Sample Size Re-estimation in the Context of Dual Endpoints Using a Promising Zone Approach – Illustrated with Two Pharmaceutical Case Studies

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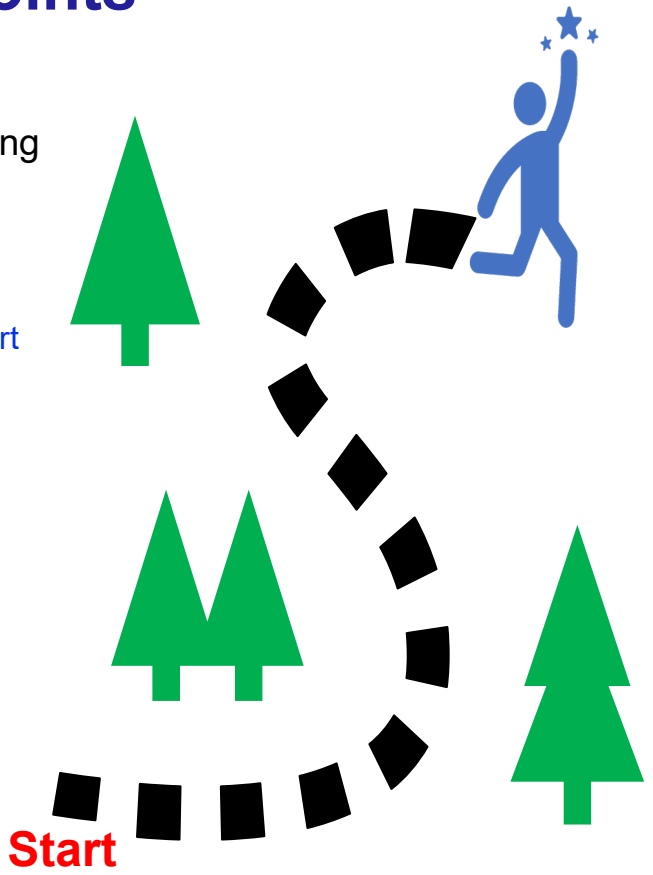
Journey to Develop SSR for Two Endpoints

1. Regulatory and Pharma positions
2. Support the clinical team to assess the requirements for SSR – Using two case studies
   - Develop the fixed design for the best effect size (Es_{best}) and minimal meaningful effect size (Es_{min})
   - Discuss the motivation for SSR that address the requirements to support Es_{best} to Es_{min}
3. Develop 2-stage design
   - Timing of interim – depends on the recruitment rate and sufficient availability of data to make a meaningful decision
   - Maximum sample size for the SSR
   - Decision Rules at interim by DMC
4. Verify and Validate your design assumptions through simulations
   - Follow the process flow for developing SSR design
   - Write a simulation report that documents decision rules, methodology, etc.



Regulatory position: Adaptive Design Concept

An adaptive design is

- Any study that includes prospectively planned opportunity for modification

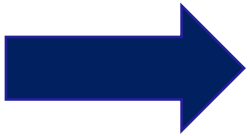
An adaptive design uses accumulating data to decide on how to modify aspect of the study

- By pre-specify decision rules and,
- Without undermining the **validity** and **integrity** of the trial

Pharma Position: Uncertainties and Adaptive Insurance Solutions

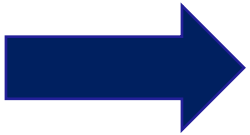
- **Uncertainty about treatment effect**
  - Early stopping for futility
  - Sample Size Re-estimation
- **Uncertainty about dose arm to take forward**
  - Dose finding followed by dose ranging
  - Dose Selection
- **Uncertainty about sub-population**
  - Population enrichment

Focus on this aspect of trial requirements



- Save underpowered trials - less phase 3 failure
- Verify trial assumptions and correct

