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Accelerating the Possibilities

ADAPTIVE POPULATION ENRICHMENT DESIGN IN CONFIRMATORY CLINICAL TRIALS

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1 **Enrichment Strategies**

2 **Methodology**

3 **Example**

Motivation

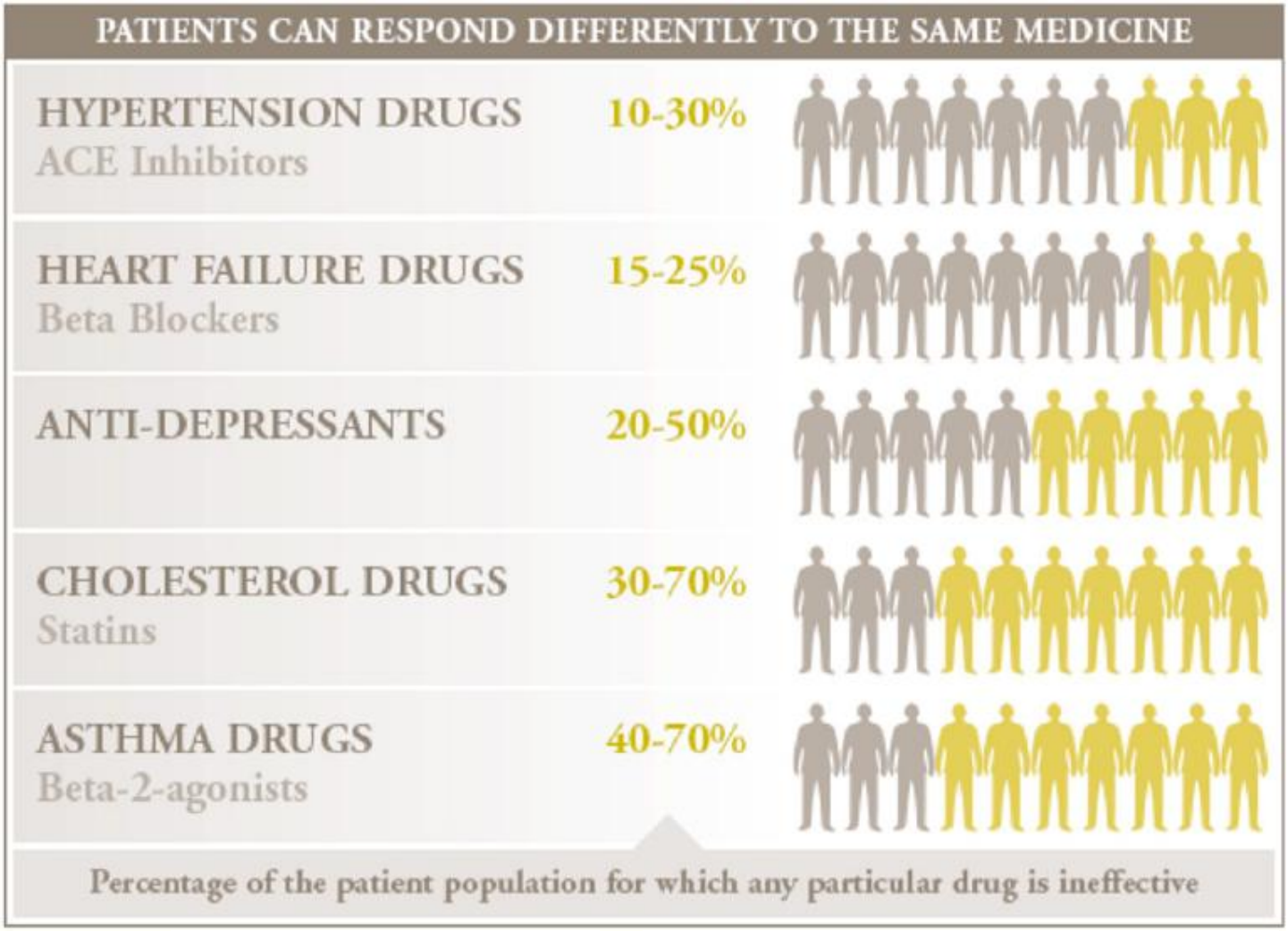
The aspect of "one size fits all" surrounding the conventional design of clinical trials has been challenged, particularly

- when the disease is considered heterogeneous
- or the experimental therapy is tailored to a specific mechanism of action

One size fits all → ***Tailoring*** → **Targeted Therapy**

create diagnostic, prognostic and therapeutic strategies tailored for specific groups of patients

Patients Can Respond Differently

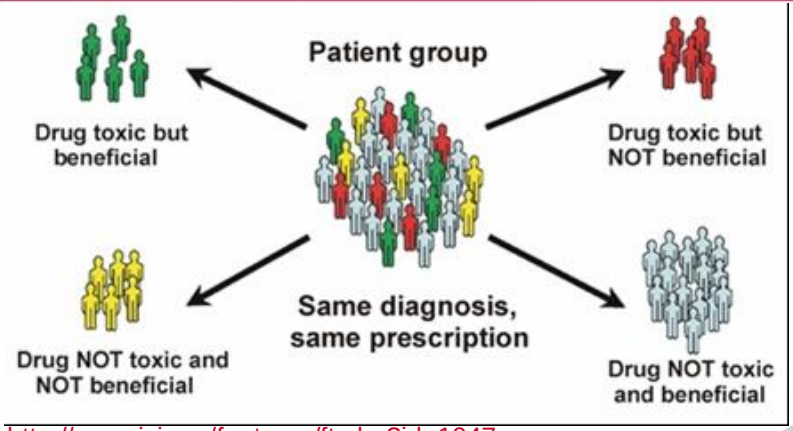


The Case for Personalized Medicine

Edward Abrahams, Ph.D.,[1] and Mike Silver, Ph.D.[2]

Journal of Diabetes Science and Technology
Volume 3, Issue 4, July 2009

A Paradigm Shift



http://www.jyi.org/features/ft.php?id=1047

Empirical Medicine

- Blockbuster drugs targeted at broad population segments
- On average, 50% of patients do not have desired therapeutic outcomes
- Significant adverse events

Precision Medicine

- Drugs targeted at subgroups of patient population
- Genomic profiles determine segmentation and therapy
- Best possible therapeutic outcome with minimal adverse events

Personalized Medicine

- Delivering the right medicine,
- to the right patient,
- at the right dose,
- at the right time

"Personalized Medicine means knowing what works, knowing why it works, knowing who it works for and applying the knowledge for patients" Michael Leavitt, Secretary of Health and Human Services

Potential Benefits

- Patients receive more effective drugs with fewer side effects giving better outcomes
- Avoid time and resources wasted trying unsuitable medicines
- Accelerating the development and availability of new diagnostics, medicines and treatment pathways benefit patients, healthcare providers and business.

FDA Draft Guidance for Industry: *Enrichment Strategies for Clinical Trials*

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

FDA Guidance: Adaptive Enrichment

Definition

Enrichment

- is prospective use of any patient characteristic
  - demographic, pathophysiologic, historical, genetic, and others
- to select a study population in which
- detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population

FDA Draft Guidance for Industry: *Enrichment Strategies for Clinical Trials*, December 2012

Reasons for enrichment

The main reason for enrichment is study efficiency

- increasing the chance of success, often with a smaller sample size
- providing major benefits of individualization,
- directing treatment where it will do the most good
- sparing potential harm to people who cannot respond

Key Concepts

- Extension from the conventional single population design objective to an objective that encompasses several possible patient sub-populations
- Allow more informative evaluation in the patients having different degrees of responsiveness to the therapy
- At an interim stage, it is decided which subpopulation is selected for further inference (including all subpopulations, i.e., full population)
- Not only selection procedures, but also other adaptive strategies (e.g., sample size reassessment, stopping rule) can be performed

