



AptivSolutionsSM
Accelerating the Possibilities

ADAPTIVE POPULATION ENRICHMENT DESIGN IN CONFIRMATORY CLINICAL TRIALS

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1

Enrichment Strategies

2

Methodology

3

Example

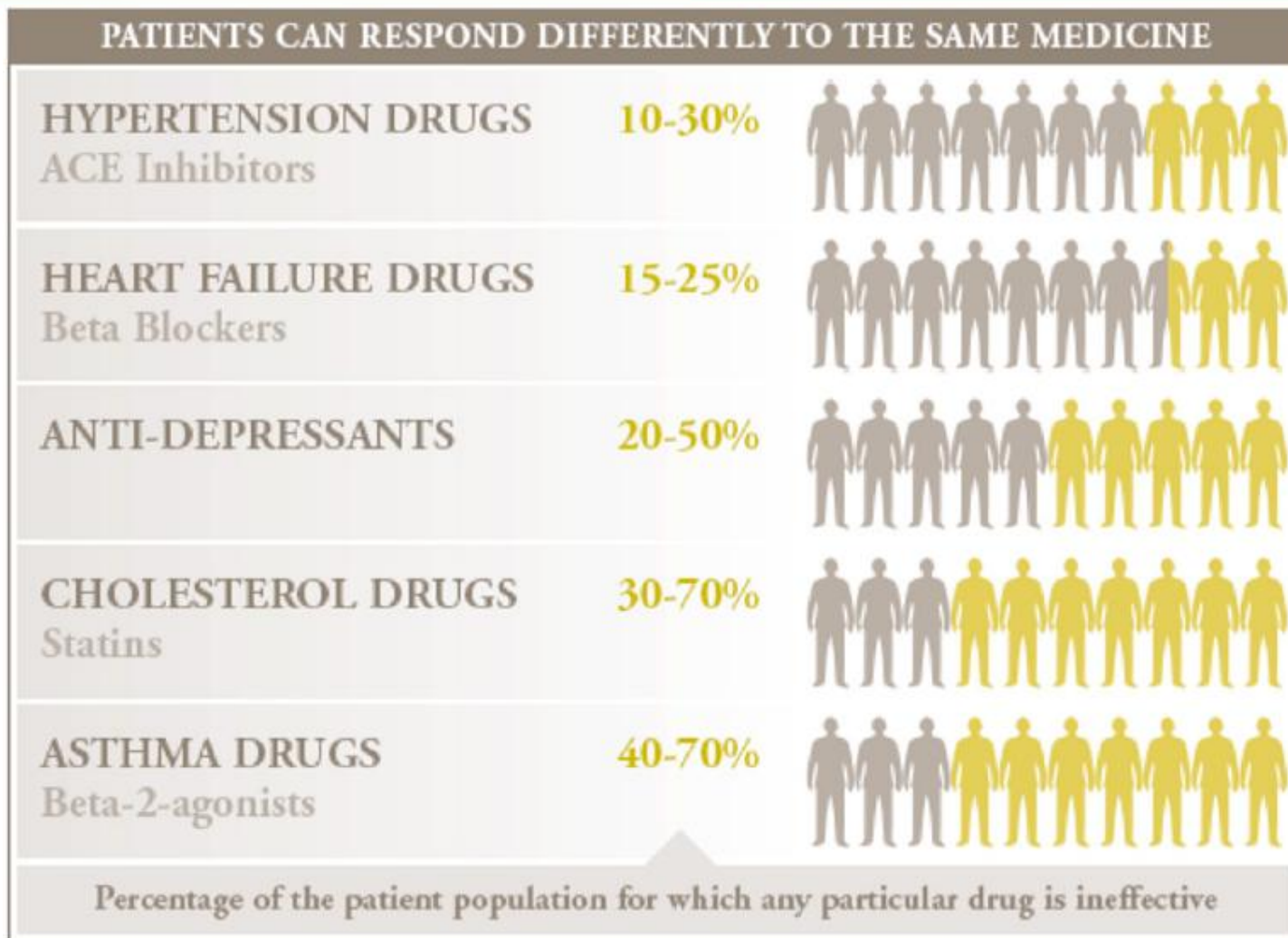
Motivation

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



Patients Can Respond Differently



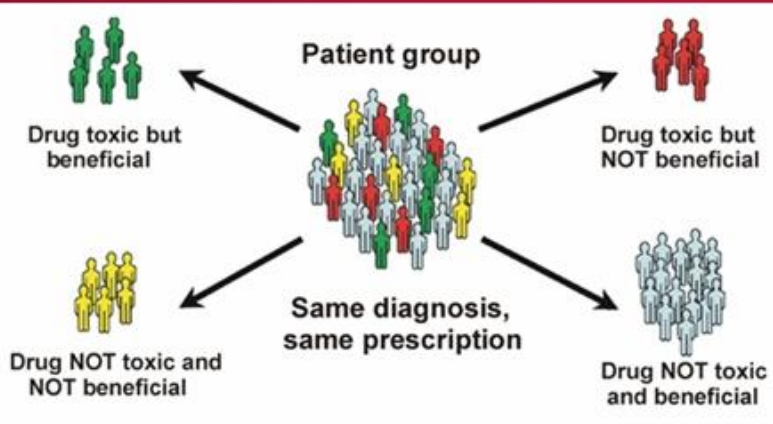
The Case for Personalized Medicine

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FDA Draft Guidance for Industry: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DRAFT GUIDANCE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