- Save time and patients,
- Select the optimal dose

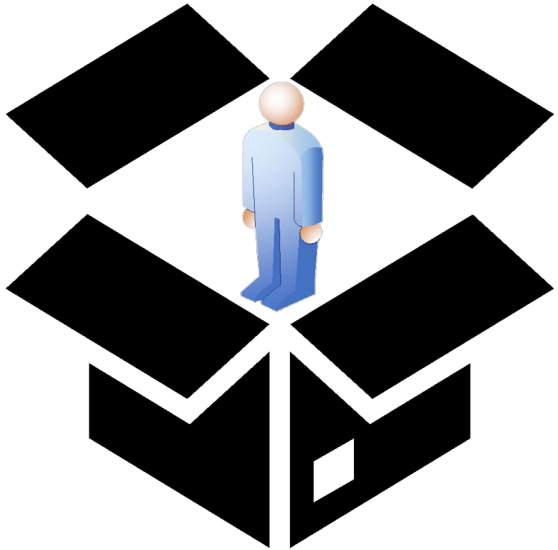


- Win on the responder subgroup if drug not efficacious on the whole population

Case Study 1:
Negative Symptoms Schizophrenia – Single Primary Endpoint

- New drug versus placebo for treatment of negative symptoms schizophrenia
- Primary endpoint is the change in negative symptoms assessment (NSA) at week 26 relative to the baseline assessment
- Based on the limited information available sponsor powers the trial to detect a 2-point improvement (**$\delta = 2$ with $\sigma = 7.5$**) with respect to NSA
- 8% dropout is anticipated
- Sponsor would like some insurance against power loss in case $\delta = 1.6$, the smallest clinically important effect

Where people appear to withdraw from the world around then, take no interest in everyday social interactions, and often appear emotionless and flat



Case Study 1:
Operating Characteristics of the Fixed Design - Des 1, Des 2

	Des 1 – Fixed – Underpowered for $\delta = 1.6$ $\sigma = 7.5$		Des 2 – Fixed – Overpowered for $\delta = 2$ $\sigma = 7.5$	
δ	**Sample size**	**Power**	**Sample size**	**Power**
1.6	442	61%	690	80%
1.7	442	66%	690	84%
1.8	442	71%	690	88%
1.9	442	76%	690	91%
2	442	80%	690	94%

We first create a single-look **Des 1 design** with 80% power to detect δ = 2 using a one-sided level 0.025 test, given σ = 7.5. With these design parameters, we can show that **Des 1** will be fully powered if a total of 442 subjects are enrolled (221/arm)

There is, however, considerable uncertainty about the true value of δ. Nevertheless, it is believed that even if the true value of were as low as 1.6 on the NSA scale, that would **constitute a clinically meaningful effect**

We therefore also create **Des 2**, having 80% power to detect δ = 1.6 using a one-sided level-0.025 test, given σ = 7.5. **Des 2** requires a total sample size of 690 subjects (345/arm)

We will consider two types of flexible designs: Group sequential and group sequential with SSR

Case Study 1:
Motivation for Mid-Course Sample Size Correction in Pivotal Trials – Des 3

- The typical fixed sample design, data is only analyzed once at the conclusion of the trial
- Group sequential has patients entering in *groups*; Data is analyzed at a certain number of specified stopping points – ***when 208 completers are available***
- We don't know what δ and σ to power the study for Prior experience limited to small pilot studies
- Hence, is makes sense to do a 2-stage design where there is an opportunity to assess the performance of the drug through GSD and then change the sample size based on the observed effect size at interim – ***we design for the best effect size but also plan for the minimal acceptable effect size through interim analysis and SSR implementation***

Recall, the current interest is to ensure that the design had sufficient sample size if the effect size between 1.6 to 2.0

Test Parameters – Des 3	
Simulation ID	CHWSim1
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Sample Size (n)	**442**
Completers @ look 1	**208**
Pipeline @ look 1	**208**
Variance	Equal
Test Statistic	t
Avg. Power	0.805
Response Generation Parameters	
Mean Control (μ_c)	0
Mean Treatment (μ_t)	**2**
SD Control (σ_c)	**7.5**
SD Treatment (σ_t)	**7.5**
Simulation Control Parameters	
Number of Simulations	10000

Sample Size Re-estimation – Des 3	
Method of Adaptation	Cui-Hung-Wang
Adapt At Look No.	1
Max. Sample Size if Adapt	
Multiplier	**1.561**
Total #	**690**
Study Duration	243.75
Target CP	0.8
Promising Zone Scale	Cond. Power
Min. CP	**0.57**
Max. CP	**0.8**

Promising Zone defined as 0.57 ≤ CP < 0.8	
Zone	**%**
Futility	0.00%
Unfavorable	31.28%
Promising	**13.12%**
Favorable	55.54%
Efficacy	0.06%

Case Study 1: Process Flow to do an GSD with SSR

Information Gathering

Discuss with the study team and assess:

1. What is a minimum effect size to consider that we have a viable therapy?
2. What is the optimal effect size that we hope to achieve in this new therapy?
3. What is the recruitment rate, dropout rate, endpoint(s) of interest that we want to market the new therapy?
4. What are the interim analysis requirements (futility, efficacy)
5. Are there any early read-out that can be used to assess the performance of the primary endpoint (is useful for the endpoint that have long-period to assess completers performance

Agree on the maximum sample size requirements based on the minimum effect size of the interest – e.g., 690 completers

Assess what the minimum sample size that the team is willing to commit to start the study – e.g., 208 completers

