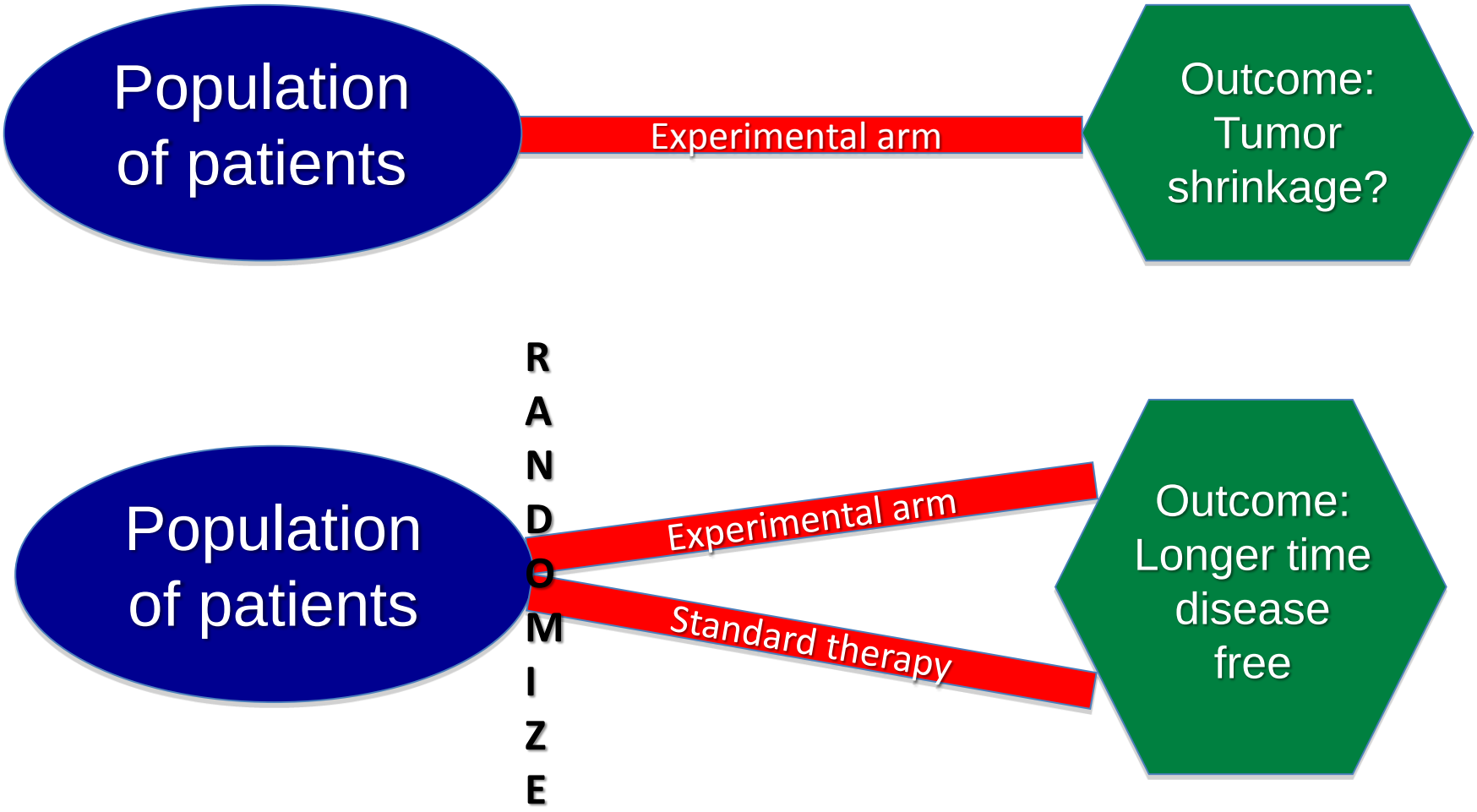
- Moderate to high-risk primary breast cancer
- Baseline biopsy: assess biomarkers
- Primary endpoint: pCR
- Model pCR based on interim MRIs
- Many drugs, each added to standard (control)



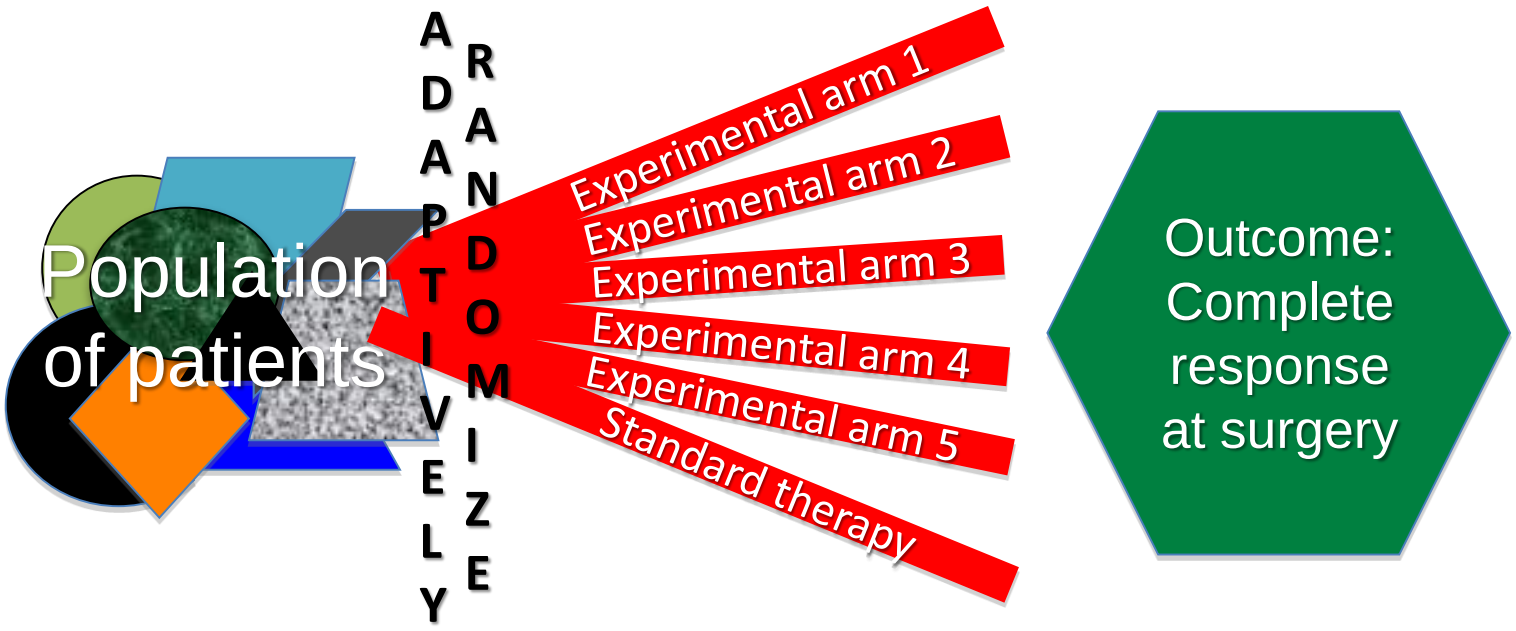
D. Berry, 10 July 2010


Randomize throughout
Experimental therapy
Control
Start
End
Interim analyses to drop non-responding subsets
Confirmatory stage
Responding population
Whole population
Biomarker subsets
Drop
Drop
Drop
EXAMPLE TRIAL

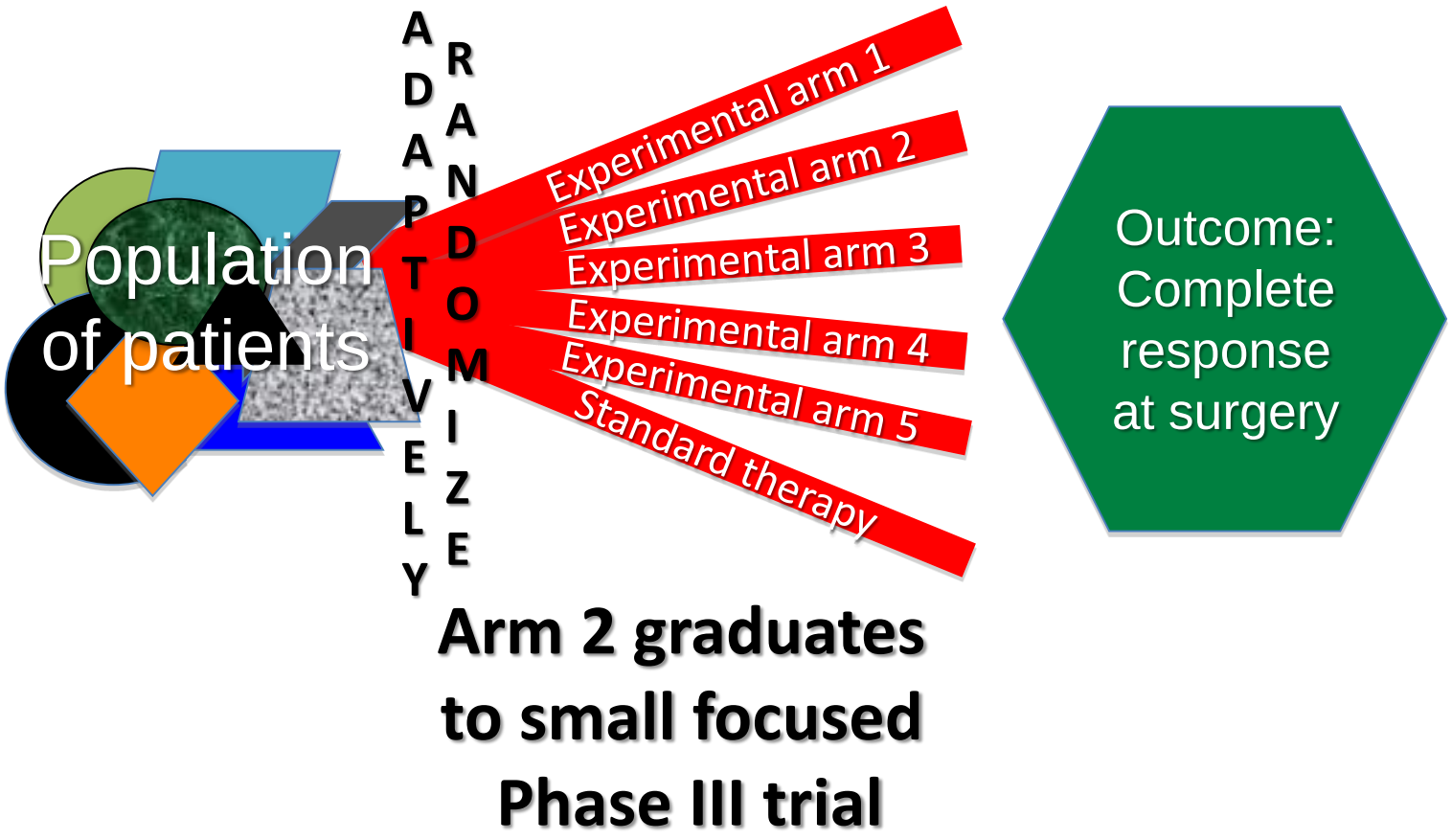
Standard Phase II Cancer Drug Trials



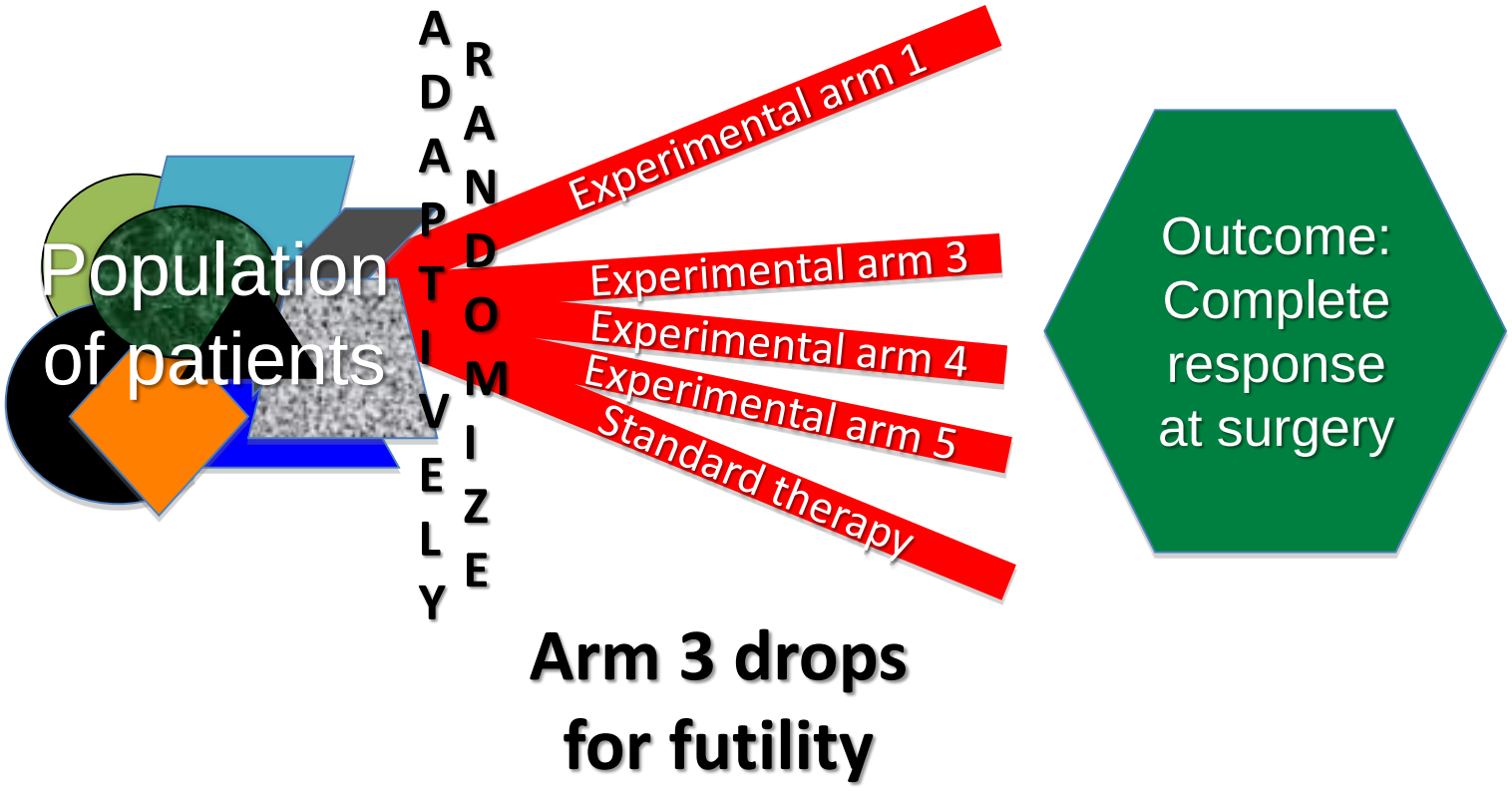
I-SPY2 TRIAL


Population of patients
ADAPTIVELY RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery

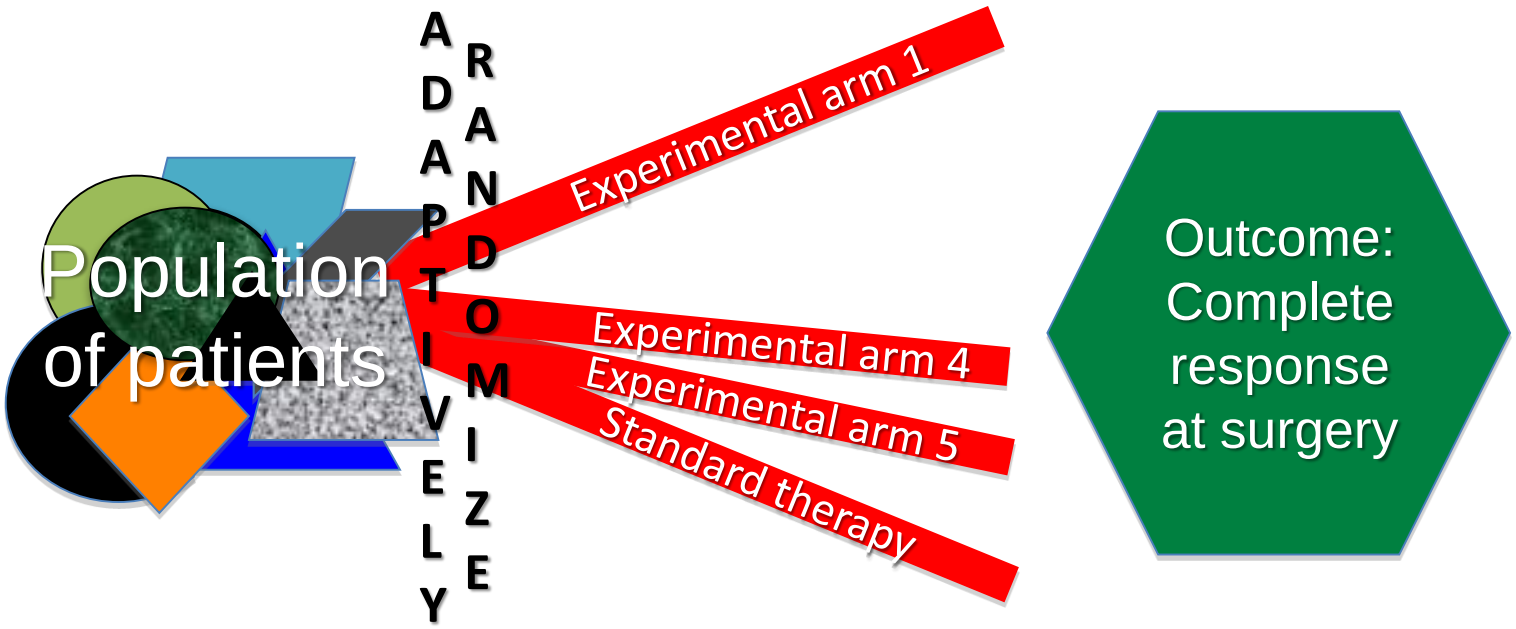
I-SPY2 TRIAL


Population of patients
ADAPTIVELY
RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery
Arm 2 graduates to small focused Phase III trial

I-SPY2 TRIAL

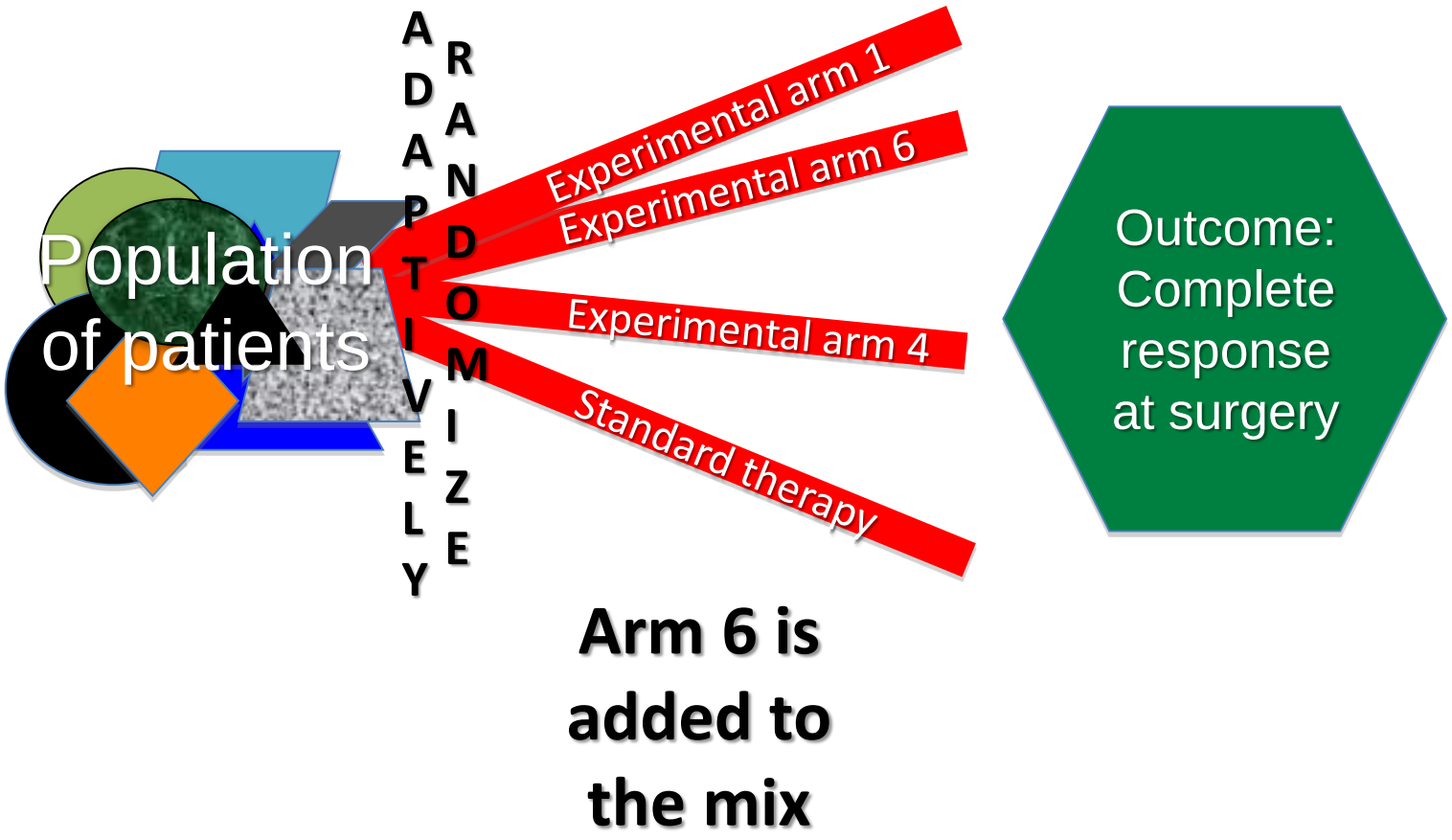

Population of patients
ADAPTIVELY
RANDOMIZE
Experimental arm 1
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery
Arm 3 drops for futility

I-SPY2 TRIAL

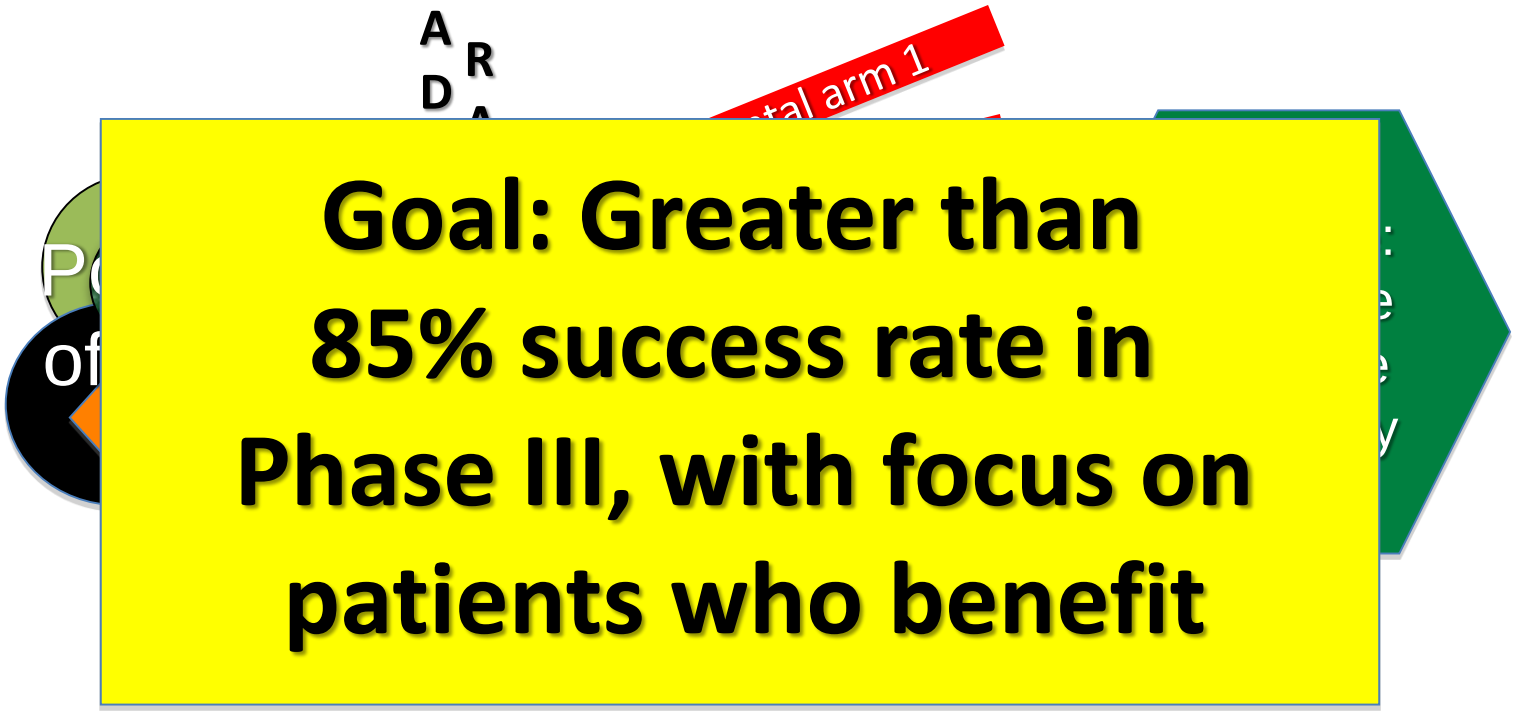


Arm 5 graduates to small focused Phase III trial

I-SPY2 TRIAL


Population of patients
ADAPTIVELY
RANDOMIZE
Experimental arm 1
Experimental arm 6
Experimental arm 4
Standard therapy
Outcome: Complete response at surgery
Arm 6 is added to the mix

I-SPY2 TRIAL


A
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Goal: Greater than
85% success rate in
Phase III, with focus on
patients who benefit
added to
the mix

Adaptive designs for dose-finding: Background and Case Study

Scott Berry
Gary Littman
Parvin Fardipour
Michael Krams

A Bayesian dose-finding trial with adaptive dose expansion to flexibly assess efficacy and safety of an investigational drug

Scott M Berry[a], Walter Spinelli[b], Gary S Littman[c], John Z Liang[b], Parvin Fardipour[b], Donald A Berry[d], Roger J Lewis[e] and Michael Krams[b]

Background Adaptive dose-ranging trials are more efficient than traditional approaches and may be designed to explicitly address the goals and decisions inherent in learn-phase drug development. We report the design, implementation, and outcome of an innovative Bayesian, response-adaptive, dose-ranging trial of an investigational drug in patients with diabetes, incorporating a dose expansion approach to flexibly address both efficacy and safety.

Purpose The design was developed to assess whether one or more doses of an investigational drug demonstrated superior efficacy to an active control while maintaining an acceptable safety profile.