V. PREDICTIVE ENRICHMENT	8
A. EMPIRIC STRATEGIES	11
1. <i>Open Trial Followed by Randomization</i>	11
2. <i>An Individual's History of Response to a Treatment Class</i>	12
3. <i>Factors Identified in Results from Previous Studies</i>	13
B. PATHOPHYSIOLOGICAL STRATEGIES	13
1. <i>Metabolism of the Test Drug</i>	13
2. <i>Effect on Tumor Metabolism</i>	14
3. <i>Proteomic Markers and Genetic Markers Linked to a Proteomic Marker</i>	14
C. GENOMIC STRATEGIES	15
D. RANDOMIZED WITHDRAWAL STUDIES	17
E. STUDIES IN NON-RESPONDERS OR PATIENTS INTOLERANT TO OTHER THERAPY	19
1. <i>Studies in Non-Responders</i>	20
2. <i>Study in Intolerants: Angiotensin Receptor Blockers (ARBs) in People Who Cough on Lisinopril</i>	22
VI. ENRICHMENT STUDY DESIGN AND OTHER CONSIDERATIONS	22
A. GENERAL CONSIDERATIONS	22
1. <i>Performance Characteristics of a Screening Strategy for Selecting Patients</i>	23
2. <i>When Should a Classifier Be Developed and Characterized?</i>	23
B. WHICH POPULATIONS TO STUDY	24
1. <i>Studying Marker-Positive Patients Only</i>	25
2. <i>Studying Both Marker Positive and Negative Patients</i>	26
3. <i>Studies in Alternative Therapy Non-Responders to Support Claim of Effectiveness in Non-Responders</i>	27
4. <i>Studies in Patients Intolerant of a Prior Treatment</i>	28
C. TYPE I ERROR RATE CONTROL FOR ENRICHED STUDY SUBPOPULATIONS	29
D. ADAPTIVE ENRICHMENT	29
E. CAUTIONS IN INTERPRETATION	30

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

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

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

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

1 cube = 10 patients

Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

New trial design

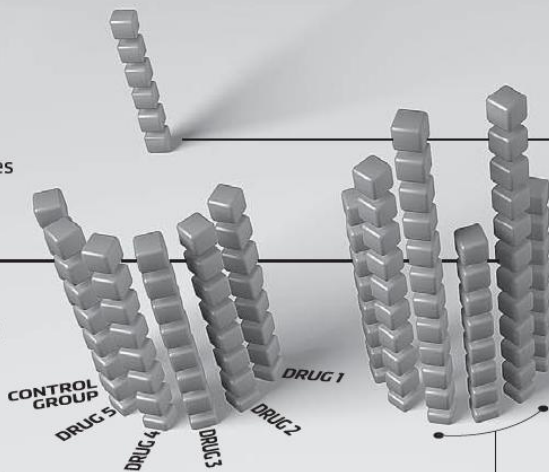
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

PHASE II

Randomized or non-randomized trial: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either standard therapy or one of five different drugs plus standard care.

Early results increase chances that patients entering the trial later will be assigned to a drug showing benefit against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

Less successful drugs are eliminated.

More successful drugs move on to phase III.

PHASE III

If a drug graduates to phase III, it typically takes 3,000 patients and about three years to determine if it is safe and effective enough for approval.



HISTORIC SUCCESS RATE
30 TO 40%

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with 300 patients selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



PROBABILITY OF SUCCESS
85%

Source: Donald Berry, M.D. Anderson Cancer Center

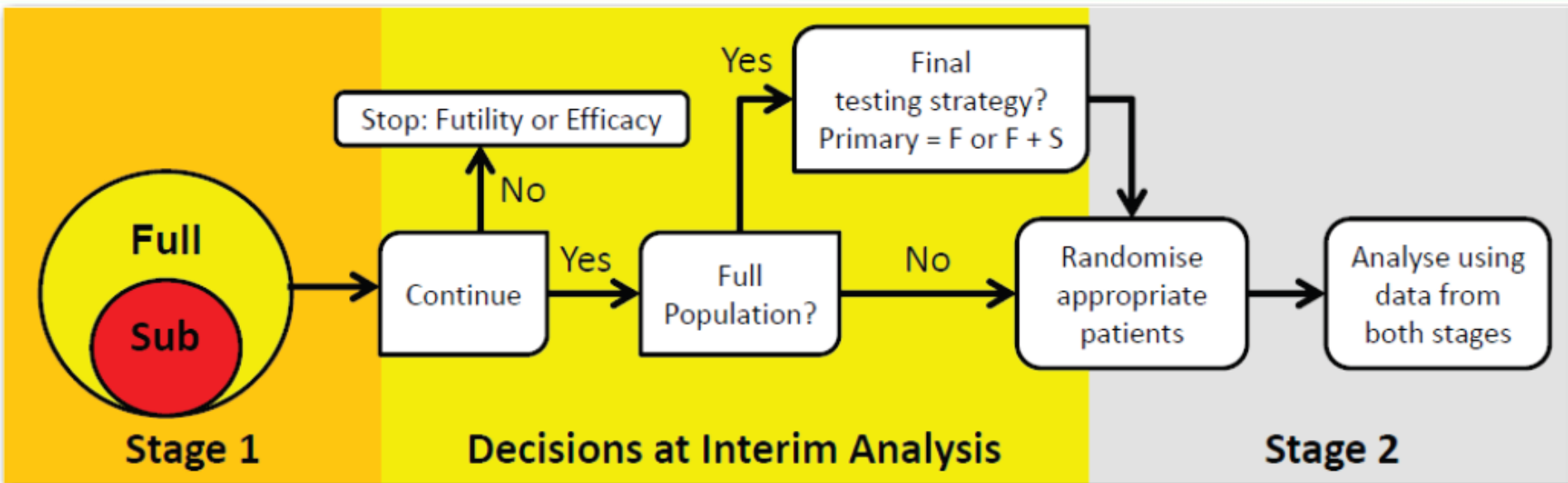
Phase 3 Study in HER2- BC Patients

- 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+

Biomarker Profile	Patient Type (HR, HER2, MP)								Est. percent Patients
	++ +	+++	+++	+++	+++	+++	+++	+++	
All									100%
HR+									49%
HR-									51%
HER2+									37%
HER2-									63%
MP+									48%
TNBC									34%
HR-/HER2+									17%
HR+/HER2+									20%
HR+/HER2-									29%