Agree on the design and the operating characteristics

Develop GSD/SSR design using the agreed sample size – e.g., 208 completers, and perform simulations

Results

APPROVED

Write Simulation Report

Case Study 1: Extended to be two endpoints

- Suppose there is a second regulatory requirement that the new treatment must also show benefit in Quality-of-Life Scale (QLS) questionnaire which is a secondary endpoint in this trial. Because there exists no previous experience with QLS in negative symptoms patients, no notion of what constitutes a clinically meaningful effect is available
- However, suppose from the literature, the teams assumes that for this score of 0.28 with standard deviation of 1.2 is clinically meaningful. Furthermore, the team believes that the score of 0.23 with standard deviation of 1.2 can be considered as minimally acceptable results for this endpoint
- Designs **des 4** and **des 5** represents the sample size for these effect sizes

Des 4 Powered for δ **= 0.28** σ = *1.2*				**Des 5** Powered for δ **= 0.23** σ = *1.2*		
δ	Power	Completers		δ	Power	Completers
0.2	51.64%	577		0.2	68.30%	855
0.21	55.62%			0.21	72.51%	
0.22	59.53%			0.22	76.42%	
0.23	63.36%			0.23	80.00%	
0.24	67.05%			0.24	83.23%	
0.25	70.59%			0.25	86.11%	
0.26	73.94%			0.26	88.63%	
0.27	77.08%			0.27	90.81%	
0.28	80.00%			0.28	92.66%	
0.29	82.68%			0.29	94.21%	
0.3	85.12%			0.3	95.49%	

If δ = 0.28, then the SS increase of =690 for the primary is sufficient but if δ = 0.23, then SS increase of = 690 is not sufficient

How do we do an SSR design to address the requirements for both endpoints?

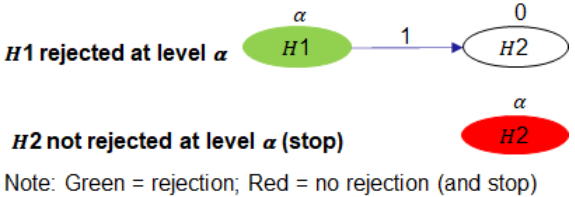
Case Study 1: Discussion – Fixed Sequence Procedure

Primary Endpoint		Secondary Endpoint	
Best Effect size	**Minimal meaningful effect size**	**Best Effect size**	**Minimal meaningful effect size**
μ = 2, σ =7.5, SS = 442 **Completers = 208**	μ = 1.6, σ =7.5 SS = 690	μ = 0.28, σ =1.2 SS = 577	μ = 0.23, σ =1.2 SS = 855

Hope for the best but prepare for the worst

- **Start** with the best effect size for the primary – completers = 208, SS_Original = 442
- Calculate the timing for the interim, which is 208/442 = 0.47
- **Take** the maximum SS increase (SSR upper limit) that can be used to assess the performance of both endpoints within the required effects size ranges for both endpoints;
  - **That is Max_SS =855 – satisfies both primary and secondary requirements**
- Calculate the SSR increase factor, which is Max_SS / SS_Original; that is 855/442 = 1.93
  - **Ensure that the team are ok with the Max_SS value**
- Ask if there is a correlation between the endpoints – **it plays a role in the simulation**

- Assume $H1 \rightarrow H2$
  - That is, $H1$ is more important than $H2$



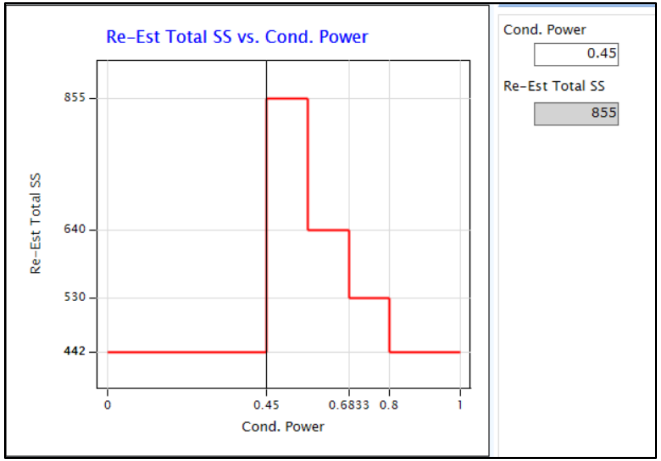
Note: Green = rejection; Red = no rejection (and stop)