Methods The trial used a two-stage design, in which patients were initially allocated equally to placebo, investigational drug at a low and a medium dose, and an active control. Movement to the second stage was contingent upon evidence of efficacy (measured by change in fasting blood glucose) to add a very low dose of the investigational drug and of safety (measured by weight gain) to add a high dose of the investigational drug. The design incorporated a longitudinal model to maximize use of incomplete data, predictive probabilities to guide the decisions to terminate the trial for futility or move on to Stage 2, and a dose-response model in Stage 2 to borrow information across adjacent doses. Extensive simulations were used to fine tune trial parameters, to define operating characteristics, and to determine the required sample sizes. A data monitoring committee was provided with frequent reports to aid in trial oversight.

Results In Stage 1, as trial data accrued, the predictive probability that either the low or medium dose of the investigational drug was superior to the active control fell to low values. Stage 1 termination was recommended after 199 subjects were randomized, out of a maximum trial size of 500 subjects, and the final sample size was 218. Thus the trial did not progress to Stage 2.

Limitations Because of the relatively narrow dose range to be assessed, and the inability to utilize the highest dose at the beginning of the trial, a fully responsive-adaptive design incorporating dose-response modeling was not considered a viable option. This limited the efficiency gains possible with a full set of adaptive design elements.

Conclusions The two-stage dose-expansion design functioned as designed, recommending early termination based on a low probability that the tested doses had efficacy greater than the active control. *Clinical Trials* 2010; 7: 121–135. http://ctj.sagepub.com

Adaptive Study Design (1)

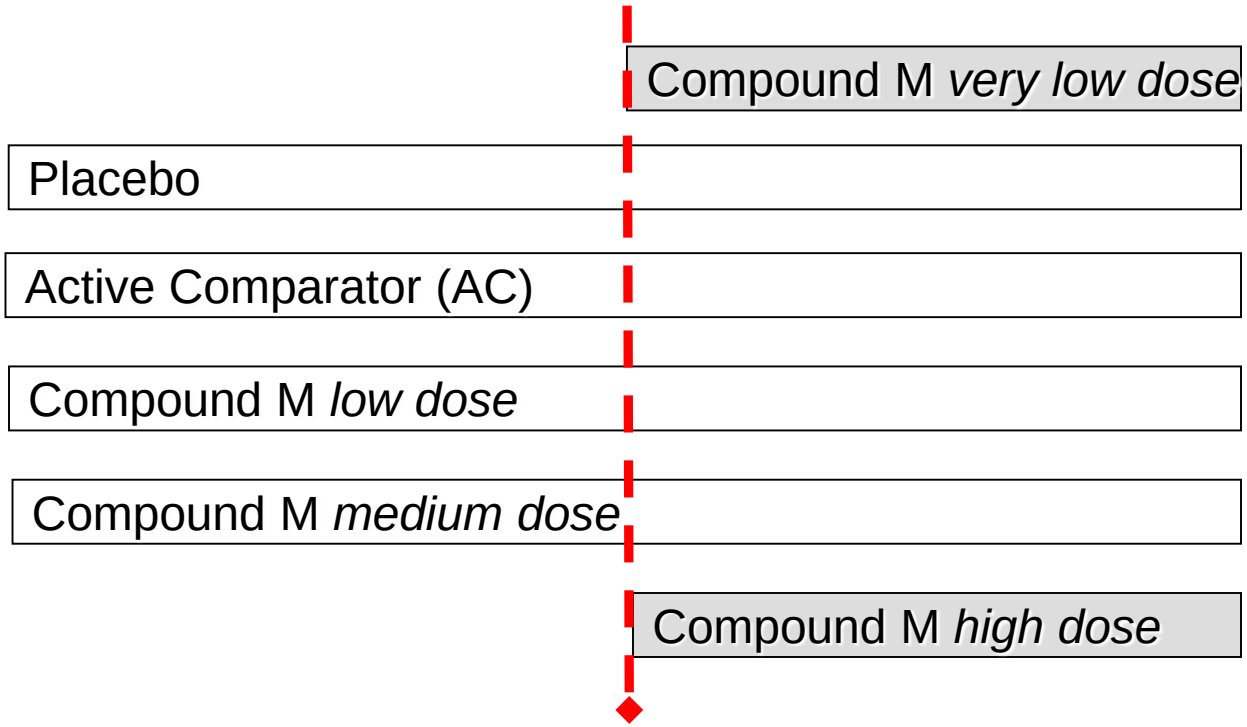
- Investigational drug: oral anti-diabetic
  - What is the impact of study drug on
    a) FPG (week 12)
    b) body weight (week 24)

- Two-stage adaptive design
  - Stage 1:
    - Compound M, low and medium dose
    - PBO
    - Active Comparator
  - Stage 2:
    - Compound M very low, low, medium, high dose
    - PBO
    - Active Comparator
  - Selection of dose range and study design informed by preclinical toxicology findings
  - Study powered to compare FPG at Week 12
  - Enrollment
    to high dose conditional on evidence of safety&efficacy at medium dose;
    to very low dose conditional on evidence of efficacy at low dose

Adaptive Study Design (2)

- Bayesian decision algorithm
  - The algorithm analyzes the full dose-response curves of all treatment arms utilizing all available data during the treatment period
  - Every week, the algorithm provided probability estimates and recommendations to the Data Monitoring Committee as to whether enrollment should continue or be terminated
- Three formal interim analyses to review emerging benefit-risk profile
  - 100 subjects with at least 4 weeks of R_x
  - 240 subjects randomized
  - 375 subjects randomized
- Additional interim analyses may be requested by the Data Monitoring Committee

Adaptive Study Design (3)
Two stages – up to 500 subjects treated for 24 weeks

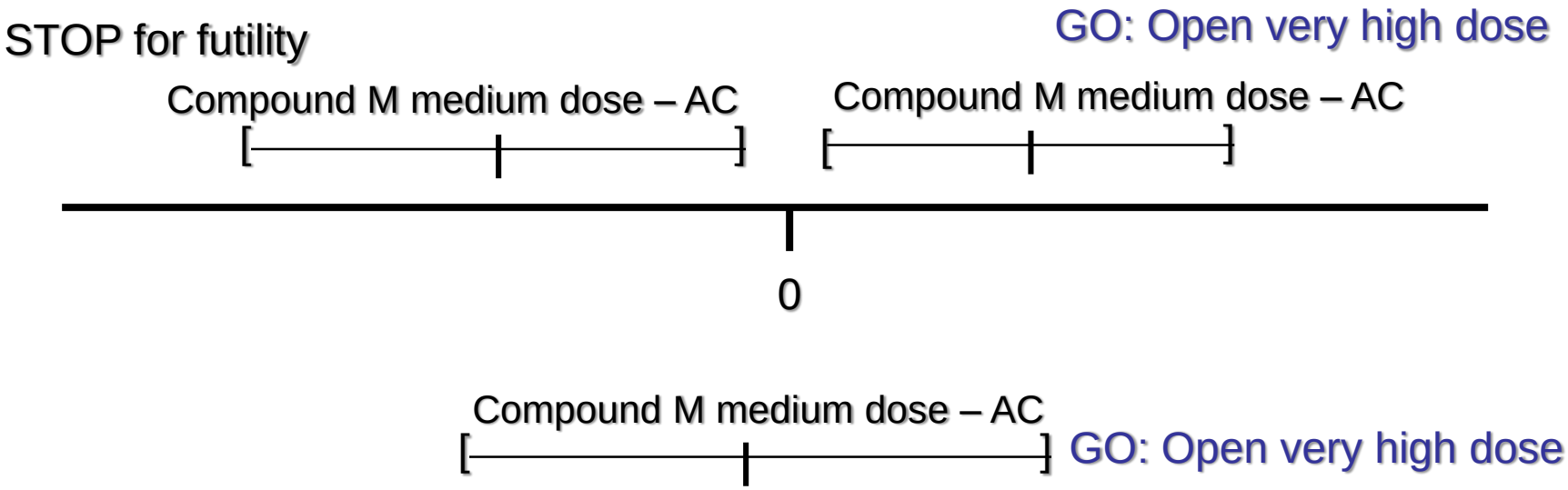


Earliest transition point to Stage 2 after 100 subj. treated for at least 4 weeks

The decision to initiate Stage 2 requires that
Compound M medium dose be at least comparable to
Active Comparator in decreasing FPG

Decision Criteria for Opening Stage 2

Difference in FPG changes at 12 weeks:



Continue with Stage 1 (up to 240 randomized subjects)

Dealing with Partial Data

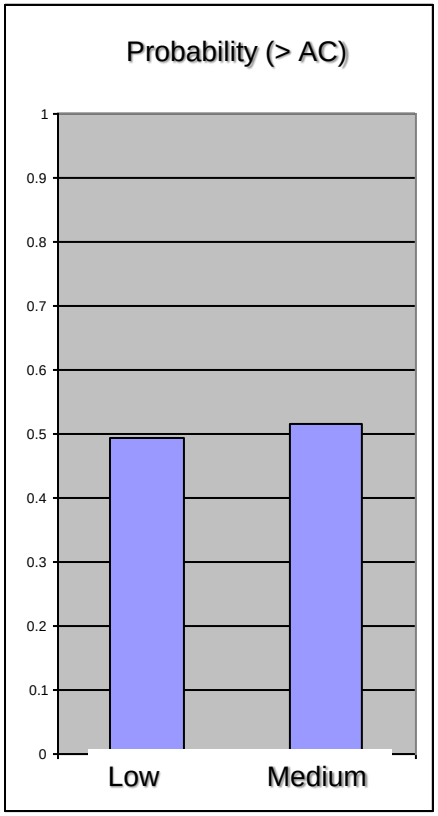
- Regression model to estimate week 12 data for patients who have not yet reached that point
- Initial model based on historical data from another compound
- Model is refined as we accumulate data from the present study
- As more patients complete 12 weeks, we become more confident in the results for two reasons
  - The percentage of actual observed (rather than model-based) data increases
  - The model becomes better as we learn from this trial
  - Therefore, we need to be cautious about making an early decision

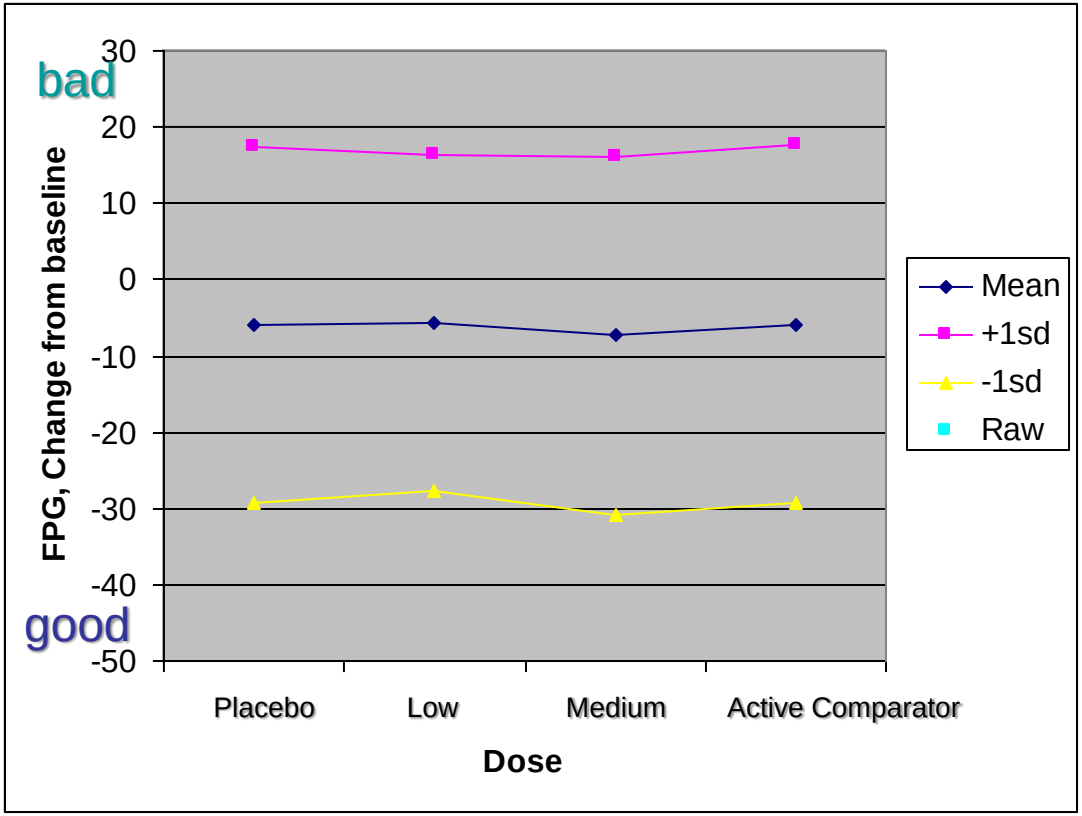
The real study

Overview and times of interim analysis findings

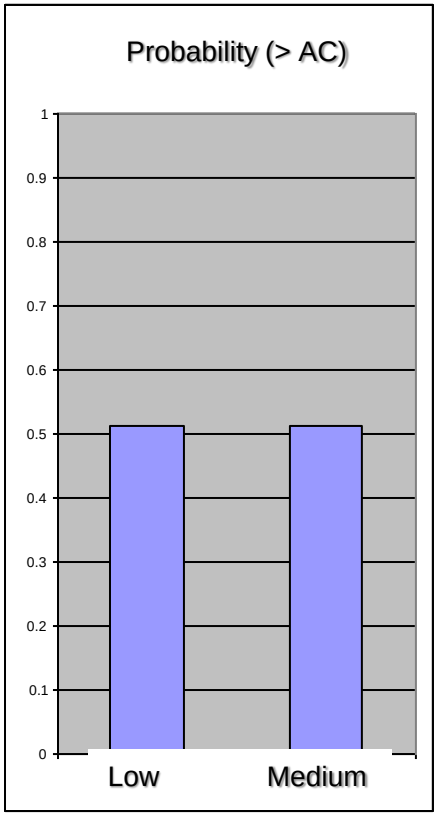
- Review of DMC findings:
  - Per protocol interim analysis: 14-Sep
    - No safety/tolerability issues necessitating early stop
    - Model on verge of futility recommendation
    - DMC recommended continuing stage 1 enrollment
  - Weekly analyses: 21-Sep, 4-Oct
    - Futility threshold crossed twice
  - *Ad hoc* Interim Analysis: 4-Oct
    - Baseline characteristics
    - Key Efficacy Results
    - Safety/Tolerability Conclusions
- DMC recommends stopping trial for futility on 4-Oct
- Executive Steering Committee reviewed the DMC recommendation to terminate the study for futility and agreed on 23-Oct