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

Adaptive Population Enrichment Design



■ Stage 1 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

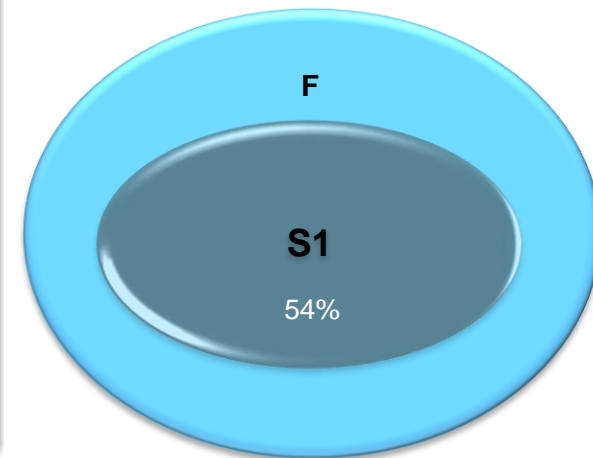
- **Primary Endpoint :** pathologic complete response (pCR) at surgery
- **Power:** 90%
- **Sign. Level:** 0.025
- **Control Rate:** pCR=0.3
- **TRT Effect:** 0.2

	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- \cap HR+: 0.23
- Total of 21 Simulation Scenarios:
 - TRT effect in TNBC: 0 to 0.3 by 0.05
 - TRT effect in HER2- \cap HR+: 0, 0.1, 0.2