EXAMPLE

I-SPY Model: A new paradigm in drug development

- Mainly focused on exploratory stage of DD
  - Match drugs with biomarker signatures
  - Savings from using a common control
  - Better therapies move through faster
  - Successful drug/biomarker pairs graduate to
    - small,
    - focused,
    - more successful Phase 3
  - based on Bayesian predictive probabilities
- Opens new opportunities in confirmatory stage of DD

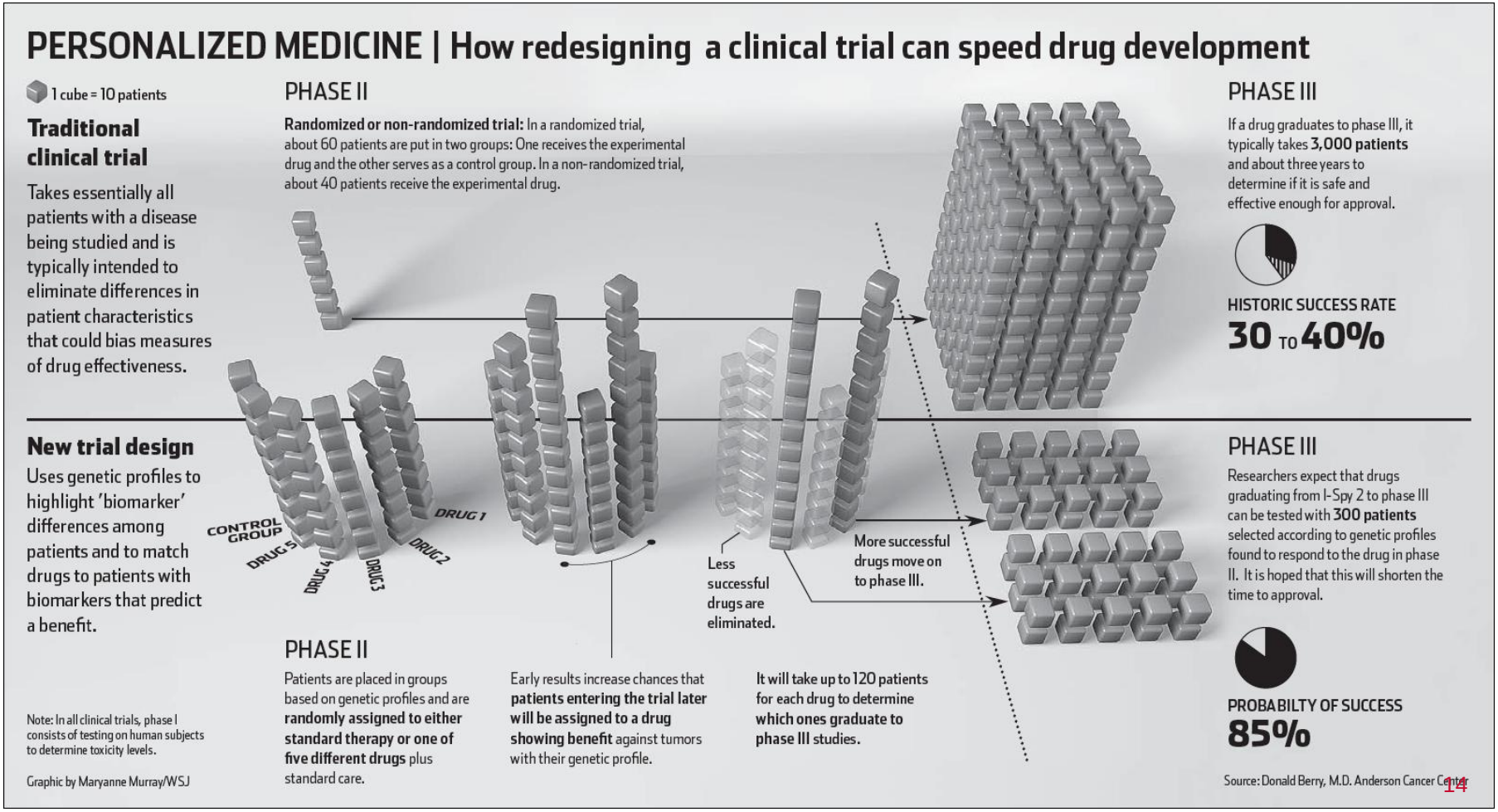
THE WALL STREET JOURNAL.
WSJ.com

THE SATURDAY ESSAY | OCTOBER 2, 2010

A New Rx for Medicine

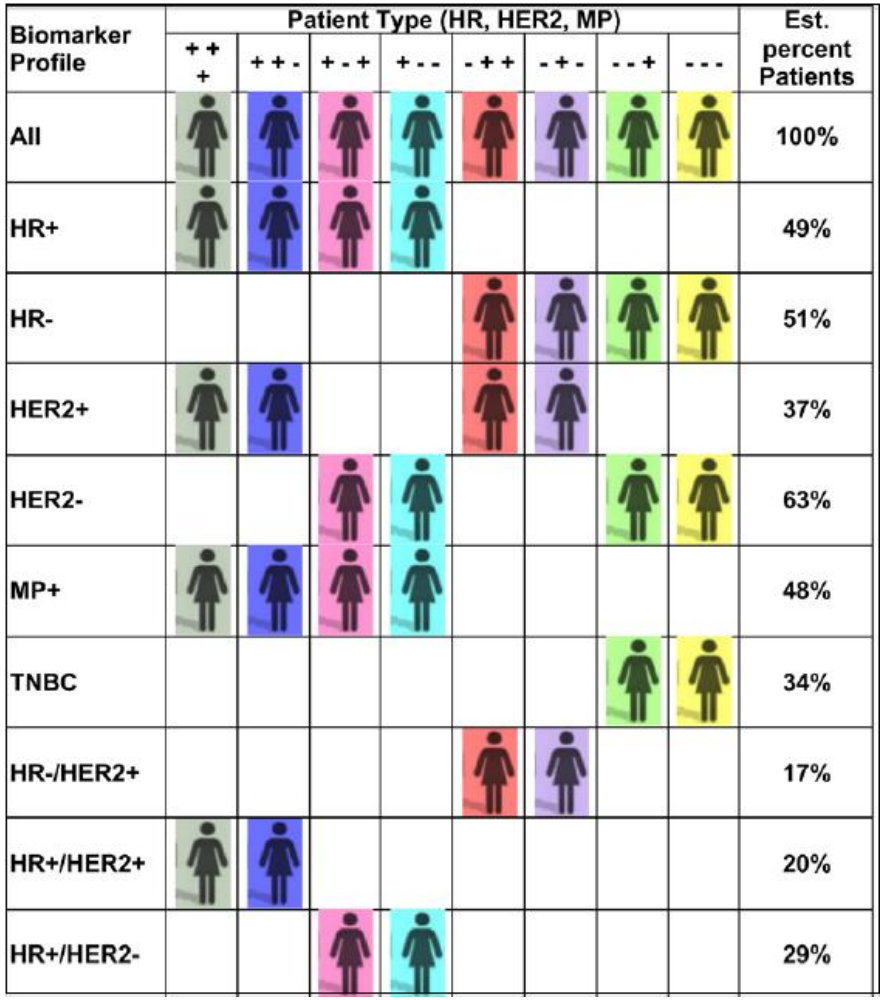
Fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments.