Case Study 1 Extended : Primary Simulation Results

Test Parameters	
Simulation ID	CHWSim_P
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Sample Size (n)	**442**
Completers @ look 1	**208**
Pipeline @ look 1	**208**
Variance	Equal
Test Statistic	t
Avg. Power	0.83
Response Generation Parameters	
Mean Control (μ_c)	0
Mean Treatment (μ_t)	**2**
SD Control (σ_c)	**7.5**
SD Treatment (σ_t)	**7.5**
Simulation Control Parameters	
Number of Simulations	10000

Sample Size Re-estimation – Des 6	
Method of Adaptation	Cui-Hung-Wang
Adapt At Look No.	1
Max. Sample Size if Adapt	
Multiplier	**1.934**
Total #	**855**
Target CP	0.8
Promising Zone	Cond. Power
Min. CP	**0.45**
Max. CP	**0.8**

Promising Zone defined as 0.45 ≤ CP < 0.8 – Des 6	
Zone	%
Futility	0.00%
Unfavorable	25.86%
Promising	**17.83%**
Favorable	56.27%
Efficacy	0.04%



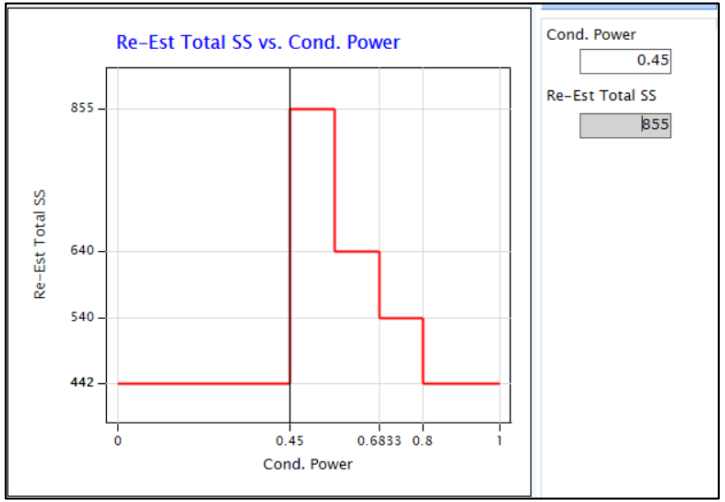
CP %	New SS	μ
CP < 0.45	442	<1.36
0.45 ≤ CP < 0.6	855	1.36 to 1.54
0.6 ≤ CP < 0.7	640	1.55 to 1.68
0.7 ≤ CP < 0.8	530	1.69 to 1.84
CP ≥ 0.8	442	≥ 1.84

Case Study 1: Secondary Simulation Results

Test Parameters – Des 7	
Simulation ID	CHWSim_S
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Sample Size (n)	442
Variance	Equal
Test Statistic	t
Avg. Power at	**0.704**
Response Generation Parameters	
Generate Data Using	Individual Means
Mean Control (μ_c)	0
Mean Treatment (μ_t)	**0.28**
SD Control (σ_c)	1.2
SD Treatment (σ_t)	1.2