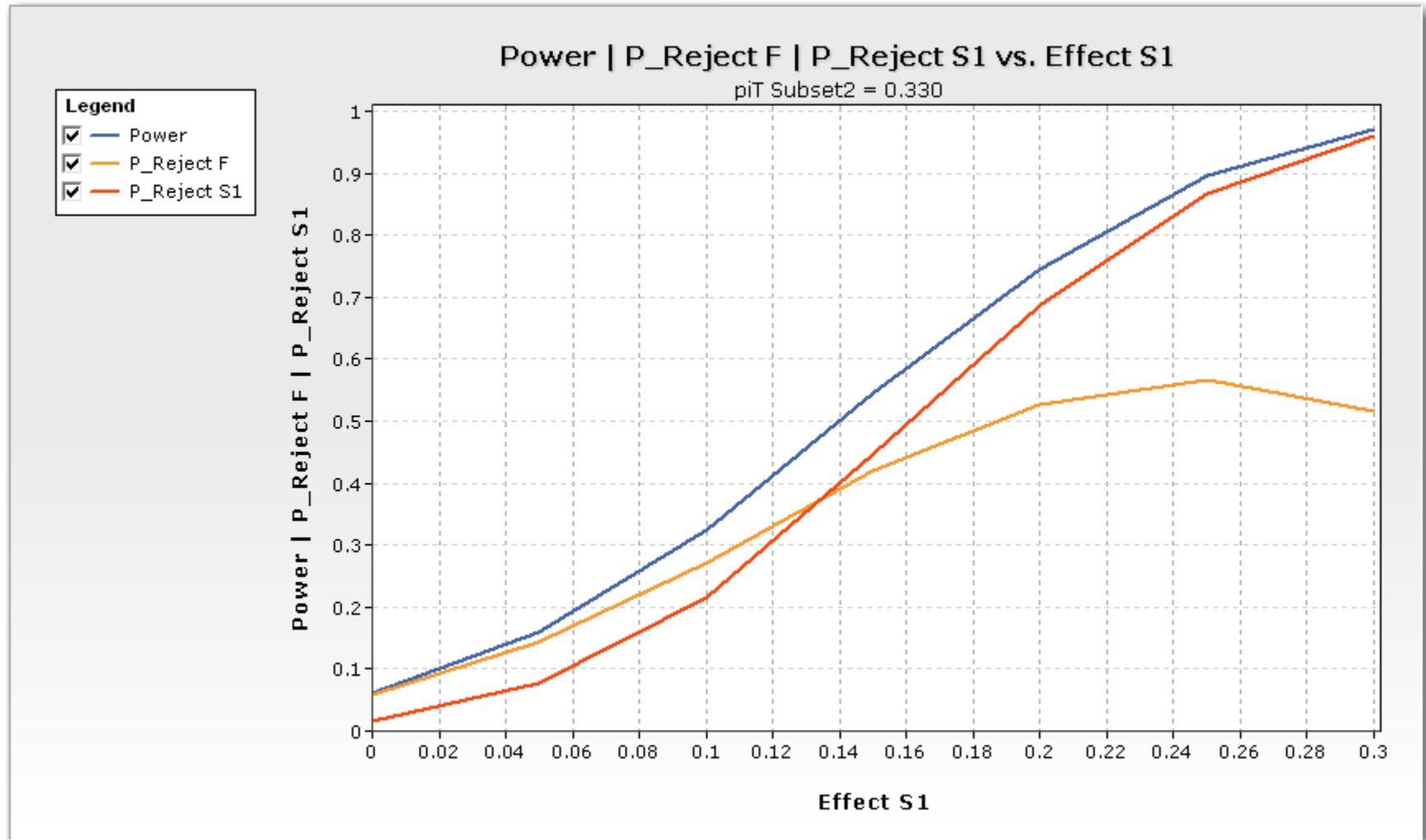
Design

- 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

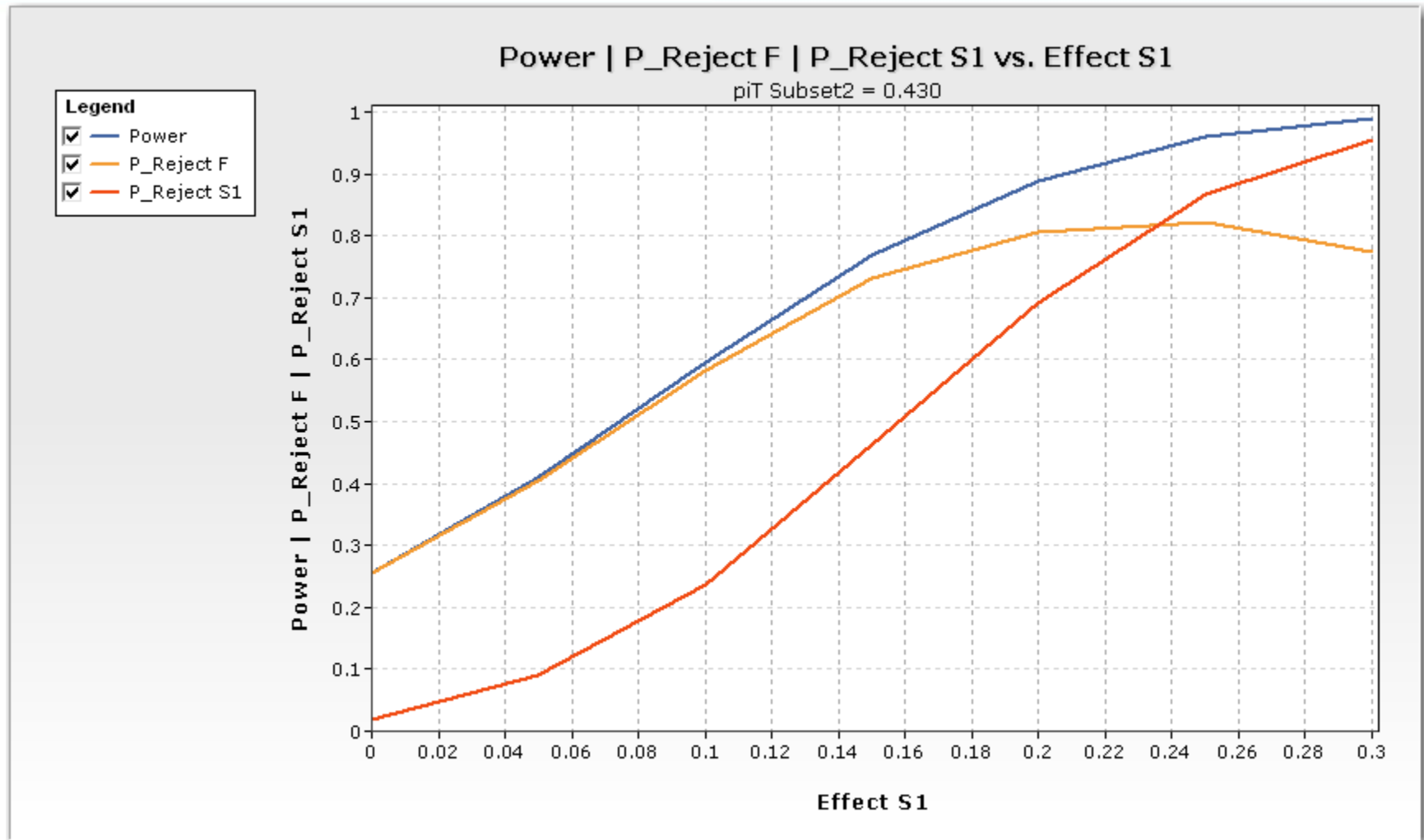
Operating Characteristics:



Operating Characteristics:



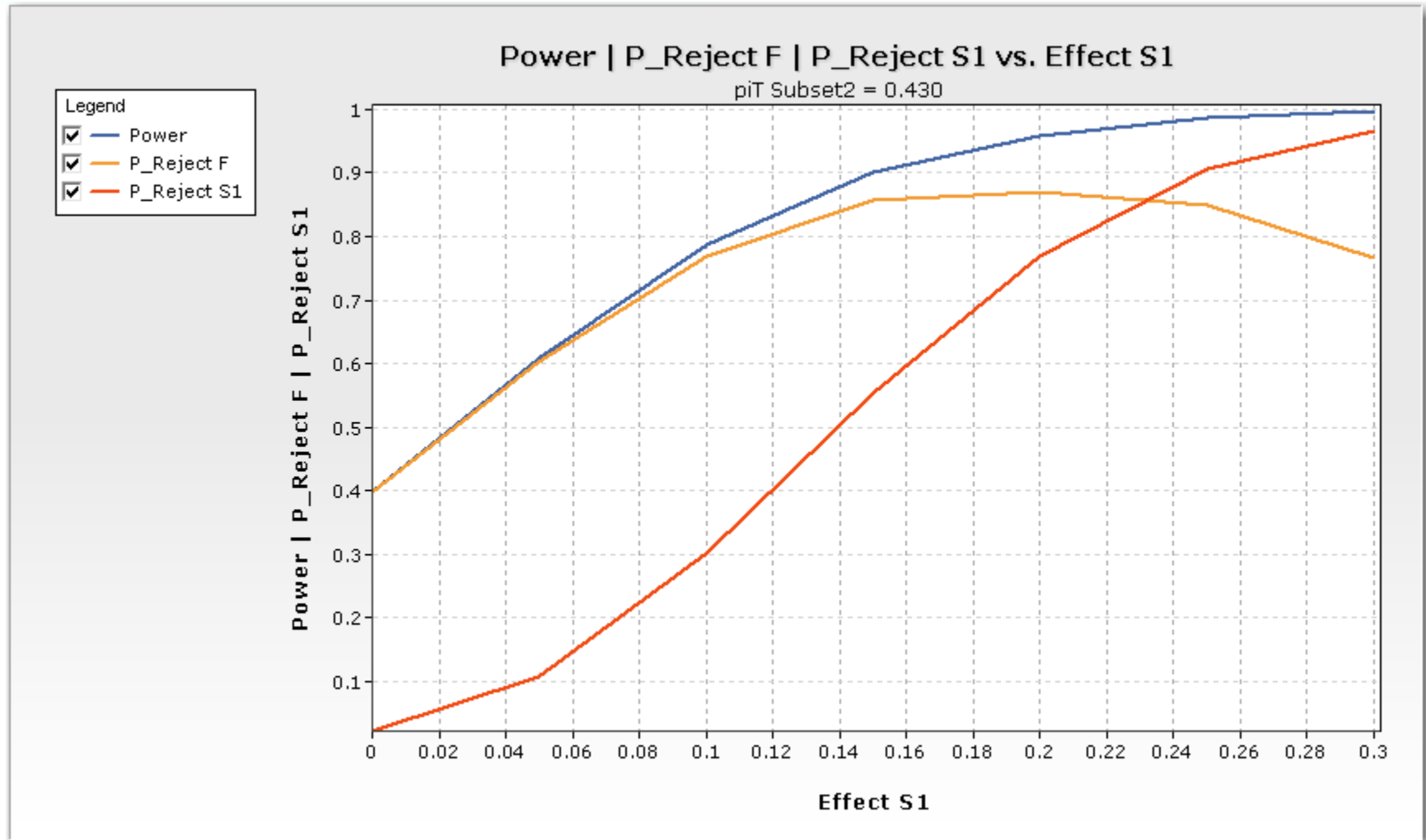
Operating Characteristics:



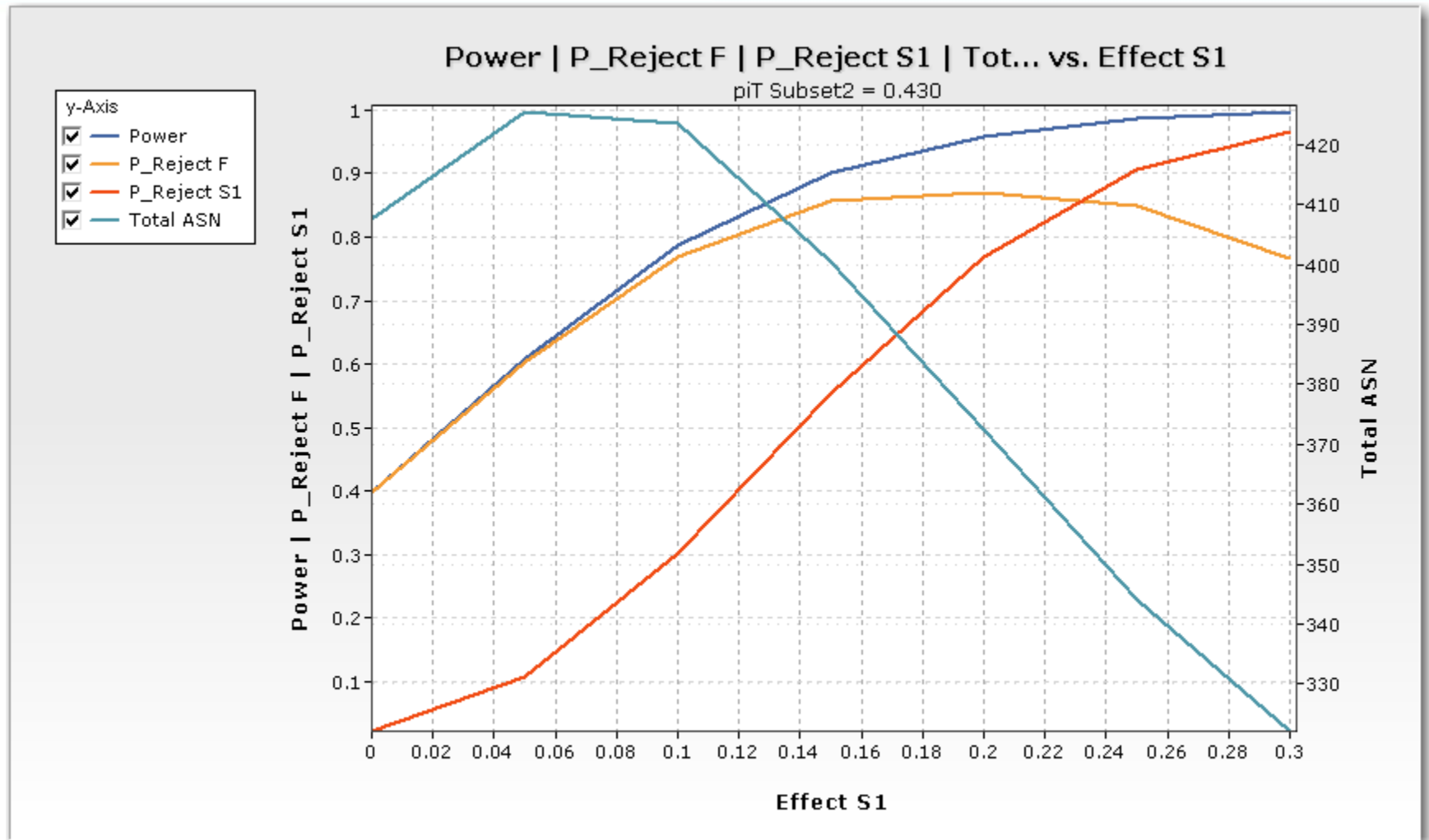
Sample Size Reestimation

- 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

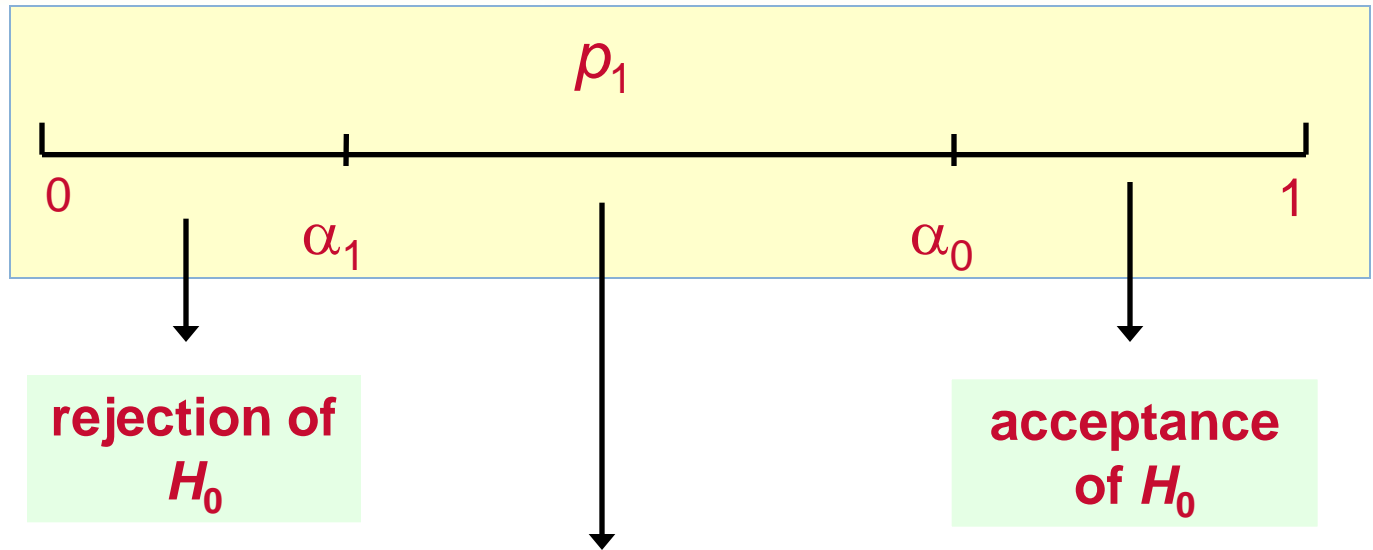
All information available in an interim analysis may be used for planning the subsequent stages of the trial, under control of the prespecified Type I error rate.