By RON WINSLOW



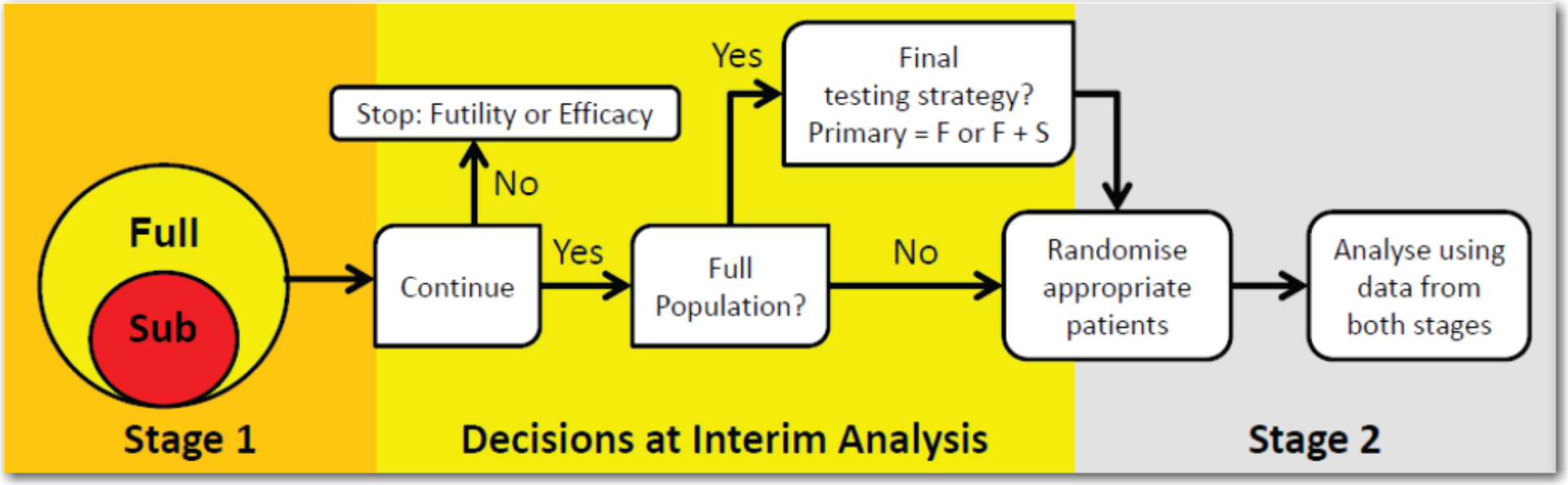
Phase 3 Study in HER2- BC Patients

- Assume that one of the experimental drugs has been graduated from the I-SPY 2 trial with the biomarker signature of triple negative breast cancer (TNBC) but also with some promising effect in HER2- biomarker signature.
- **Option 1**: a confirmatory Phase 3 trial in TNBC patients only
  - prevalence of TNBC is only 34%
- **Option 2**: a confirmatory Phase 3 trial in HER2- patients
  - prevalence of HER2- is 63%
- **Option 3**: Adaptive enrichment design
  - run a confirmatory trial with a two-stage enrichment design
  - starting with the full population (HER2- patients),
  - but with the preplanned option of selecting only the TNBC patients after the 1st stage in case the observed effect is not promising in the HER2- patients with positive hormone-receptor status HR+



Acknowledgment: D. Berry. I-SPY-1 Results

Adaptive Population Enrichment Design



- Stage1 objective
  - Stop for futility/efficacy
  - To continue with HER2- (Full) population
  - To confirm greater benefit in TNBC Subpopulation (Sub)
  - To adjust the sample size
- Stage 2 data and the relevant groups from Stage 1 data combined

Ballpark Sample Size Calculations

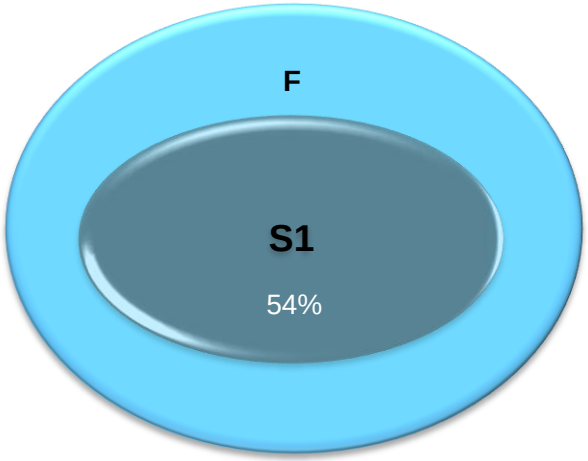
- Primary Endpoint : pathologic complete response (pCR) at surgery
- Power: 90%
- Sign. Level: 0.025
- Control Rate: pCR=0.3
- TRT Effect: 0.2

	Plan 1 Rates	Plan 2 Rates	Plan 3 Rates	Plan 4 Rates
alpha	0.0125	0.0125	0.0125	0.0125
Futility stops	-	-	-	-
tails	1	1	1	1
K	1	1	1	1
Design	-	-	-	-
Information rates	-	-	-	-
Hypothesis	diff<=0	diff<=0	diff<=0	diff<=0
Parameters	pi1=0.3 pi2=0.4	pi1=0.3 pi2=0.45	pi1=0.3 pi2=0.5	pi1=0.3 pi2=0.55
Power %	90.0	90.0	90.0	90.0
Total ASN H0	-	-	-	-
Total ASN H01	-	-	-	-
Total ASN H1	-	-	-	-
Total maximum N	1124.9	512.6	293.3	189.5
Allocation	1	1	1	1

Possible TRT Effect Range: [0.1 – 0.25]

Population Enrichment Simulation

Patient Profile	MP- Her2+ HR+	MP- Her2+ HR-	MP- Her2- HR+	MP- Her2- HR-	MP+ Her2+ HR+	MP+ Her2+ HR-	MP+ Her2- HR+	MP+ Her2- HR-
								
Prevalence	16%	7%	23%	6%	4%	10%	6%	28%
Predicted pCR	47%	67%	25%	43%	35%	55%	17%	32%



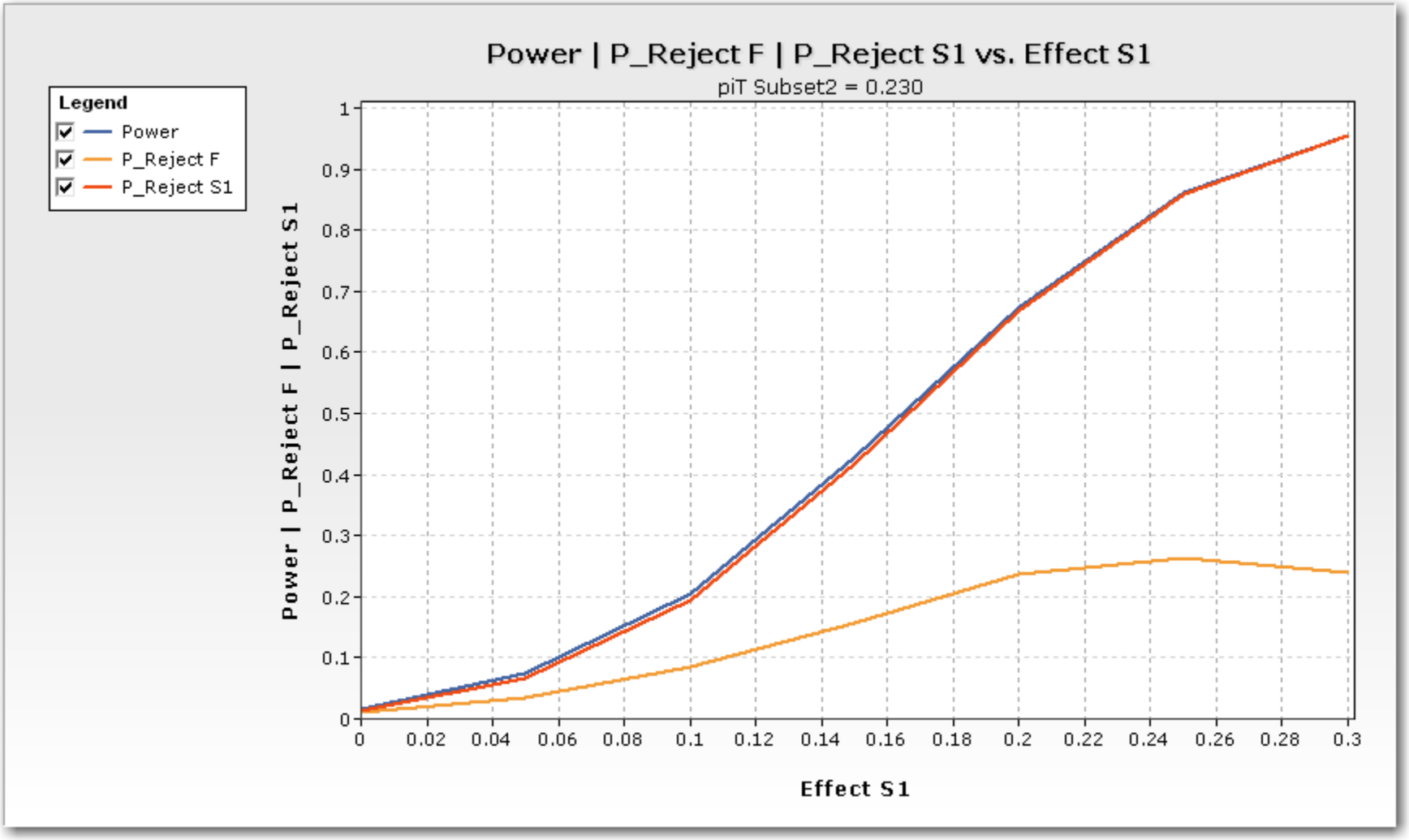
Acknowledgment: D. Berry. I-SPY-1 Results