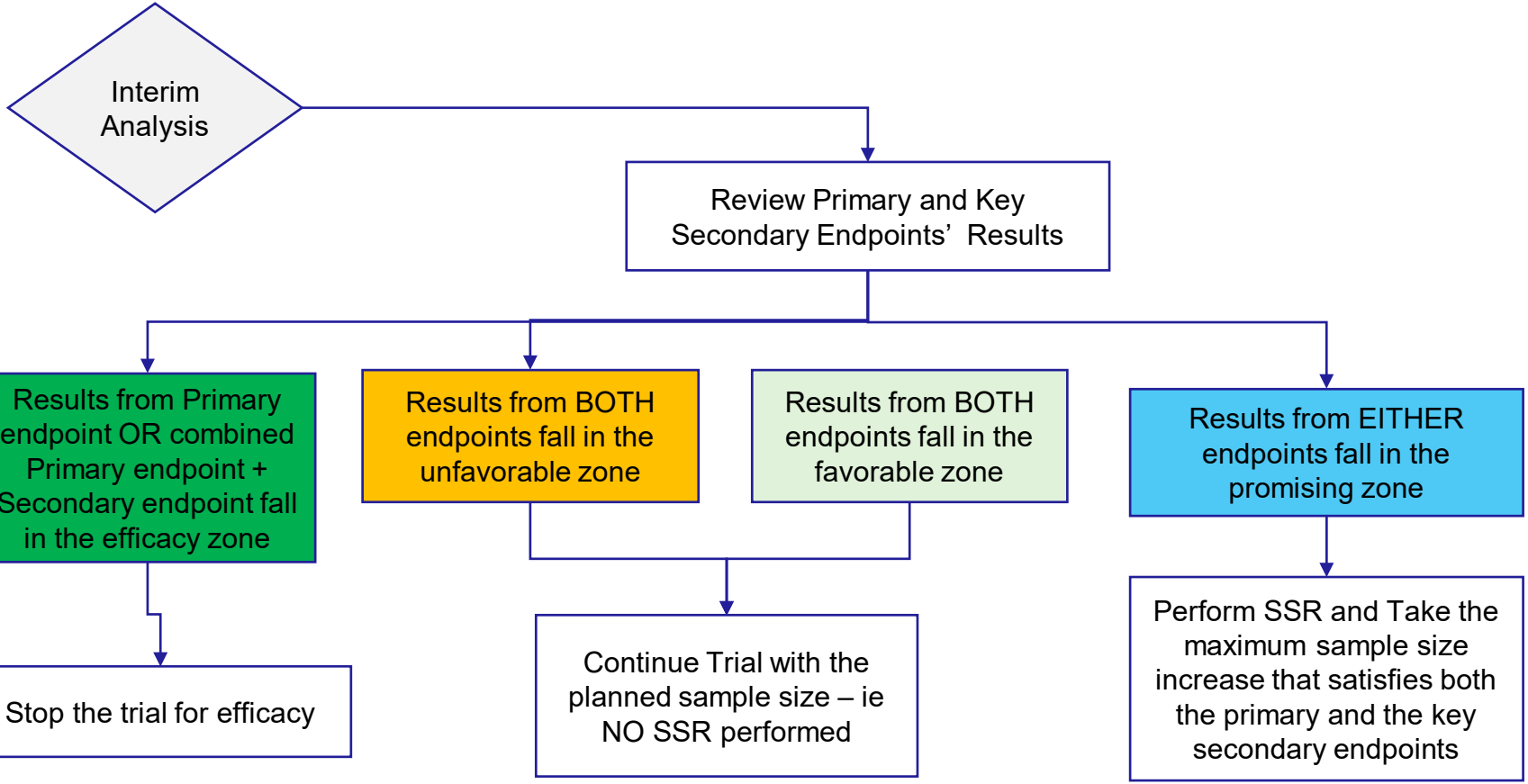
Sample Size Re-estimation – Des 7	
Method of Adaptation	Cui-Hung-Wang
Adapt At Look No.	1
Max. Sample Size if Adapt	
Multiplier	**1.934**
Total #	**855**
Target CP	0.8
Promising Zone	Cond. Power
Min. CP	**0.45**
Max. CP	**0.8**

Promising Zone defined as 0.45 ≤ CP < 0.8 – Des 7	
Zone	**%**
Futility	0.00%
Unfavorable	34.52%
Promising	19.06%
Favorable	46.40%
Efficacy	0.02%



CP %	New SS	μ
CP < 0.45	442	<0.218
0.45 ≤ CP < 0.6	**855**	0.218 to 0.245
0.6 ≤ CP < 0.7	650	0.245 to 0.268
0.7 ≤ CP < 0.8	540	0.268 to 0.294
CP ≥ 0.8	442	≥ 0.294

Case Study 1:
Process Flow - Decision Rules For Dual Endpoints – Fixed Sequence



Case Study 1: Logistical Requirement: Tables for the Data Monitoring Committee
Fixed Sequence

SSR Interim Decision Zone		Primary Endpoint				
Notification to the DMC		CP < 0.45	0.45 ≤ CP < 0.6	0.6 ≤ CP <0.7	0.7 ≤ CP <0.8	CP ≥ 0.8
Secondary Endpoint	CP < 0.45	Primary endpoint is in unfavorable zone and hence the trial continues as planned with the original sample size, which is 440	Primary endpoint is the driver and requires the maximum SS is 855 - which is the maximum SS allowed	Primary endpoint requires 640 so the minimum SS for this boundary is 640	Primary endpoint requires 530 so the minimum SS for this boundary is 530	Primary endpoint requires 440 so the minimum SS for this boundary is 442 – which is the minimum SS allowed
	0.45 ≤ CP < 0.6					
	0.6 ≤ CP < 0.7					
	0.7 ≤ CP < 0.8					
	CP ≥ 0.8					

Note that SSR is driven by the primary endpoint effect size (fixed sequence testing)

Case Study 2: Lung Disease – Fallback Sequence

- Forced expiratory volume in the first second (FEV1) can be useful to categorize the severity of obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD)
- The sponsor that is engaged in developing a drug for this therapeutic area, is also interested in testing the Forced vital capacity (FVC) which is the total amount of air exhaled during the FEV test as a co-primary endpoint
- Let us consider a trial with FEV1 as it's primary endpoint and FVC as it's coprimary endpoint
- The operating characteristics of this trial are as follows:
    - Active vs placebo
    - FEV1 – the effect size (μ/s) ranges from 0.41 to 0.53
    - Power = 90
    - a = 0.05
    - FVC – difference of proportion of 0.14 to 0.19 with πc = 0.05 and πt= (0.1, 0.11, 0.12, 0.13, 0.14)
- Further discussion leads to conclusion that the client would like to claim success **on both endpoints**