Two pioneering proposals:

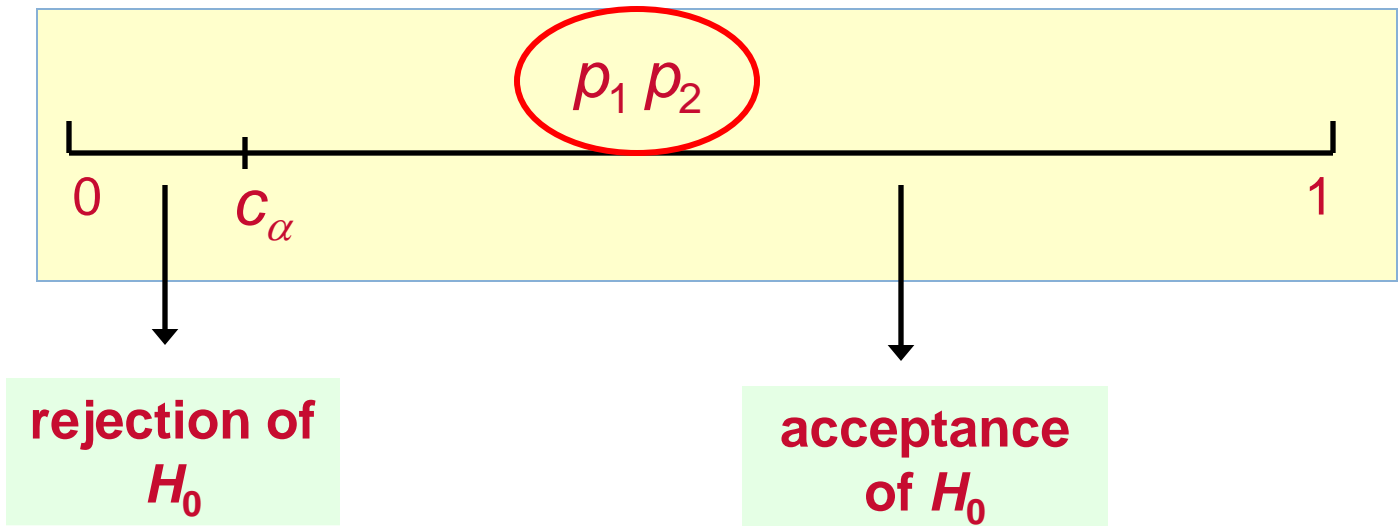
1. Bauer & Köhne (Biometrics, 1994):
Combination of p -values with a specific combination function (Bauer, 1989)
2. Proschan & Hunsberger (Biometrics, 1995):
Specification of a conditional error function

Procedure of Bauer & Köhne (1994)

Stage 1:



Stage 2:



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

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

- 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, $k = 1, 2, \dots, K$:

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

$\Phi^{-1}(1 - p_k) \sim N(0; 1)$ 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

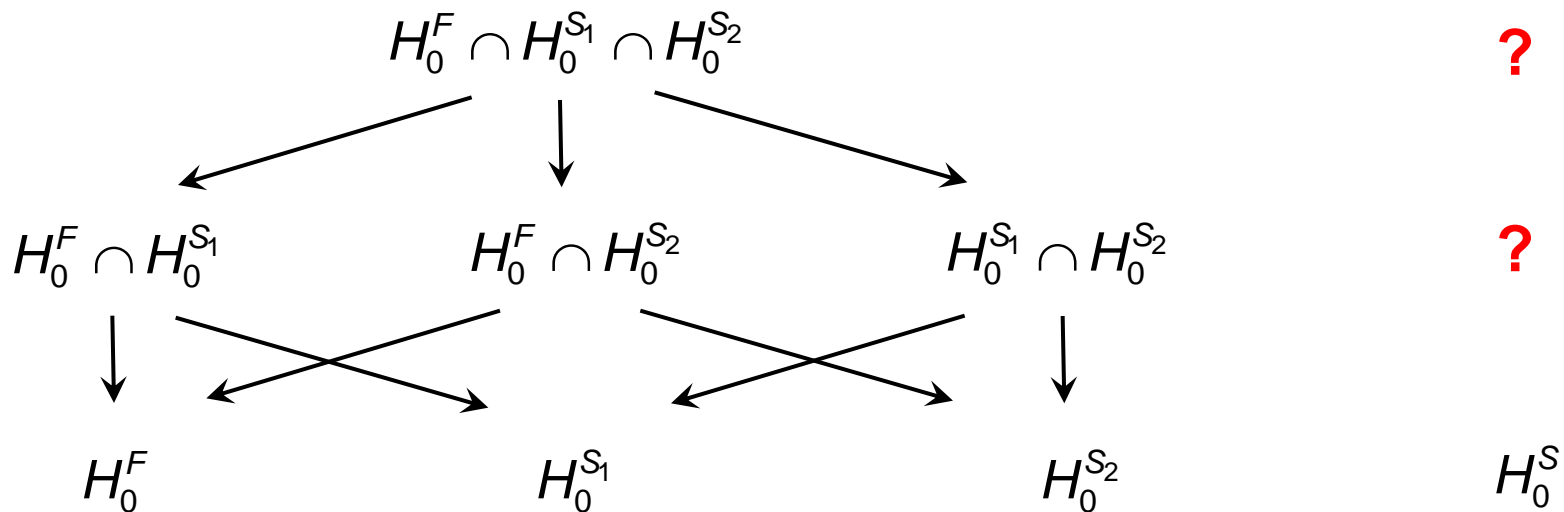
The Enrichment Test Procedure

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

Stage I

Stage II ...