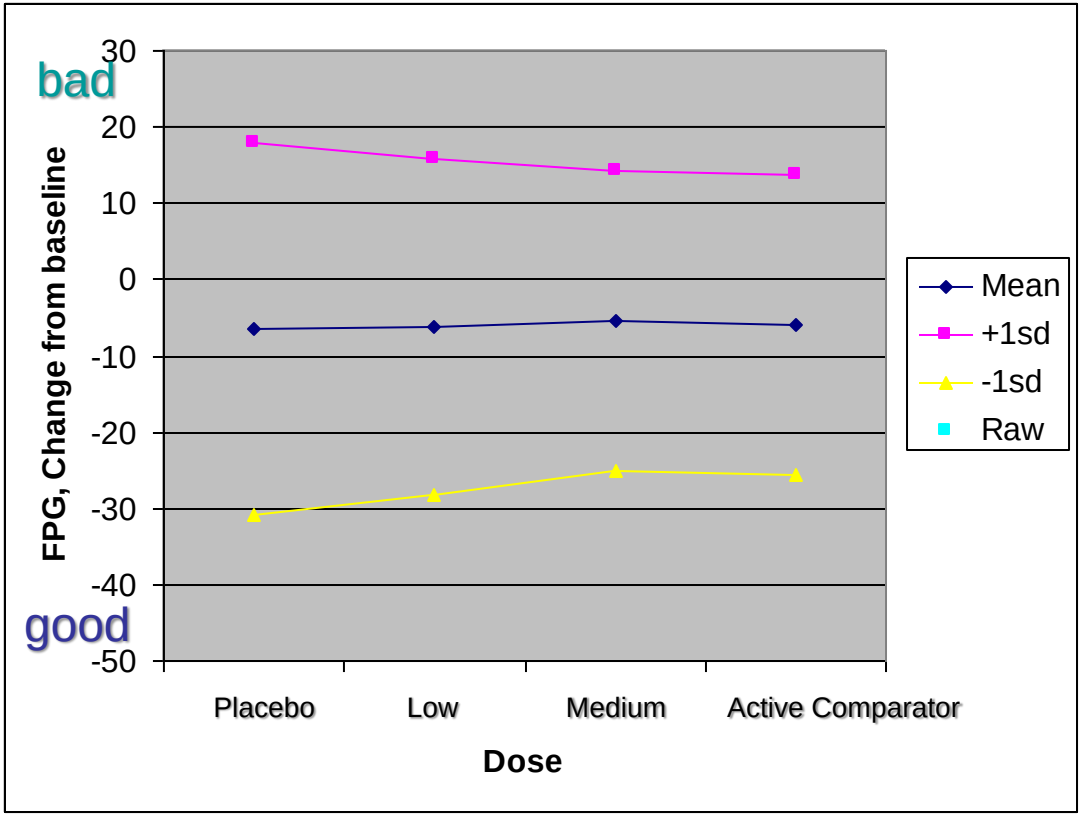
Mar 29 24 Subjects



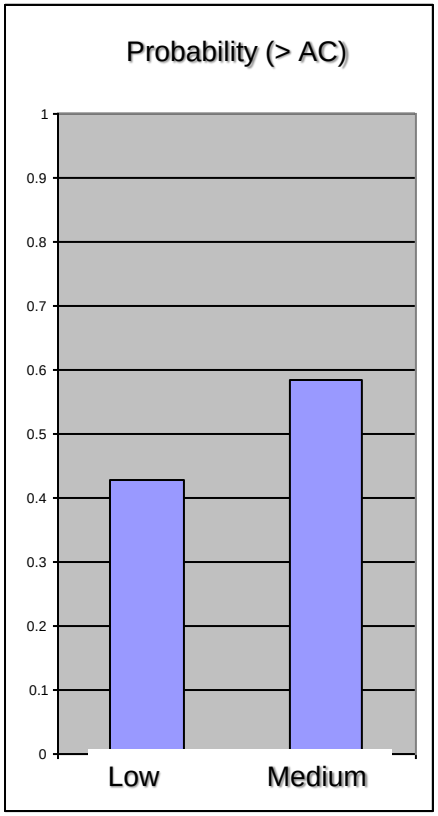


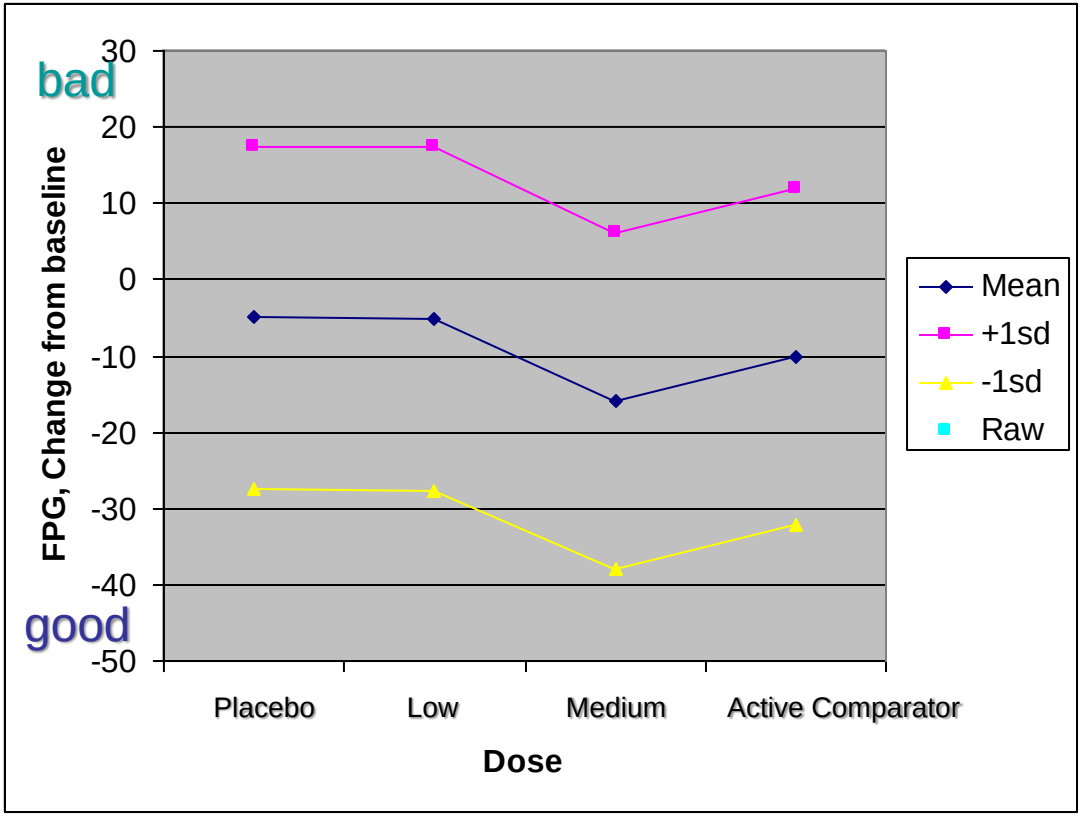
Apr 11 28 Subjects



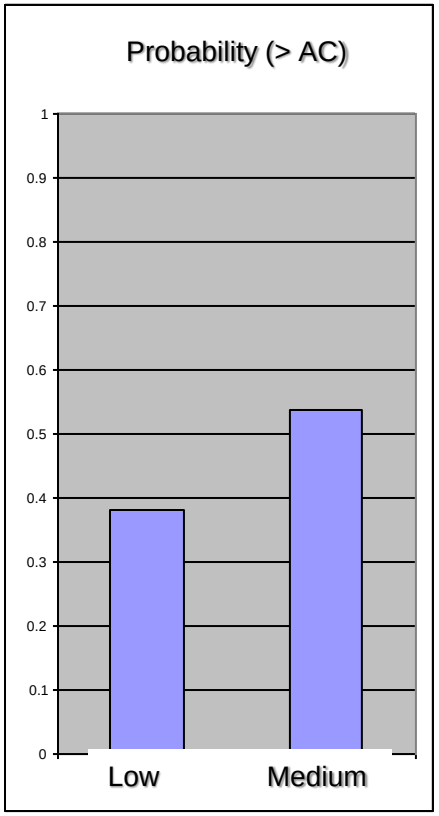


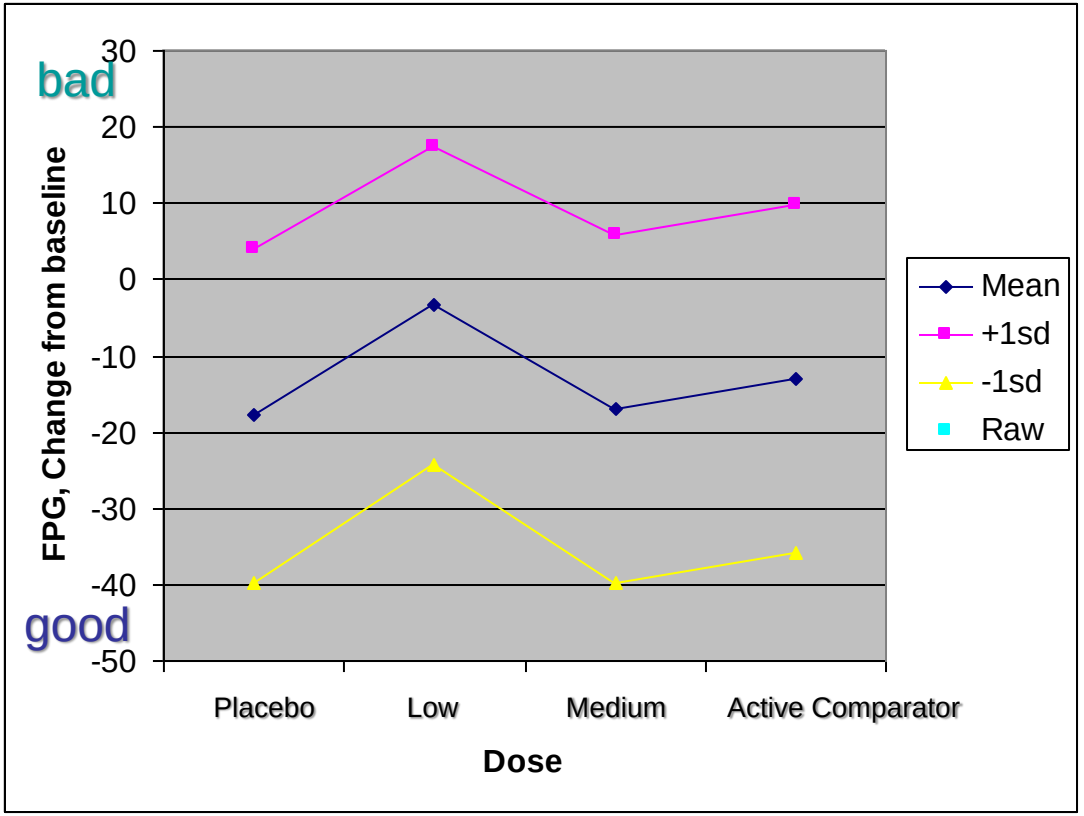
Apr 30 36 Subjects



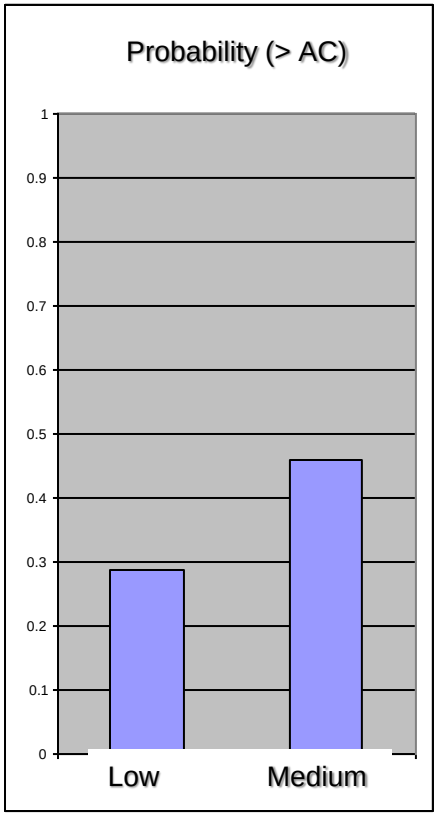


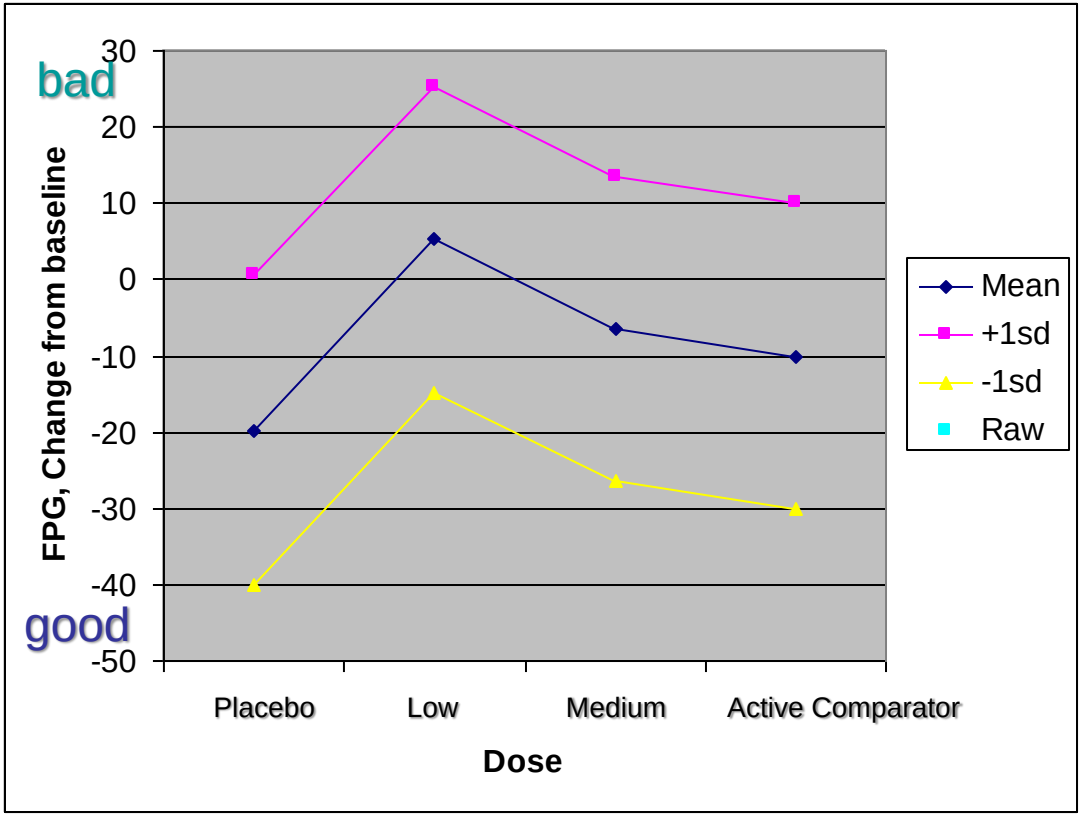
May 8 37 Subjects