Case Study 2: Comparison of Effect Size vs Power

Forced expiratory volume in the first second (FEV1)		
Test Parameters	**Minimal-Clinical-Significance Design**	**Best Expected Design**
Design Type	Superiority	Superiority
No. of Looks	1	1
Test Type	1-Sided	1-Sided
Specified α	0.025	0.025
Power	0.901	0.901
Model Parameters		
Allocation Ratio	1	1
Input Method	Standardized Diff. of Means	
Standardized Diff. ((μt- μc)/σ)	0.41	0.53
Test Statistic	Z	Z
Maximum Sample Size	**251**	**150**
Maximum Duration	83.375	79.25

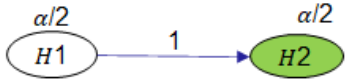
Forced vital capacity (FVC)		
Test Parameters	**Minimal-Clinical-Significance Design**	**Best Expected Design**
Design Type	Superiority	Superiority
No. of Looks	1	1
Test Type	1-Sided	1-Sided
Specified α	0.025	0.025
Power	0.9	0.9
Model Parameters		
Allocation Ratio	1	1
Proportion under Control (πc)	0.05	0.05
Proportion under Treatment (πt)	0.15	0.19
Diff. in Prop. (πt - πc)	0.1	0.14
Variance	Unpooled Estimate	
Maximum Sample Size	**368**	**216**
Maximum Duration	98	79

Case Study 2: Discussion – Fallback Sequence

Primary Endpoint		Co-Primary Endpoint	
Best Effect Size	Minimal Acceptable Effect Size	Best Effect Size	Minimal Acceptable Effect Size
Effect size: 0.53 SS = 150	Effect size: 0.41 SS = 251	Diff in Proposition: 0.14 SS = 216	Diff in Proposition: 0.1 SS = 368

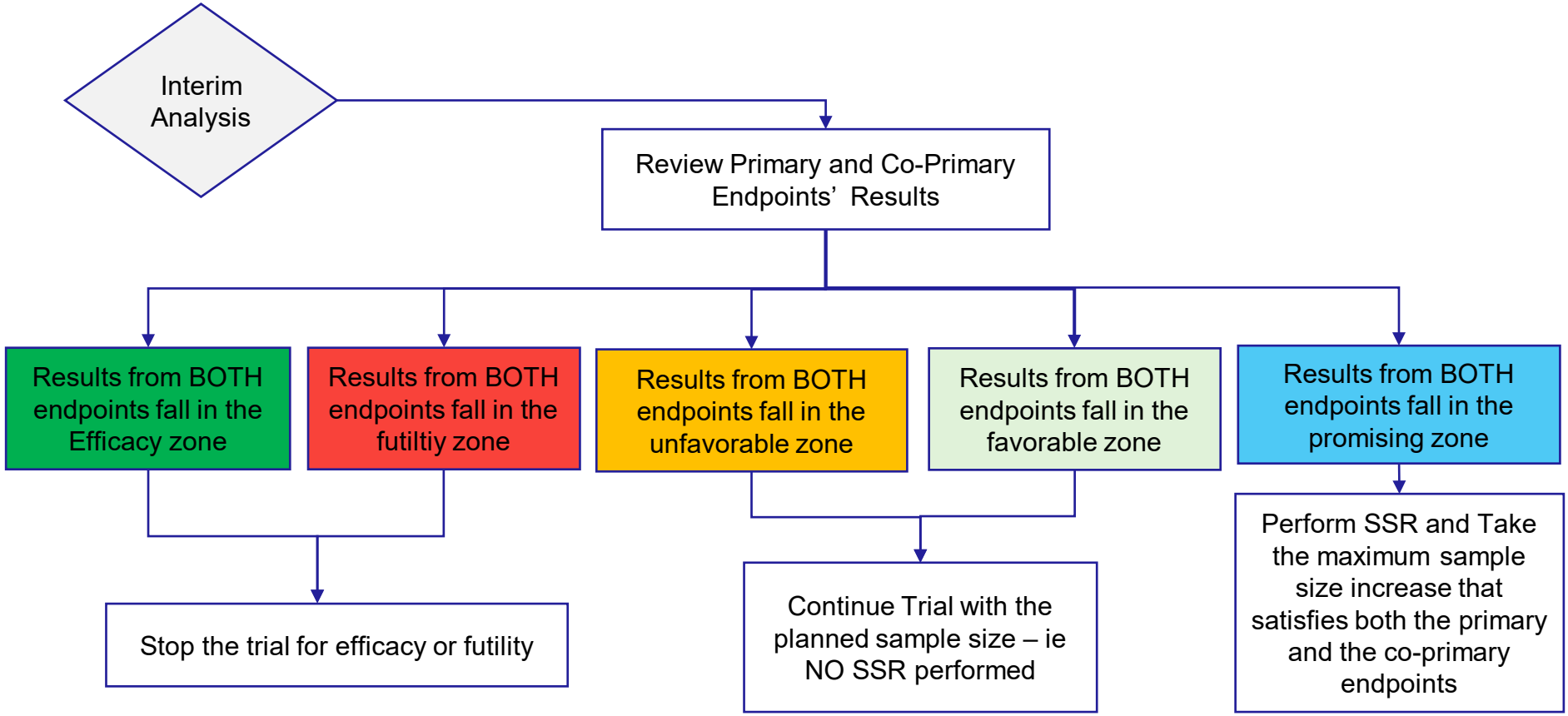
- **Considering IA when 50% of subjects completed 52 weeks**
- **Start** with the minimal effect size for the primary and co-primary = 216
- The timing for the interim analysis is around 50%
- **Take** the maximum SS that can be used to assess the performance of both endpoints within the required effects size ranges for both endpoints;
  - **That is Max_SS =368 – satisfies both primary and co-primary endpoint**
- Calculate the SSR increase factor, which is Max_SS / SS_Original; that is 368/216 = 1.7
  - **Ensure that the team are ok with the Max_SS value**
- Ask if there is a correlation between the endpoints – **it plays a role in the simulation**