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

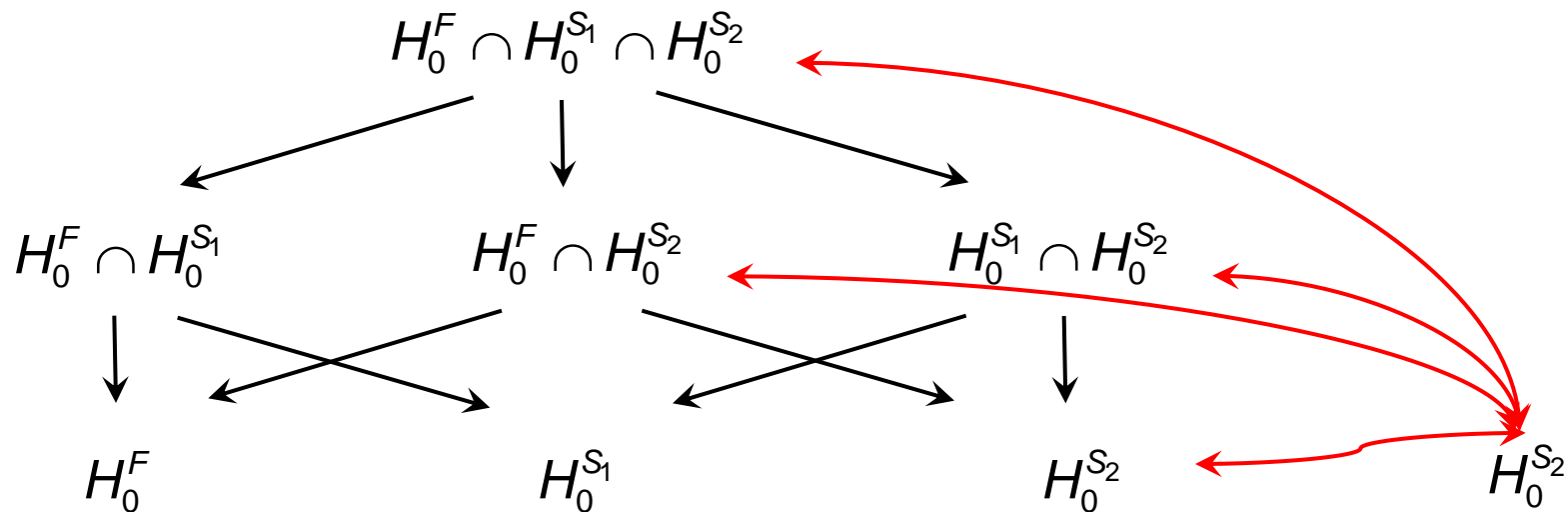
H_0^S can be rejected if all combination tests exceed the critical value u_2 .

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

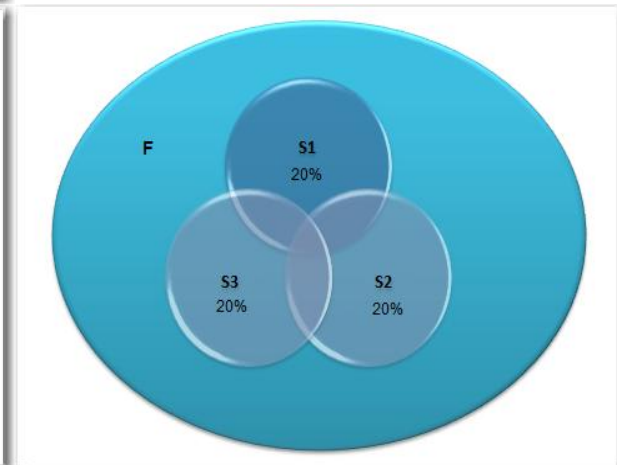
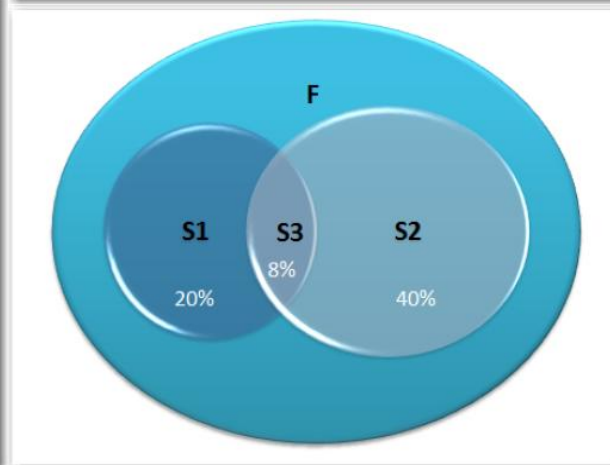
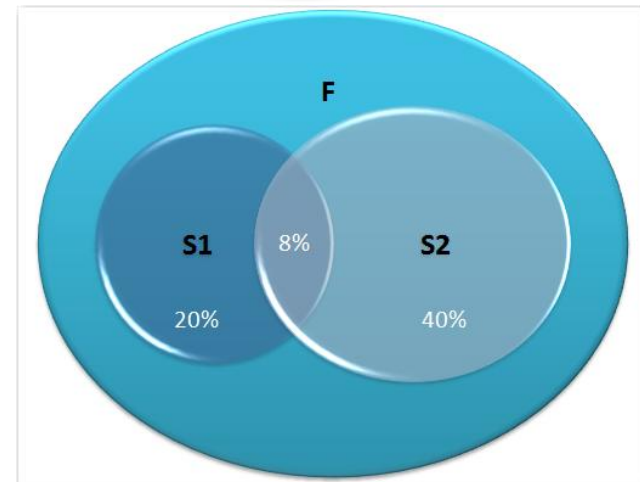
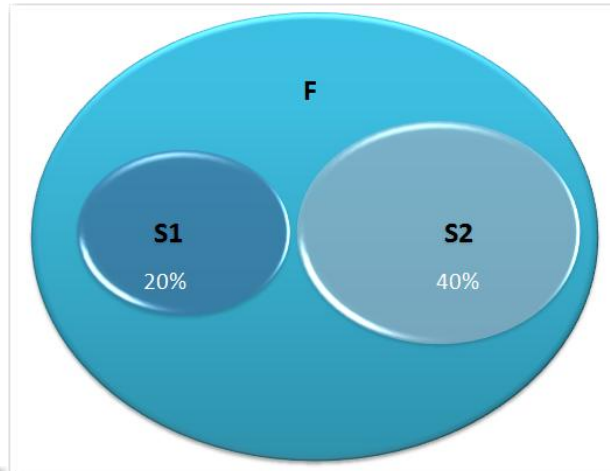
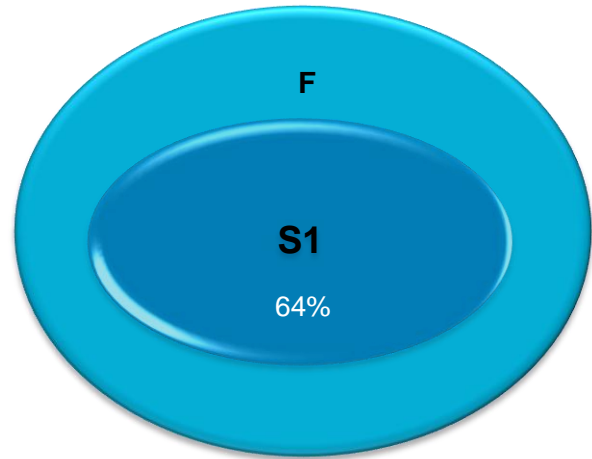
Test strategies