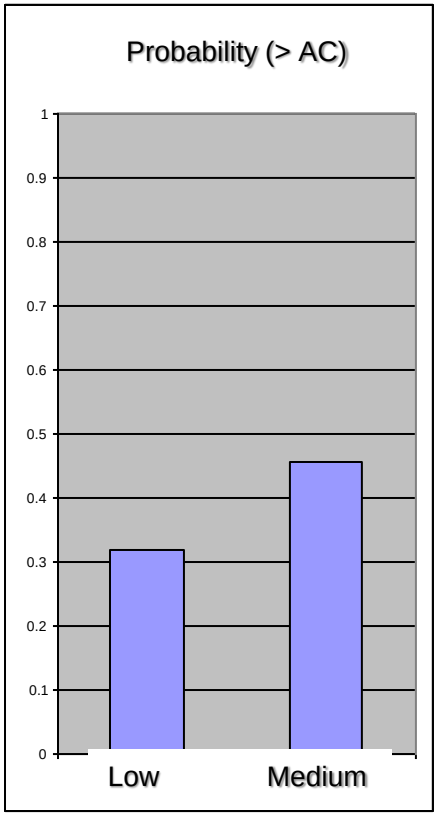


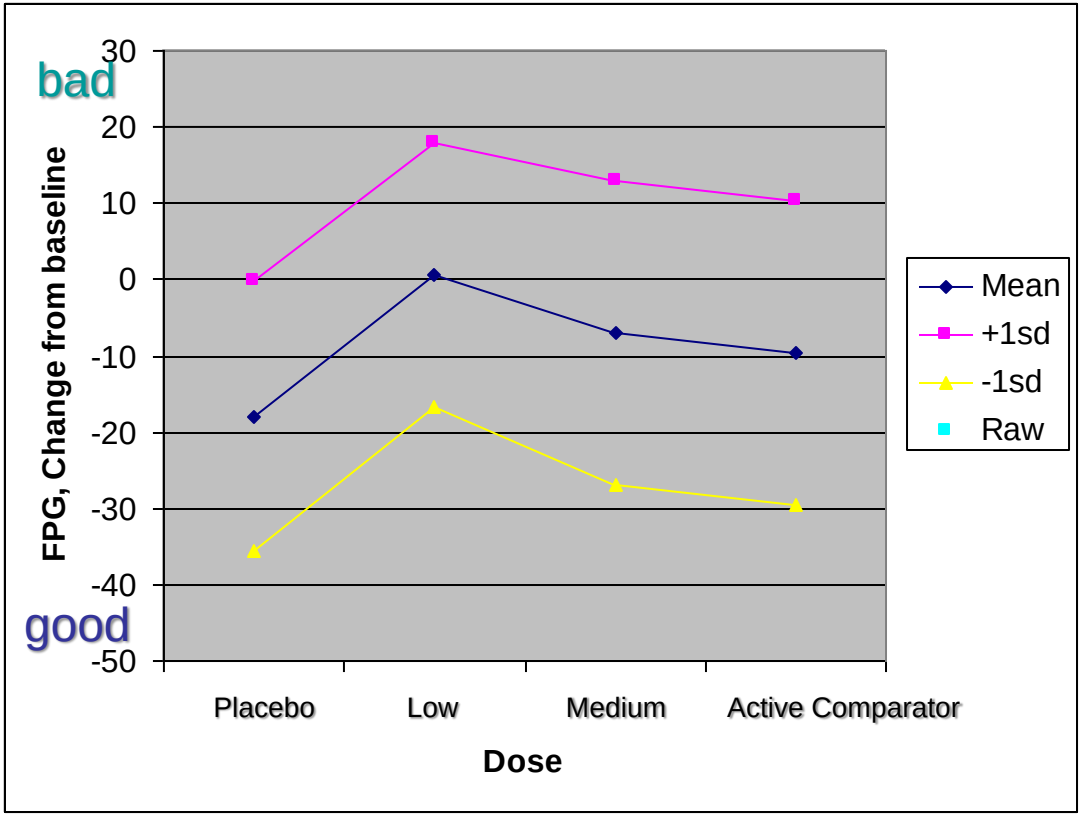
May 30 49 Subjects , 1 complete





Jun 8 57 Subjects, 1 complete





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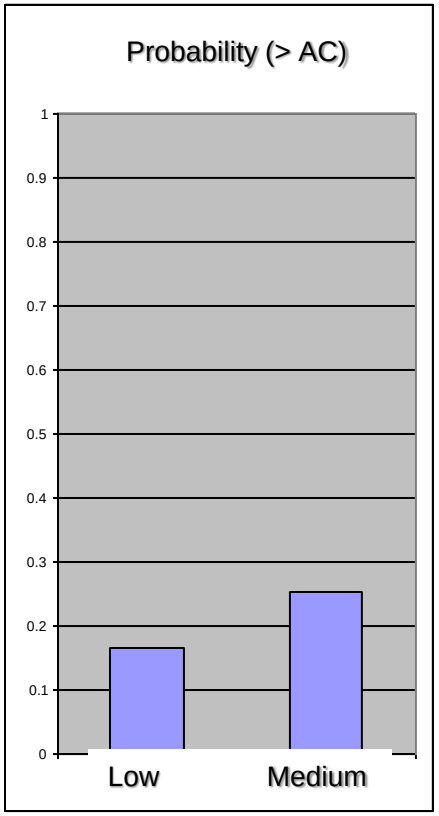
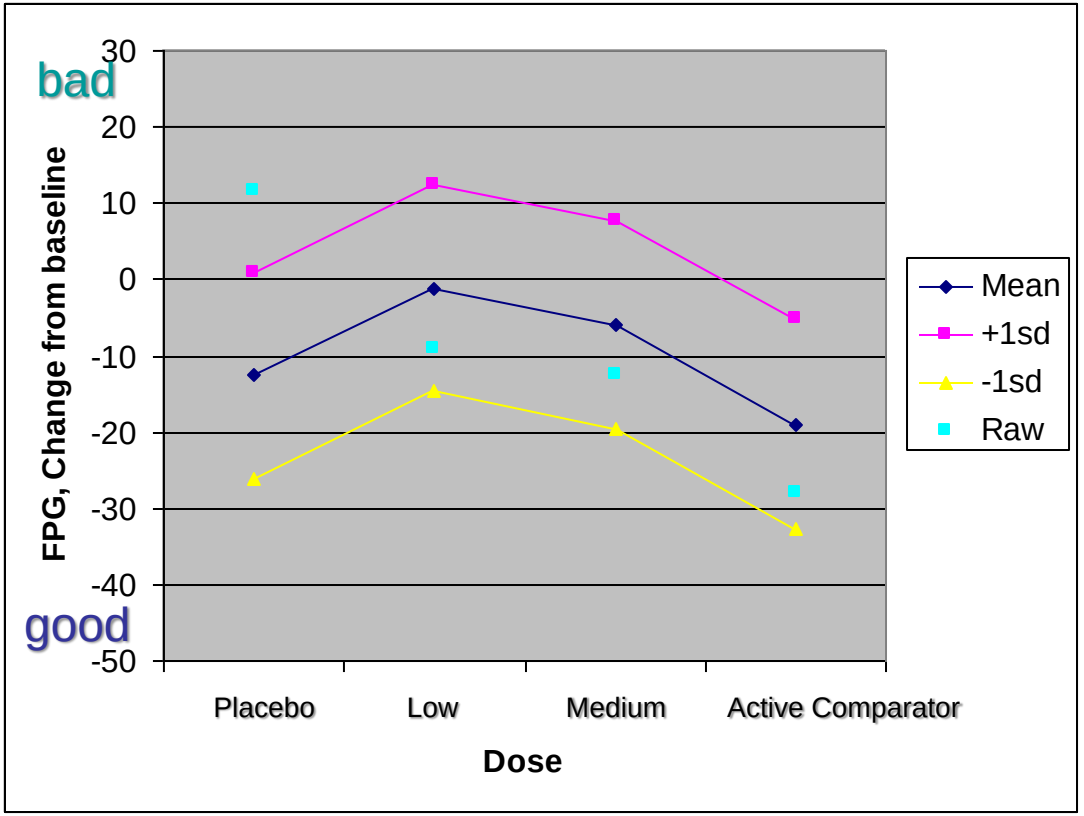
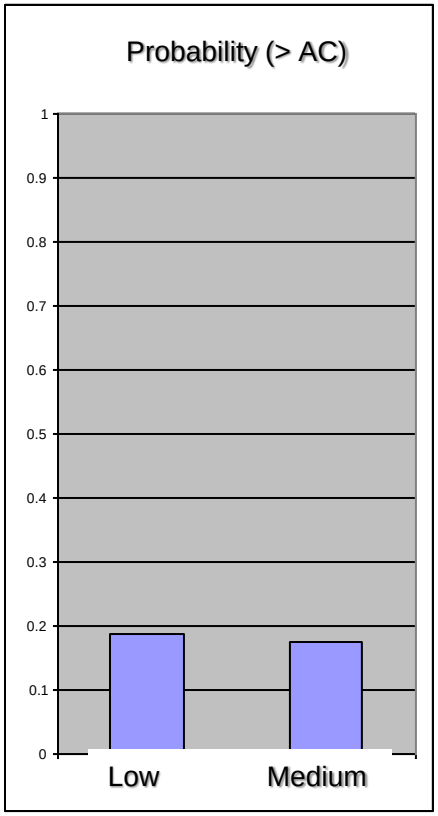
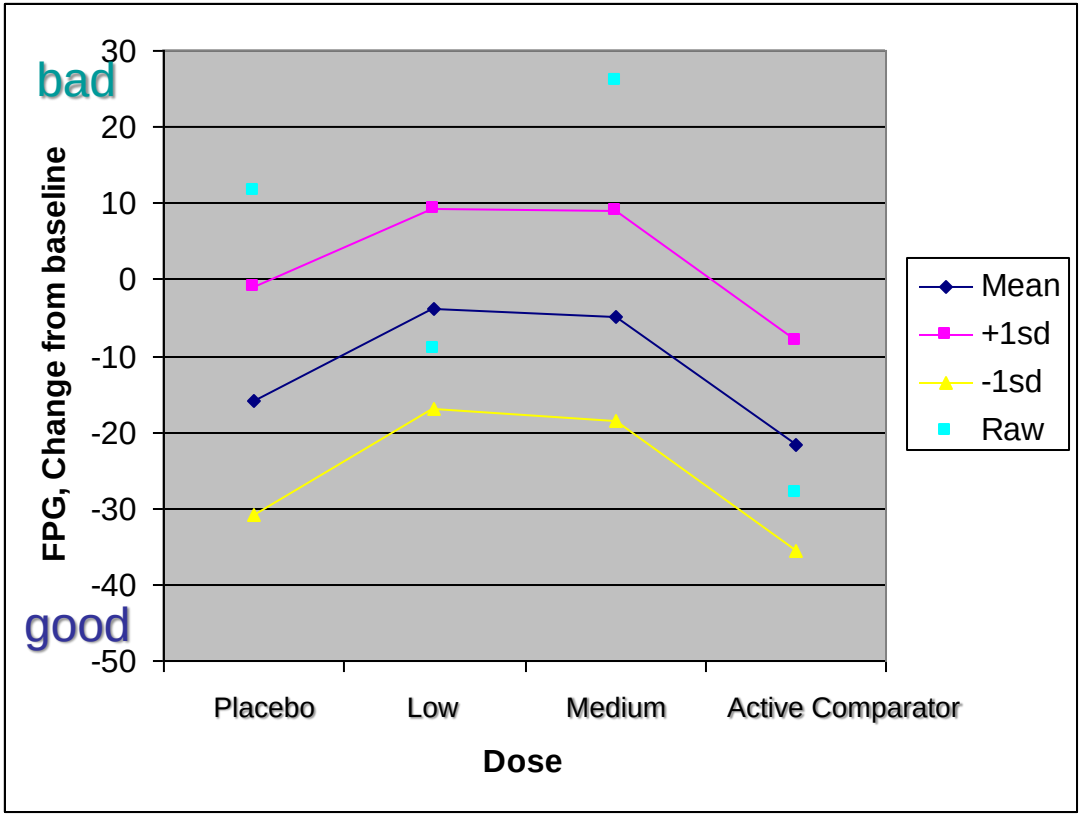