- Prevalence of TNBC in HER2- : 54%
- Control pCR Rate in TNBC: 0.34
- Control pCR Rate in HER2- ∩ HR+: 0.23
- Total of 21 Simulation Scenarios:
  - TRT effect in TNBC: 0 to 0.3 by 0.05
  - TRT effect in HER2- ∩ HR+: 0, 0.1, 0.2

Design

- Total sample size: 300 patients
- Stage 1 sample size:150 pats
- Testing strategy: inverse normal p-value combination
- Intersection test: Bonferroni
- Selection rule: $\varepsilon = 0.1$ rule

Operating Characteristics:



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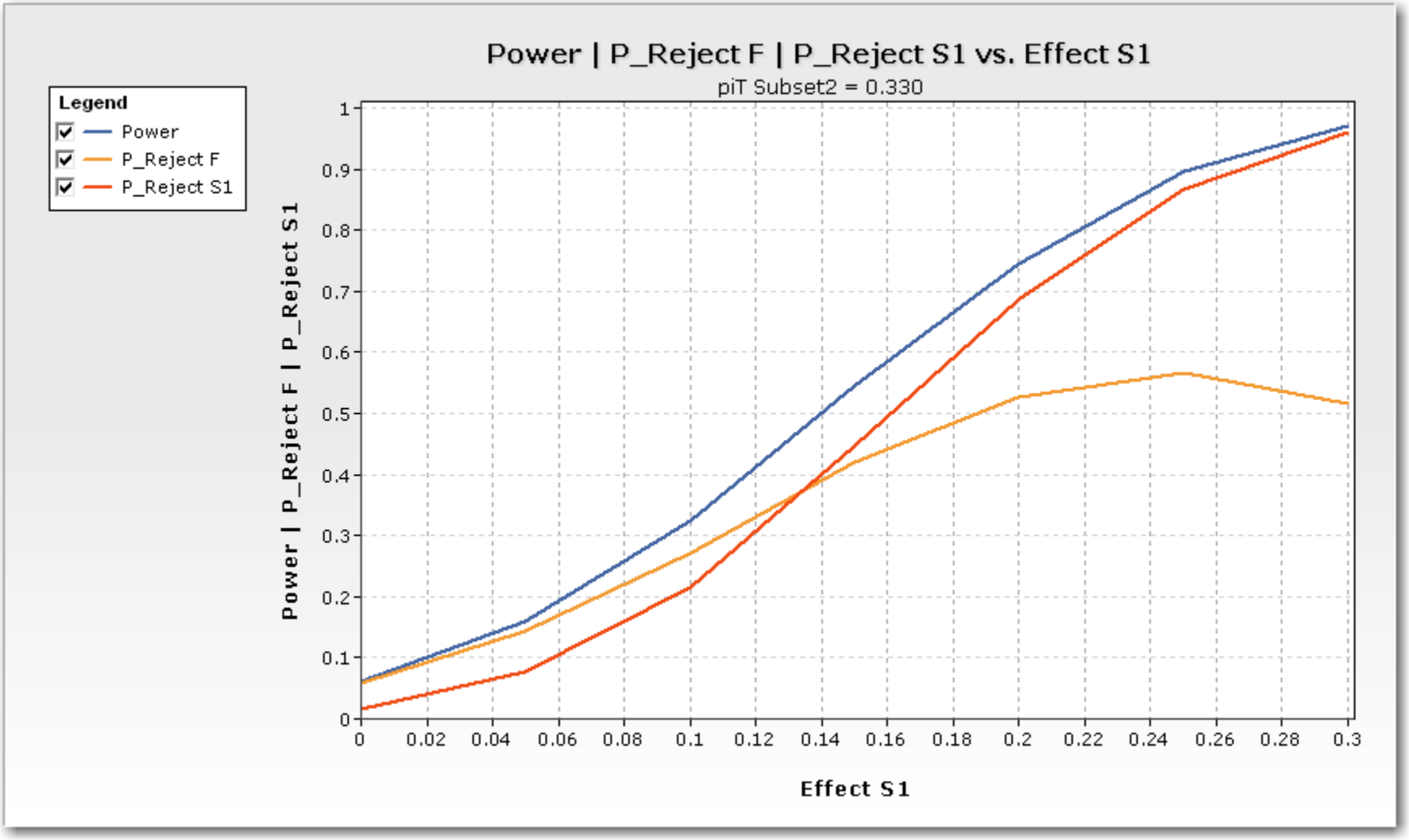