Initial



Note: Green = rejection

Case Study 2:
Process Flow - Decision Rules For Dual Endpoints – Fallback Sequence



Case Study 2: Simulation Results

Completers: 127 for both endpoints

Promising Zone defined as 0.64 ≤ CP < 0.971 Primary	
Zone	**%**
Futility	0.55%
Unfavorable	9.30%
Promising	19.68%
Favorable	9.10%
Efficacy	61.37%

Promising Zone defined as 0.64 ≤ CP < 0.9 Co-Primary	
Zone	**%**
Futility	3.42%
Unfavorable	18.61%
Promising	17.21%
Favorable	24.06%
Efficacy	36.70%

Primary		
CP	**New SS**	**((μt- μc)/σ)**
CP < 0.6	216	<0.305
0.64 ≤ CP < 0.7	368	0.305
0.7 ≤ CP < 0.8	330	0.316
0.8 ≤ CP < 0.9	270	0.345
CP ≥ 0.9	216	≥ 0.39

The trial is overpowered for the primary by (216/150 = 1.44) to satisfy the co-primary endpoint

Co-Primary		
CP	**New SS**	**(πt)**
CP < 0.6	216	<0.141
0.64 ≤ CP < 0.7	368	0.141 to 0.154
0.7 ≤ CP < 0.8	320	0.155 to 0.18
0.8 ≤ CP < 0.9	260	0.18 to 0.19
CP ≥ 0.9	216	≥ 0.199

Note: The πc= 0.05

Case Study 2: Logistical Requirement: Tables for the Data Monitoring Committee – Fallback Sequence