Jul 9 71 Subjects , 9 complete





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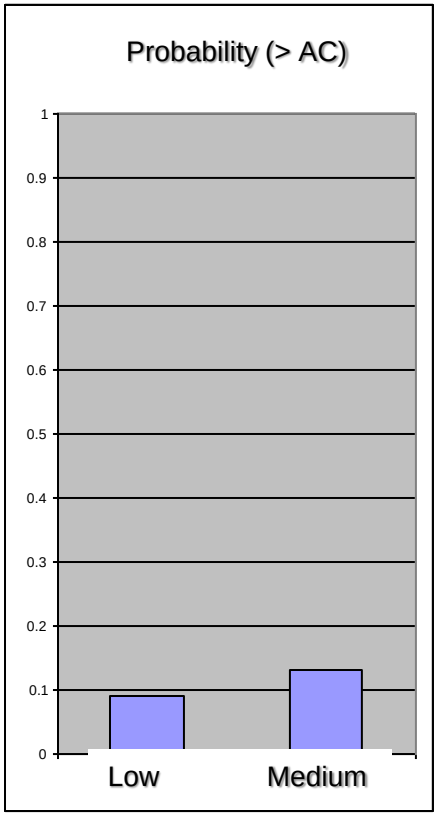
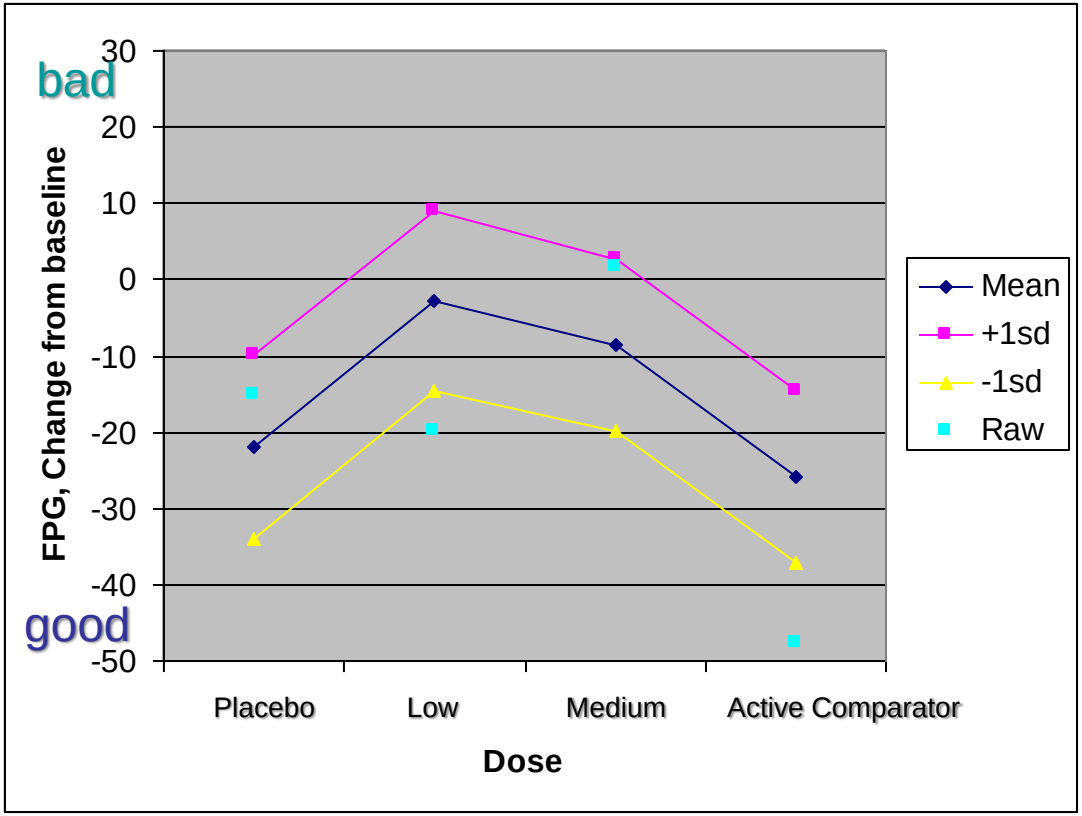
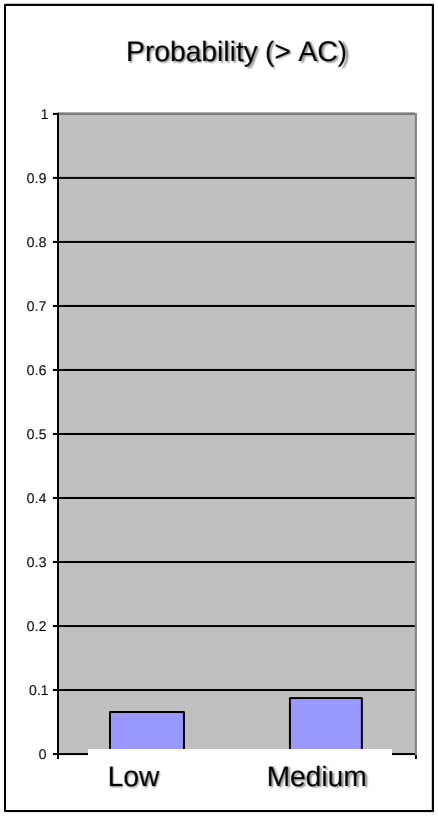
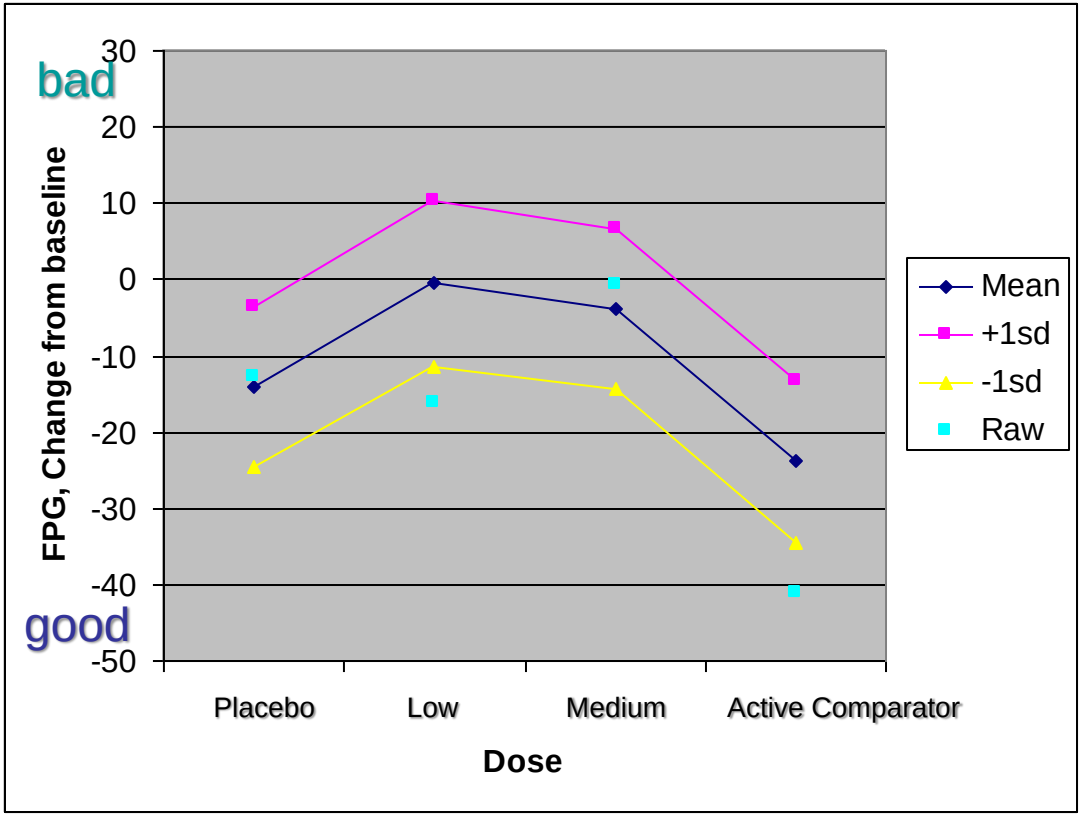