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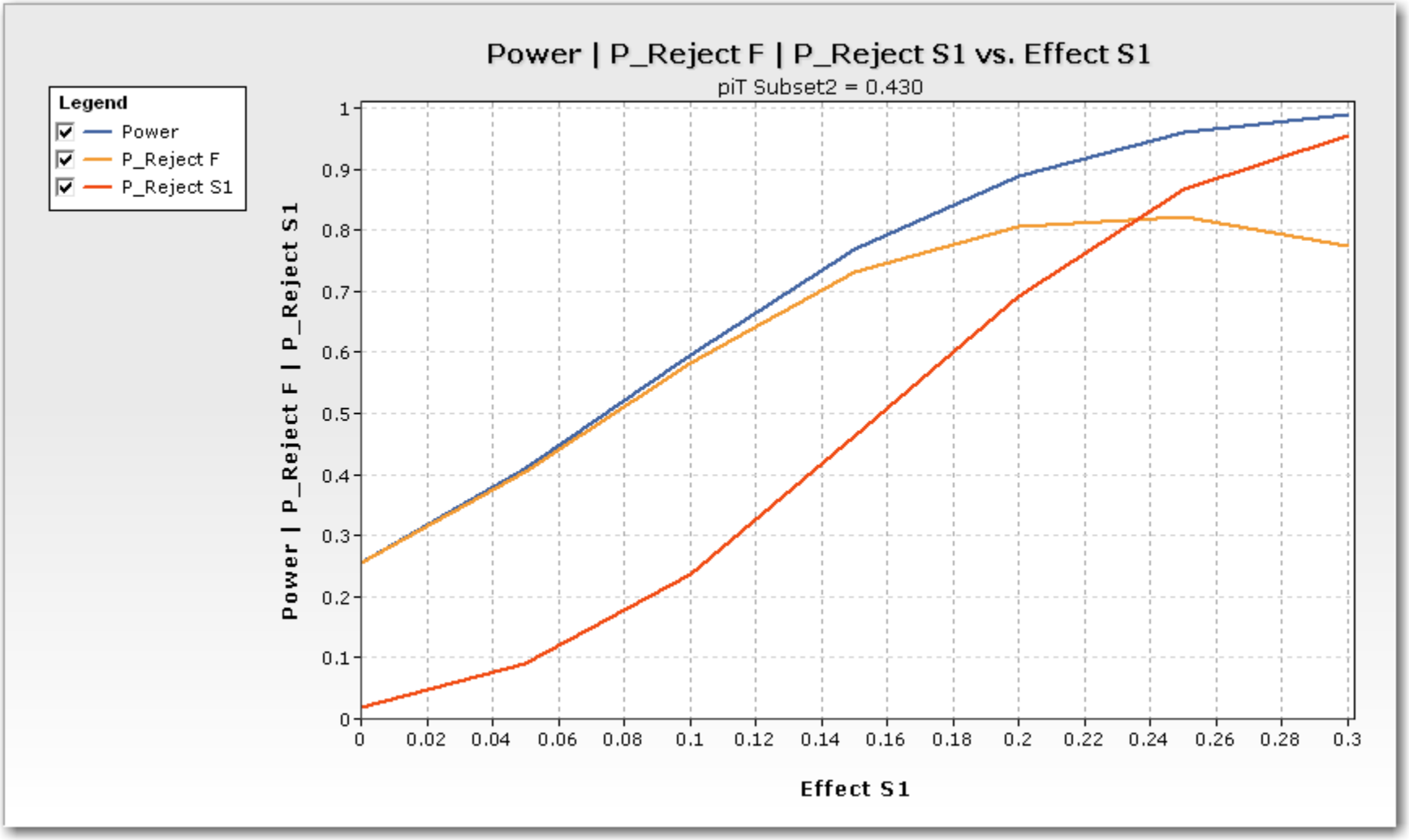
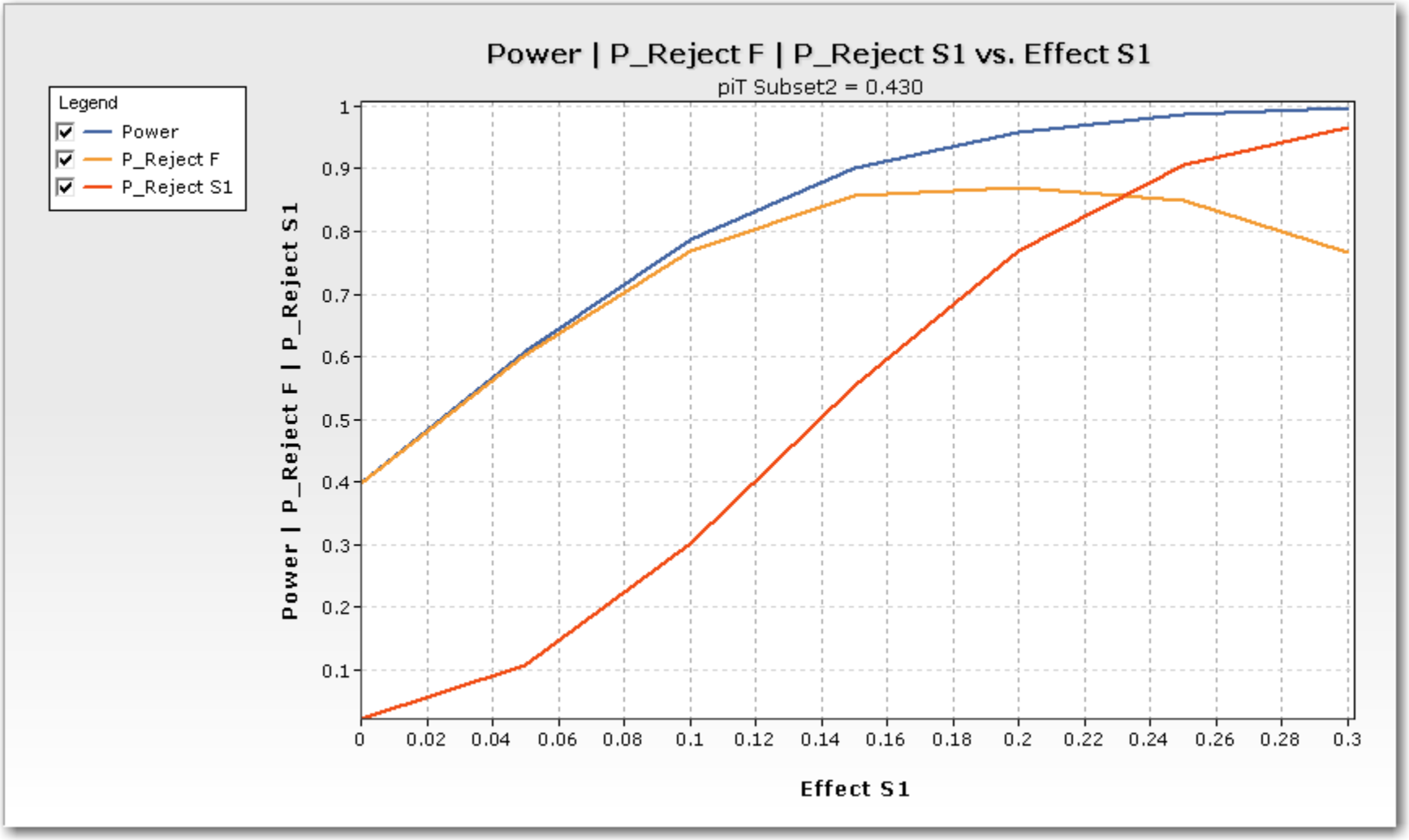


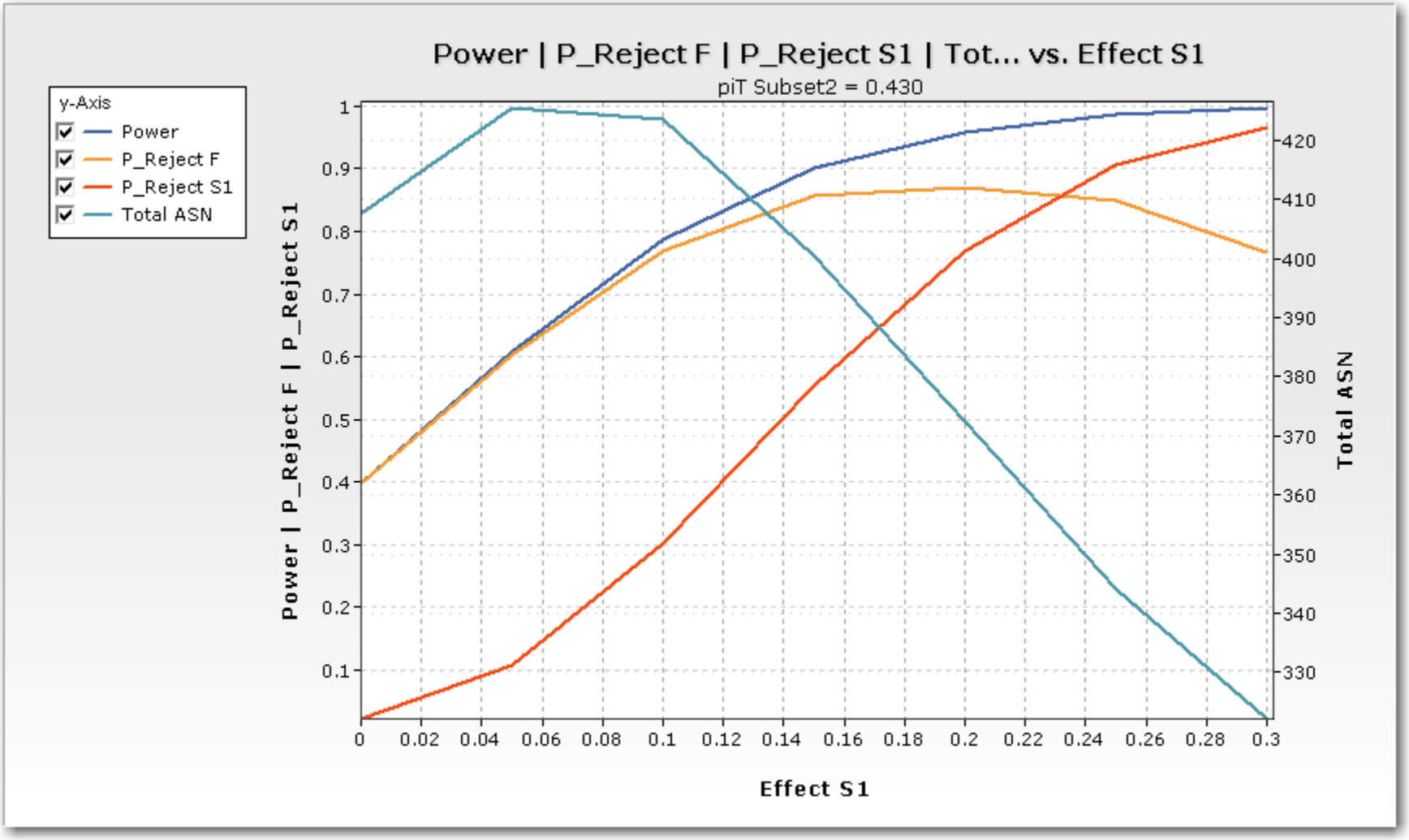
Sample Size Reestimation

- Allow up to a 3-fold sample size increase for Stage 2
- 90% Conditional Power based on observed TRT effect
- Total Sample Size: 300 - 600