- 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

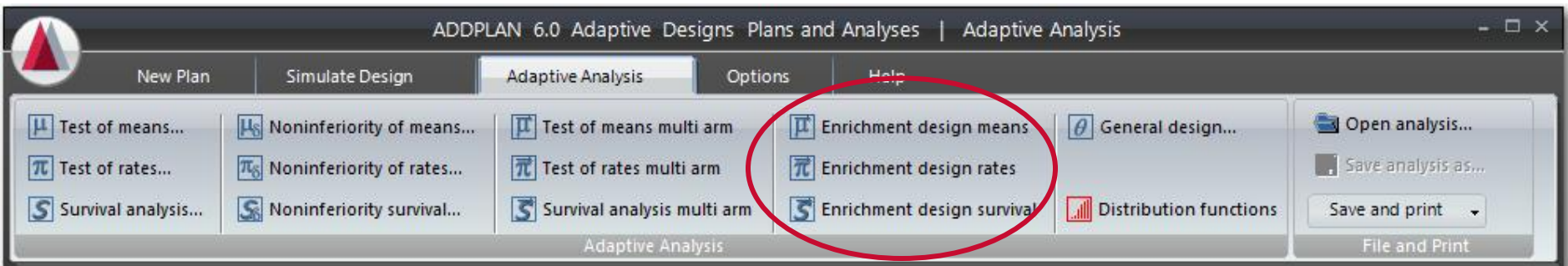
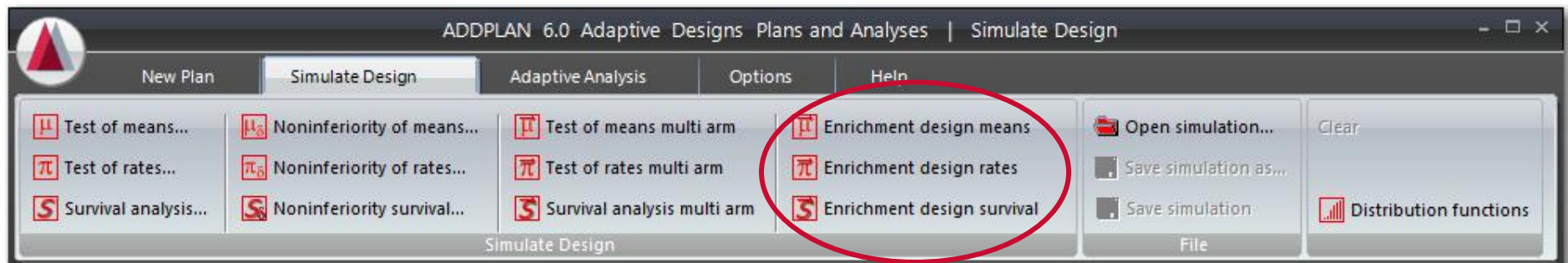
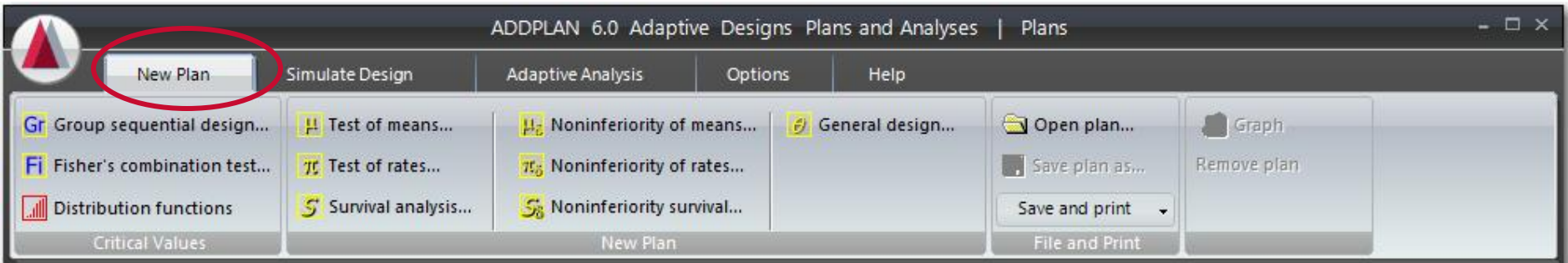
Selection Procedure

- 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