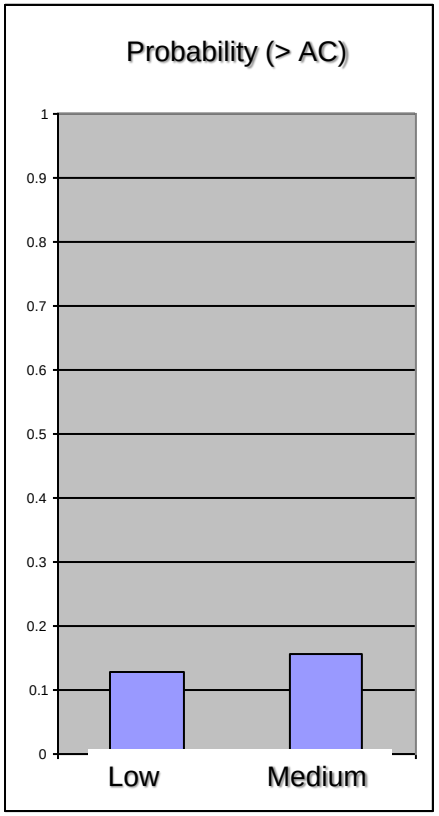


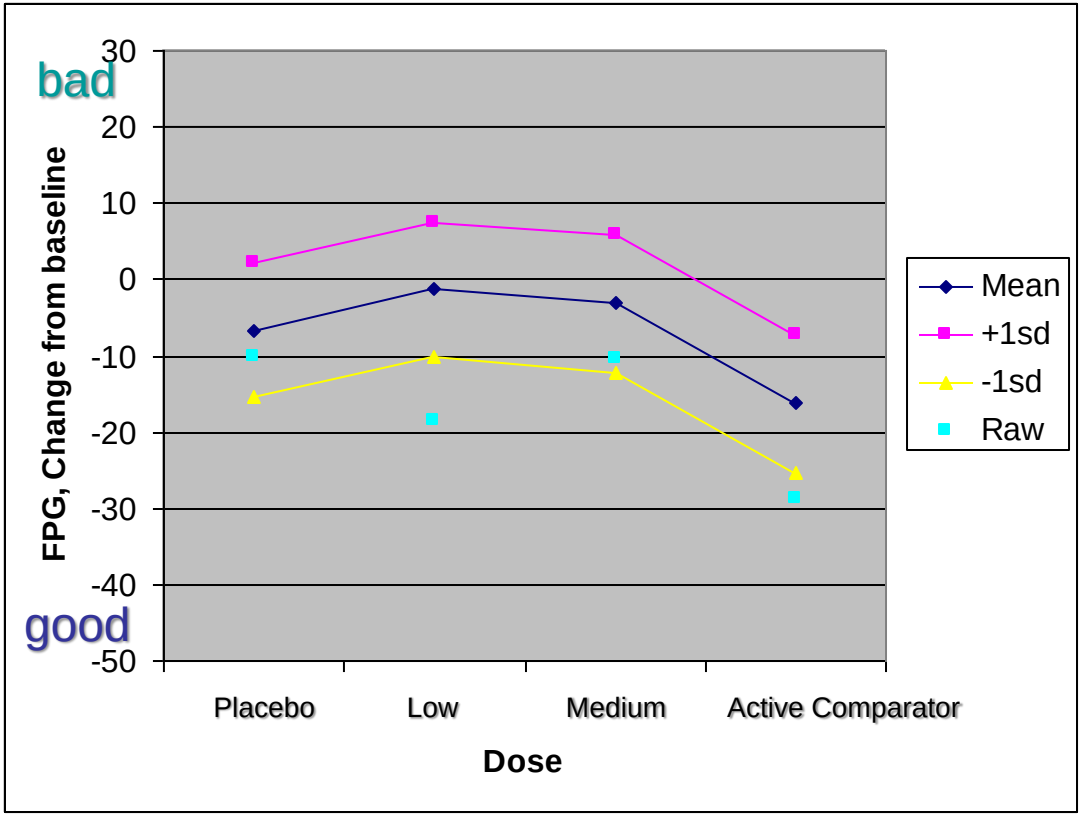
Aug 5 95 Subjects , 25 complete



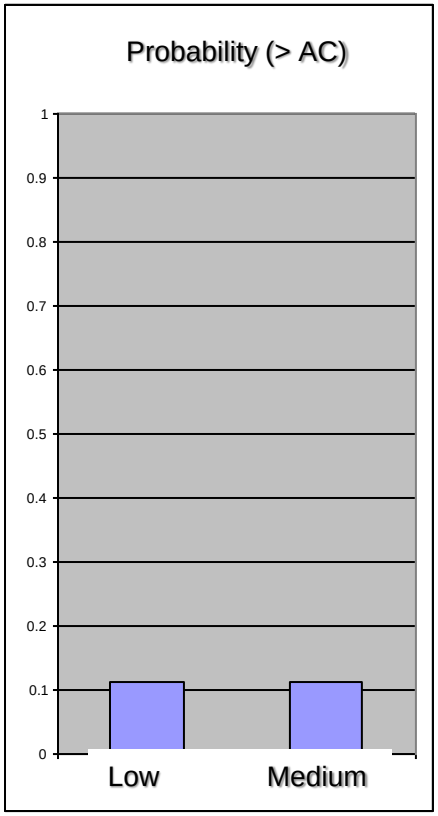


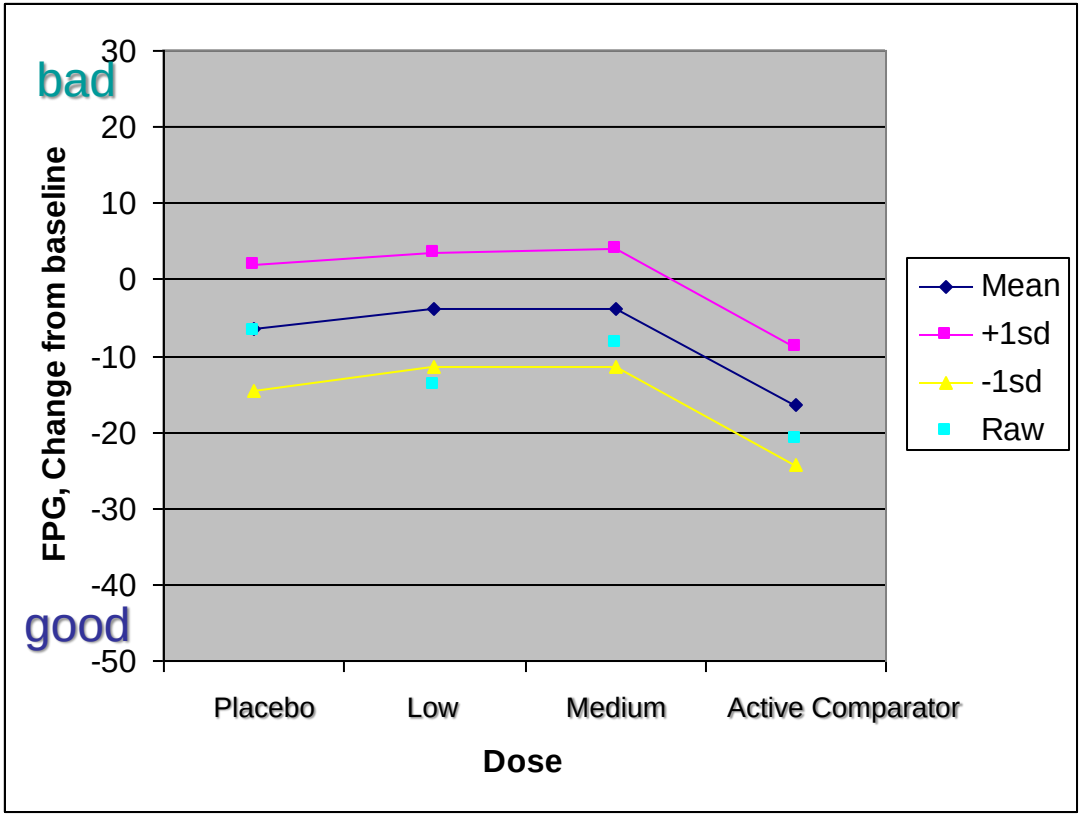
Aug 15 109 Subjects , 35 complete



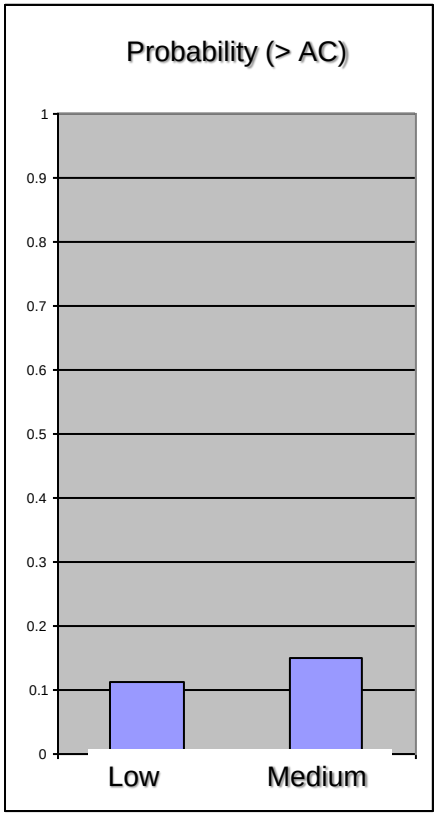


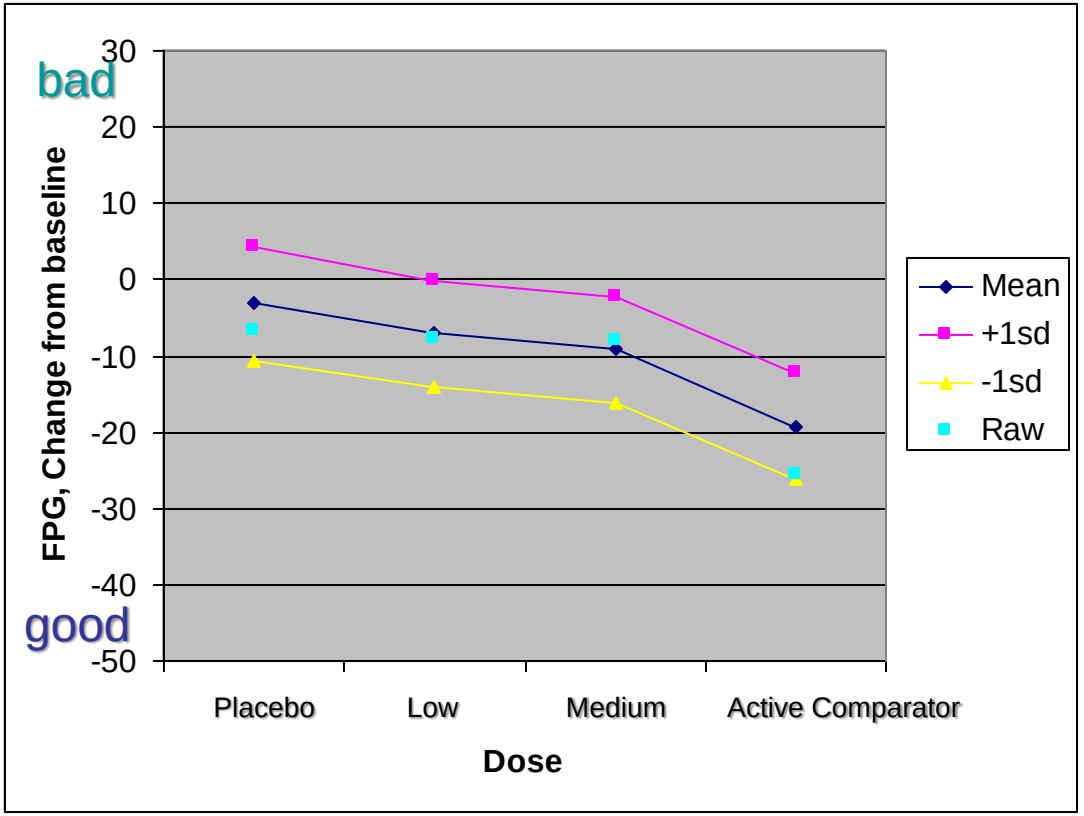
Sep 5 133 Subjects , 46 complete





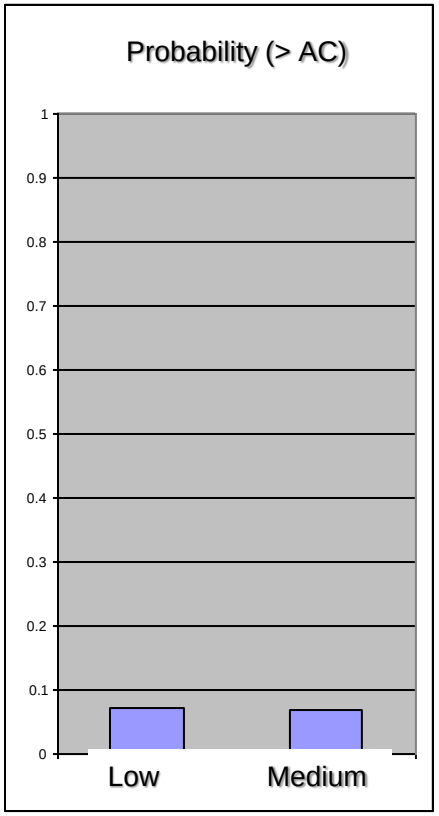
Sep 14 147 Subjects , 53 complete

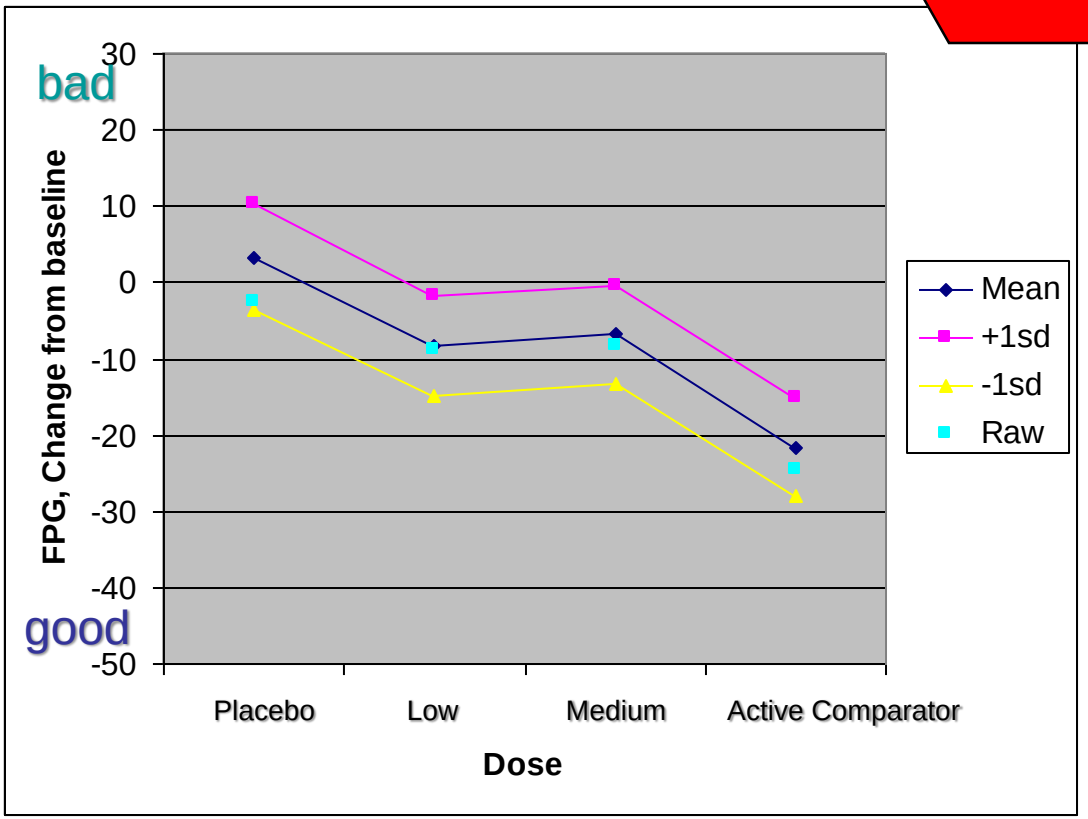




Oct 1 171 Subjects , 61 complete

STOP





Oct 4 179 Subjects , 63 complete