Operating Characteristics



Operating Characteristics



METHODOLOGY

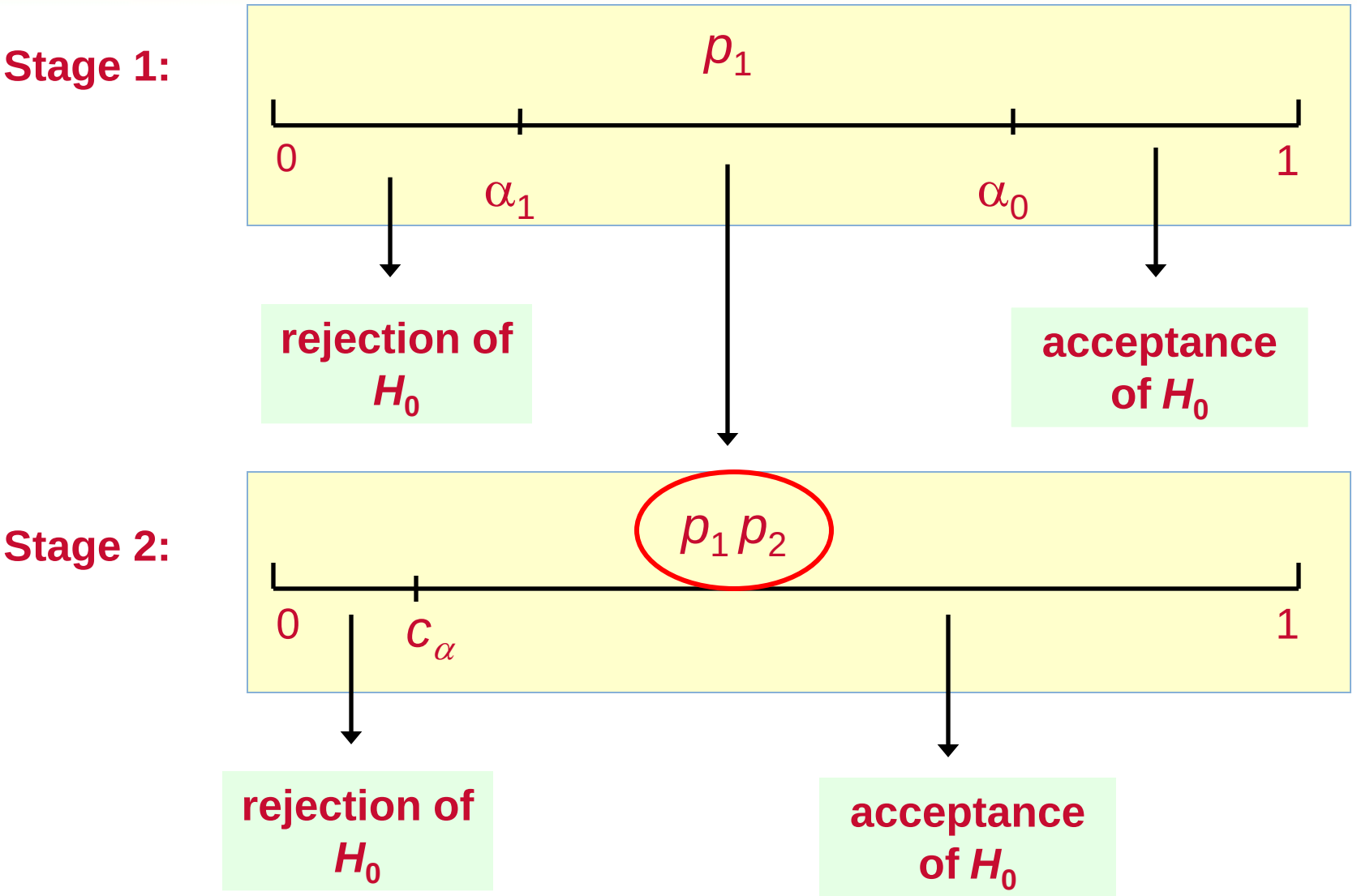
Adaptive Confirmatory Designs

All information available in an interim analysis may be used for planning the subsequent stages of the trial, under control of the prespecified Type I error rate.

Two pioneering proposals:

1. Bauer & Köhne (Biometrics, 1994):
   Combination of *p*-values with a specific combination function (Bauer, 1989)
2. Proschan & Hunsberger (Biometrics, 1995):
   Specification of a conditional error function

Procedure of Bauer & Köhne (1994)



Procedure of Bauer & Köhne (1994)

- Use of Fisher´s combination test to combine the separate stage *p*-values p_1 and p_2, i.e., $C(p_1,p_2) = p_1 p_2$
- Under H_0, the *p*-values are stochastically independent, irrespective of the choice of the design for the second stage.
- H_0 is rejected after the second stage if

$$p_1 p_2 \leq c_\alpha = \exp(-1/2\,\chi^2_{4,\alpha})$$

- Other combination functions $C(p_1,p_2)$ and/or more than two stages can also be considered.
- In the two stages, different hypotheses can be considered, the considered global test is a test for $H_0 = H_0^1 \cap H_0^2$

Adaptive Design using the *inverse normal* method

Consider at *k*th stage, $k = 1,2,...,K$:

$$T_k^* = C(p_1,\ldots,p_k) = \frac{\Phi^{-1}(1-p_1)+\Phi^{-1}(1-p_2)+\ldots+\Phi^{-1}(1-p_k)}{\sqrt{k}}$$

$\Phi^{-1}(1-p_k) \sim N(0;1)$ if p_k uniformly distributed on [0; 1]

Under H_0, the same distributional assumption as for the group sequential tests applies and, therefore, the decision regions of the traditional group sequential tests can be used.

Lehmacher & Wassmer, 1999

Properties

- Decision regions of group sequential tests can be used
- Generalization to more than two stages and more general designs straightforward
- Use *unweighted* mean of test statistics from the separate stages also for unequal and arbitrarily (data dependent) fixed sample sizes.
- Effect on power is small unless „dramatic“ changes in sample size were performed
- Can also be used in testing situations with nuisance parameters
- If no design changes were performed, the inverse normal technique yields the traditional test

Methodology for Population Enrichment

- Sources for alpha inflation
  - Interim analyses
  - Sample size reassessment
  - Selection from multiple sub-populations
- The adaptive procedure strongly controls the pre-specified family-wise Type I error rate
- The procedure is based on the application of the closed test procedure together with combination tests

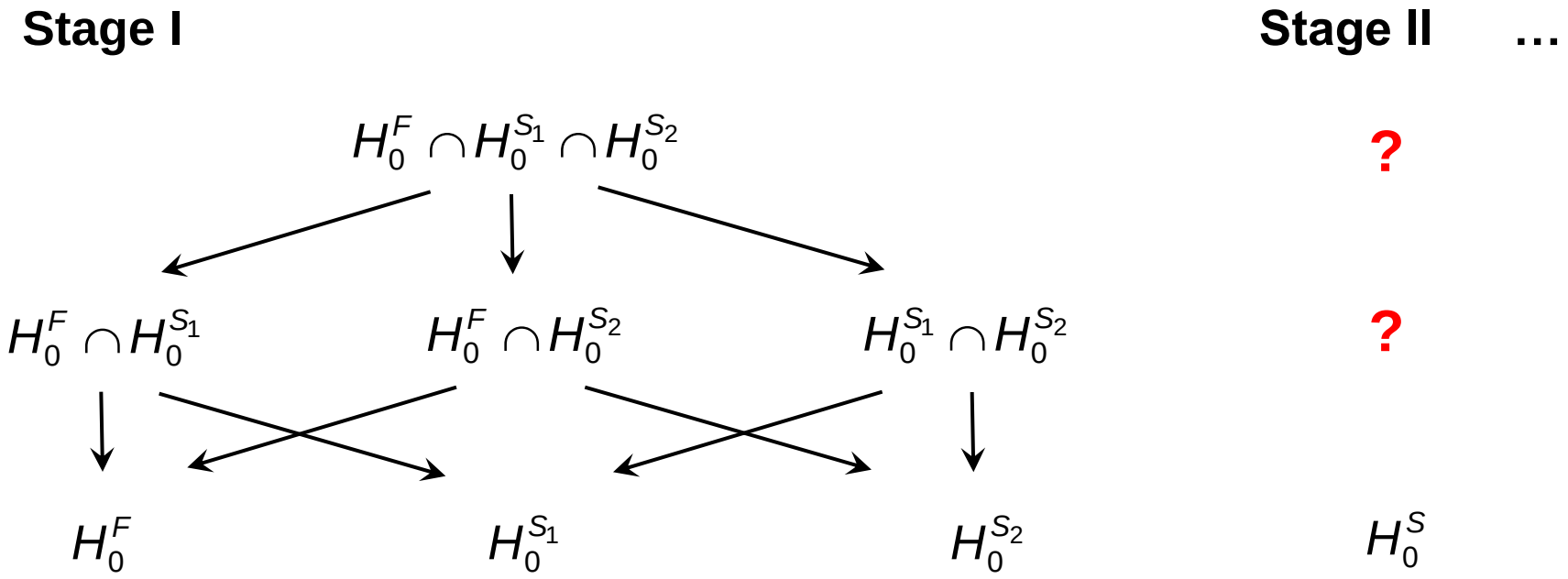
The Enrichment Test Procedure

- Consider prespecified subpopulation(s) $S_1,\ldots,S_G$, which can be nested, and a full population F:

$$S_G \subset \ldots \subset S_1 \subset F$$

- The proposed adaptive procedure fulfills the regulatory requirements for the analysis of adaptive trials in that it strongly controls the prespecified (familywise) Type I error rate

Closed testing procedure



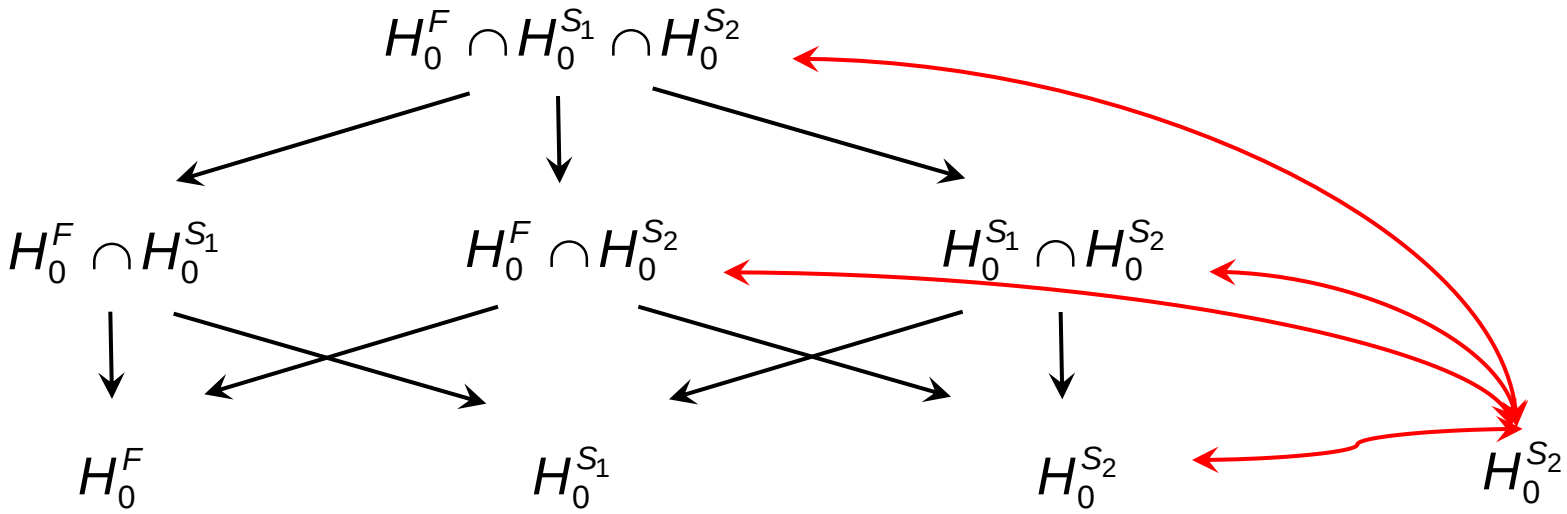
Simple “trick”: Test of intersection hypotheses are formally performed as tests for H_0^S.

H_0^S can be rejected if all combination tests exceed the critical value u_2.

Closed testing procedure: Stage II

Example $S = S_2$

Stage I **Stage II** **…**



- $H_0^{S_2}$ can be rejected if all combination tests exceed the critical value u_2.
- The choice of tests for intersection hypotheses is free. One might use Bonferroni, Simes or Sidak tests.
- For one subgroup also Dunnett‘s test can be applied

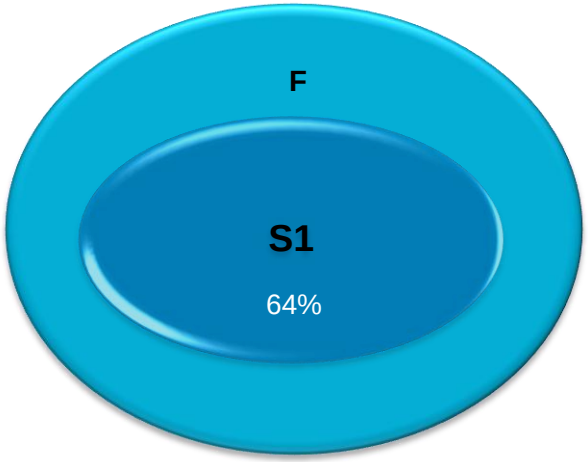
Test strategies

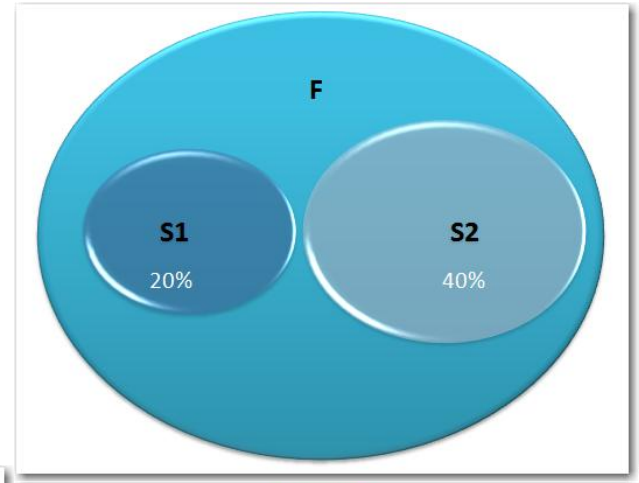
- Combination test:
  - Inverse normal method
  - Fisher's combination test
- Separate Phase II/III:
  - Phase II only for sub-population selection
  - Phase III is group sequential
- Intersection Tests:
  - Dunnett
  - Bonferroni
  - Sidak
  - Simes
  - Hierarchical