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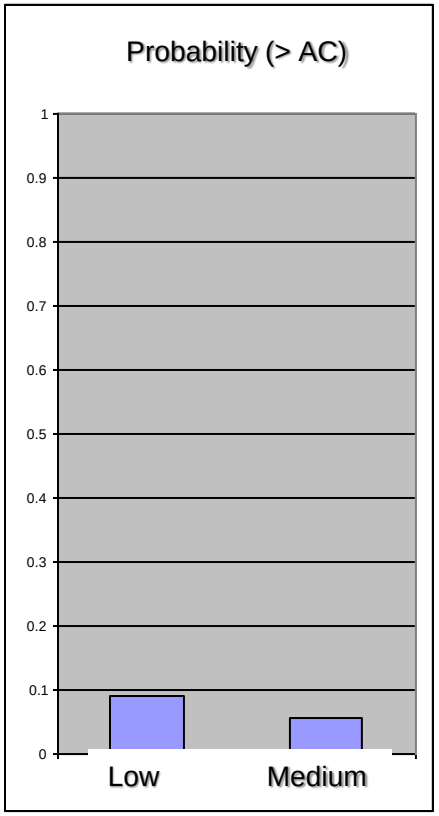
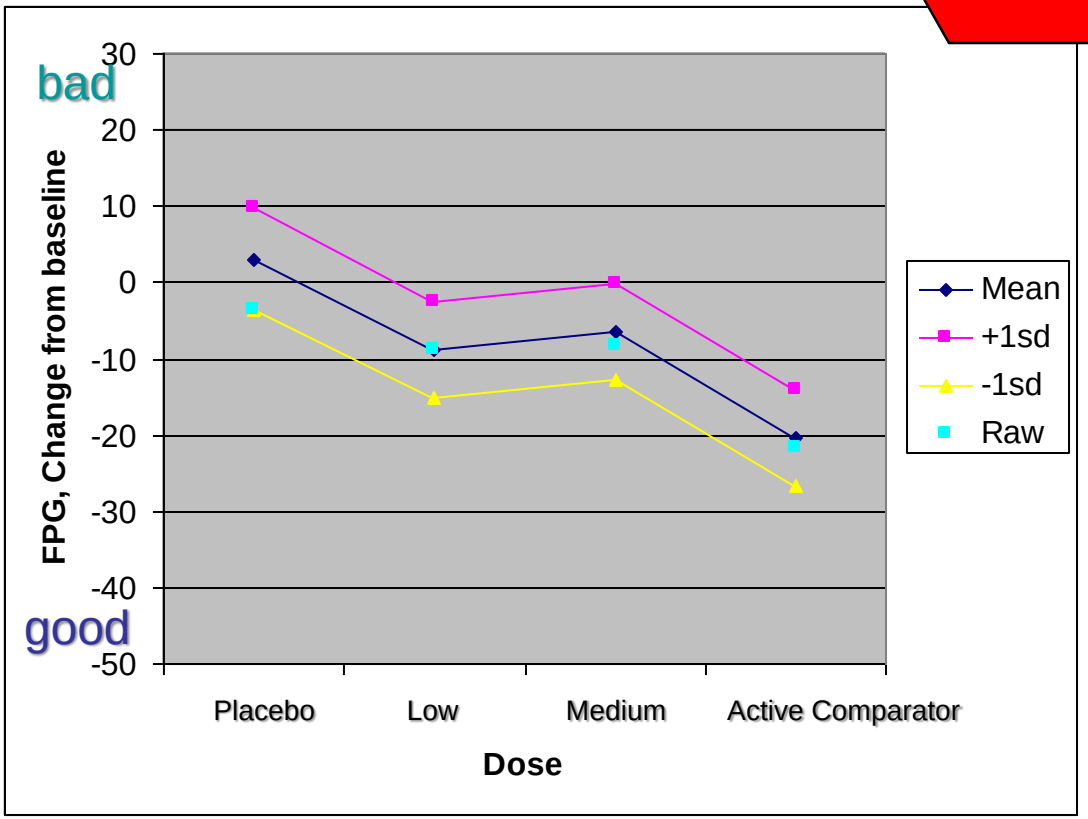
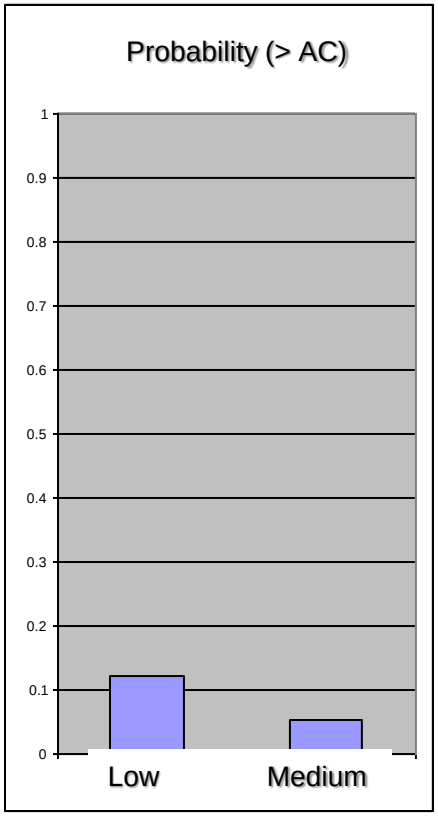
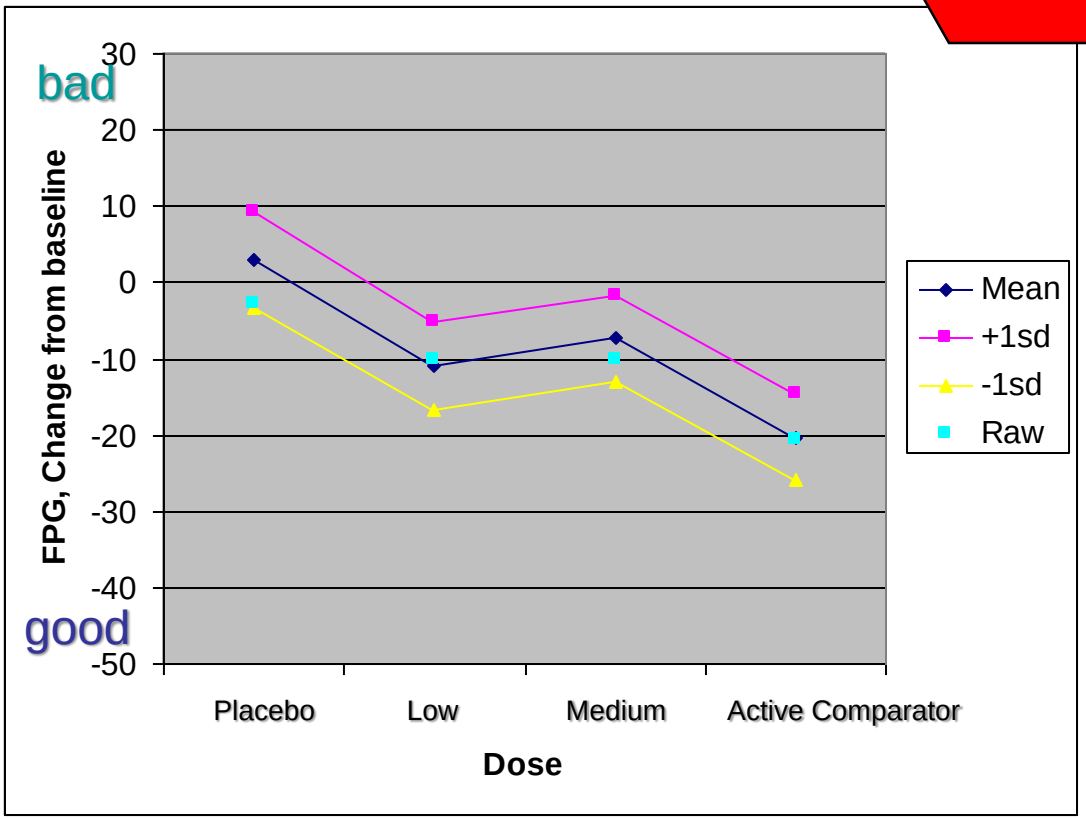




Oct 15 190 Subjects , 70 complete

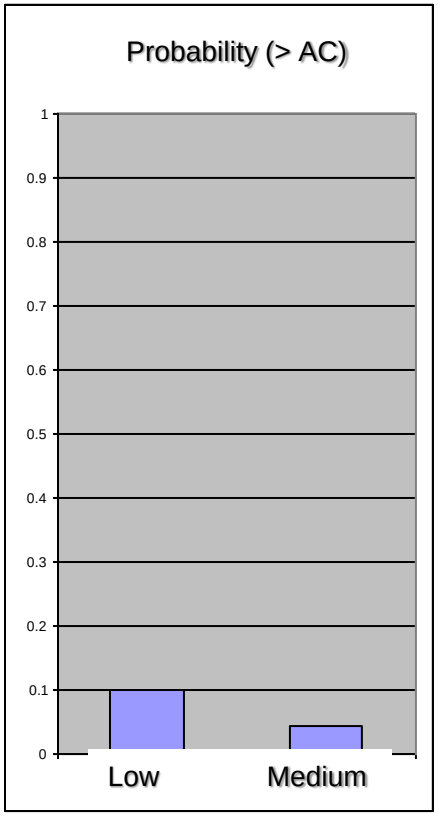
STOP

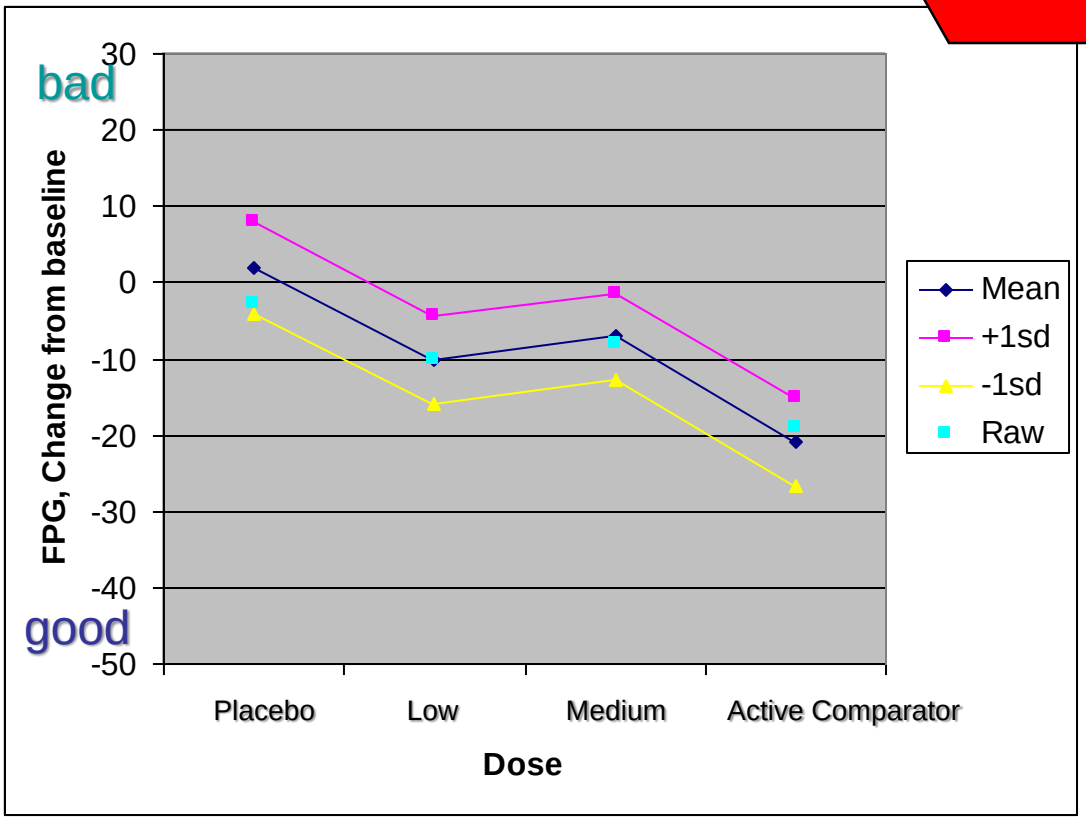




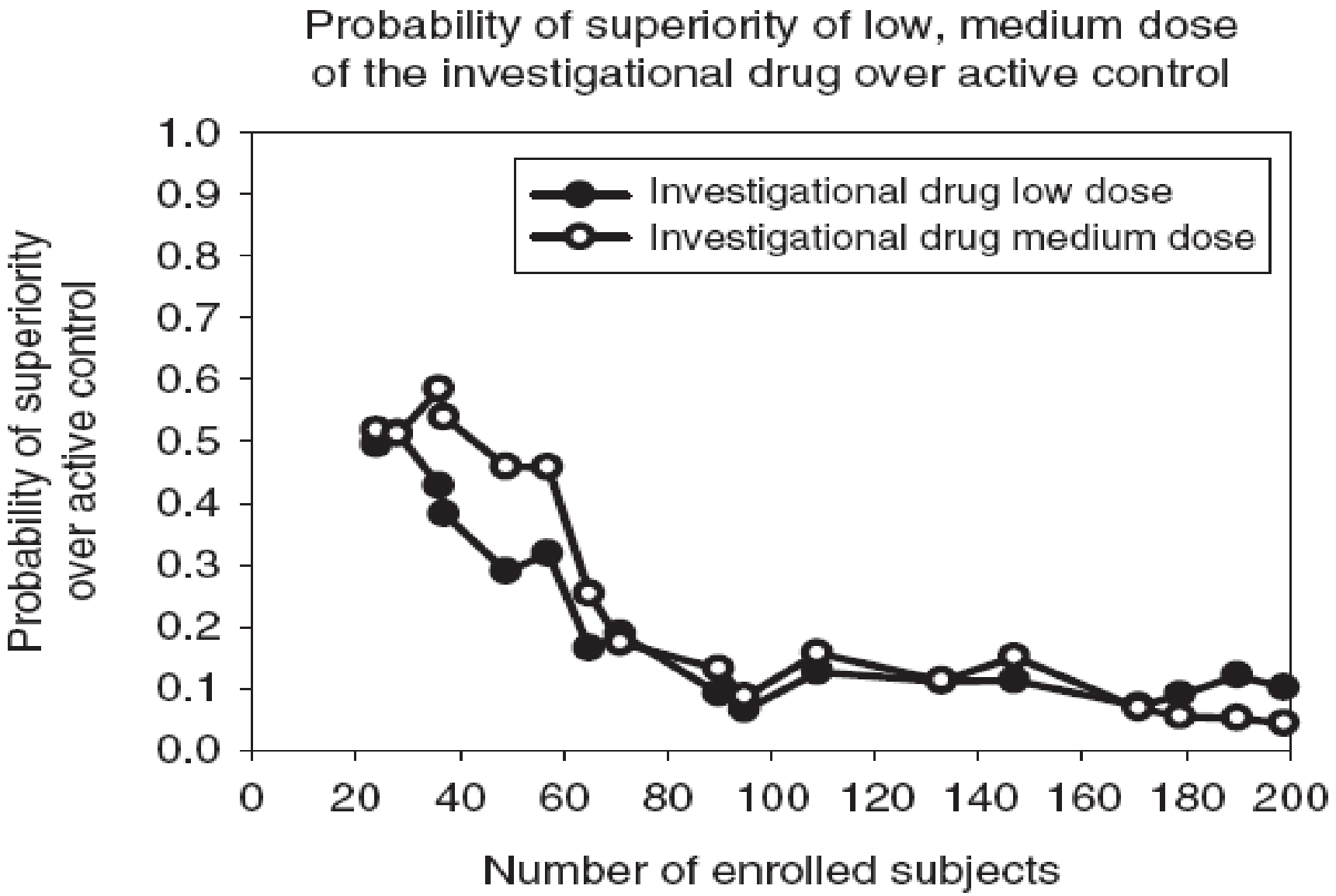
Oct 18 199 Subjects , 71 complete

STOP





Learning in real time - Early stopping



Berry et al. Clin Trials 2010; 7: 121–135

Organizational structure