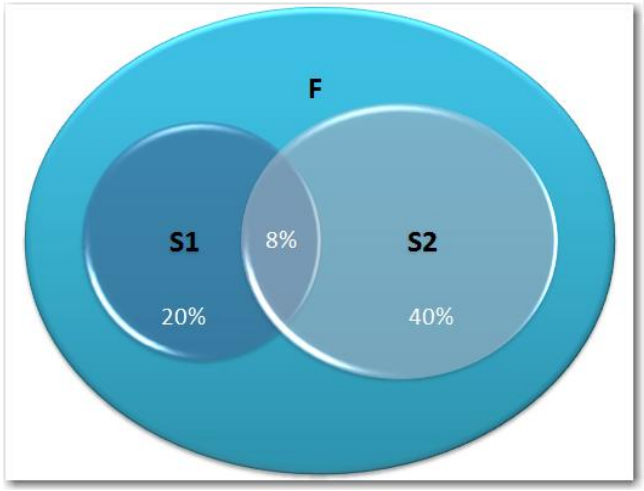
Selection Procedure

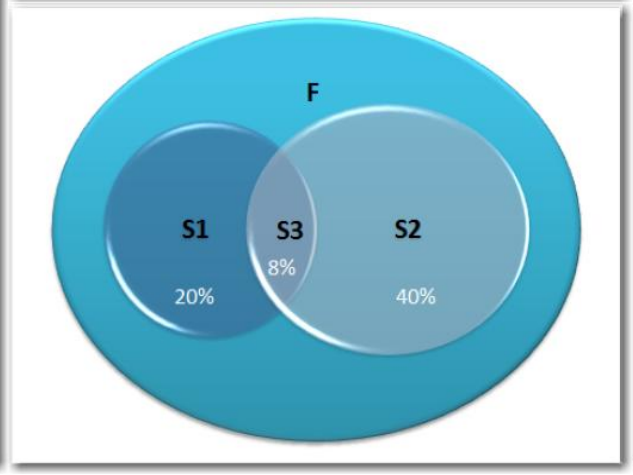
- Select the (sub)population with the largest effect
- Select *r* sets with largest effect
- Select sets with effect compared to full population not worse than ε
- Select *i*-th set
- Select a set if effect exceeds a threshold *t*
- Drop a set if $CP < x$
- Effect measured on test statistic or mean effect scale

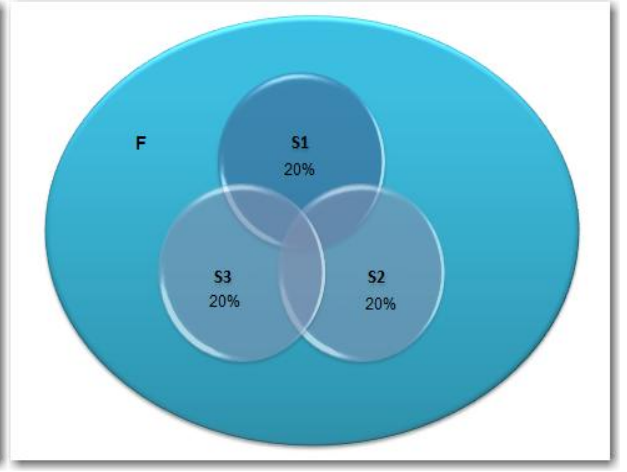
Different Configurations



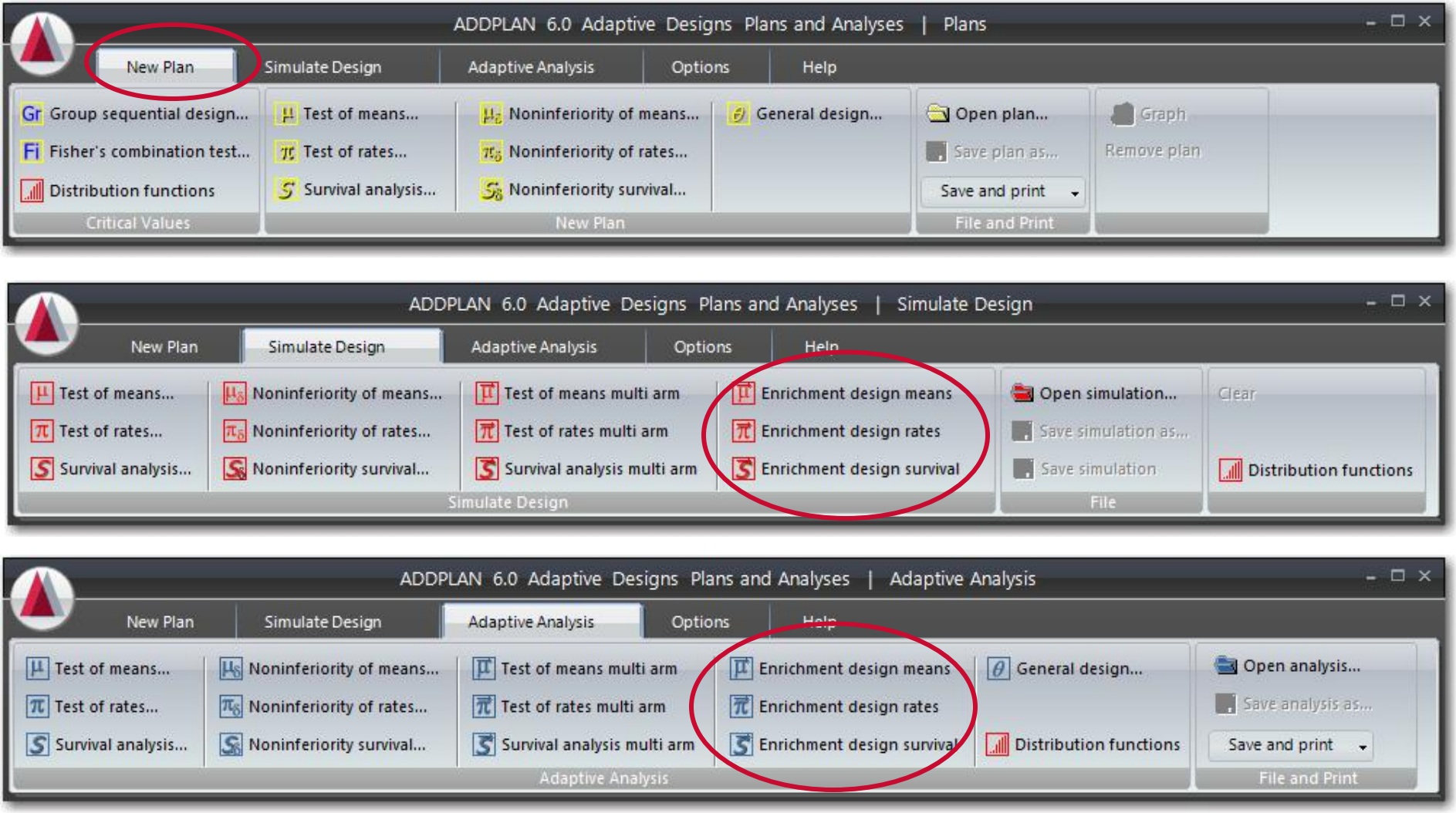








ADDPLAN 6.0



Summary

- Attractive and general procedure for adaptive confirmatory design that controls Type I error rate
- The “rules” for adaptation and stopping for futility
  - Do not need to be pre-specified
  - Adaptations may depend on all interim data including secondary and safety endpoints.
  - Can make use of Bayesian principles integrating all information available, also external to the study
  - Should be evaluated (e.g. via simulations) and preferred version recommended, e.g., in the Simulation Report or DMC Charter
- Comparison of different strategies and options for analyses is mandatory. The role of simulation becomes increasingly important