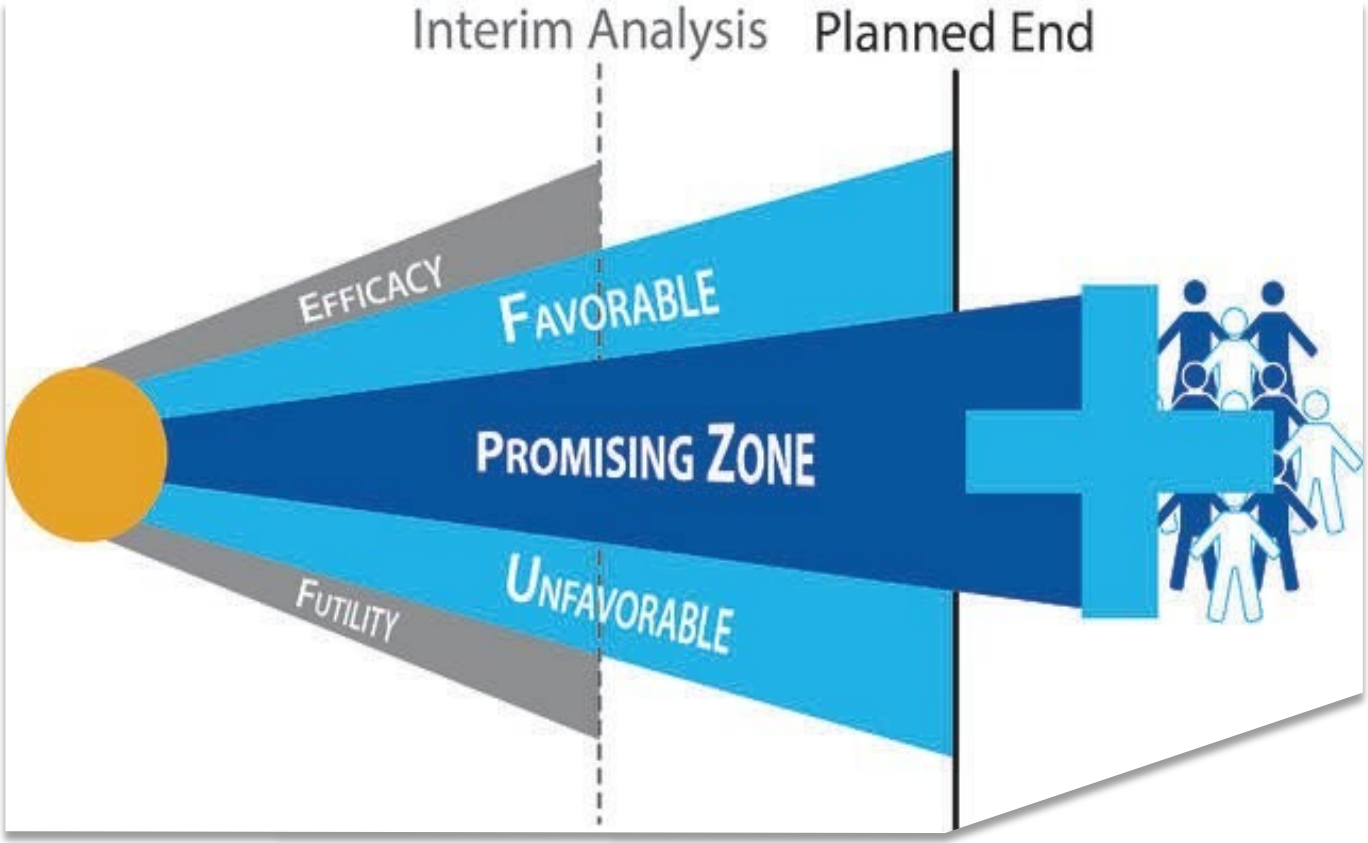
SSR Interim Decision Zone		Primary Endpoint - Standardized difference of means is 0.41 to 0.53				
Notification to the DMC		CP < 0.6	0.64 ≤ CP < 0.7	0.7 ≤ CP < 0.8	0.8 ≤ CP < 0.9	CP ≥ 0.9
Secondary Endpoint – Difference of Proportion 0.1 to 0.14	CP < 0.6	216				216
	0.64 ≤ CP < 0.7		368			
	0.7 ≤ CP < 0.8			330		
	0.8 ≤ CP < 0.9	216			270	
	CP ≥ 0.9					216

Take the maximum SS required by both endpoints

Concluding Remarks

- Adaptive trials require a considerable amount of planning up-front. One of the most versatile tools for the planning phase is simulation
- The simulations clarify the risks and benefits of the proposed approach by putting probabilities on each possible outcome
- The simulations facilitate better communication with the regulatory agencies
- The simulations facilitate greater communication between the various members of the study team by showing how different design options and trial outcomes will have different implications for:
  - Patient recruitment
  - Drug supply
  - Economic analyses
  - Clinical outcomes
  - Statistical power
  - Regulatory concerns

Assessing SSR Zones Based on the requirements



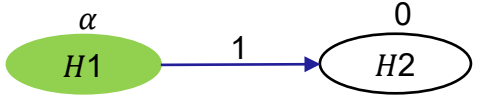
Testing Approach

•Fixed Sequence Procedure

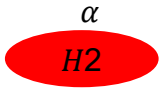
- Stepwise multiple testing procedure
- The endpoints are ordered according to their importance
- All tests will be performed at level α following the pre-specified order

- Assume $H1 \rightarrow H2$
  - That is, $H1$ is more important than $H2$

$H1$ rejected at level α



$H2$ not rejected at level α (stop)

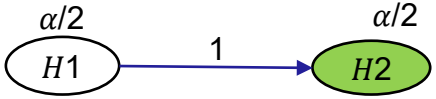


Note: Green = rejection; Red = no rejection (and stop)

•Fallback Sequence Procedure

- same as fixed sequence procedure. Hypotheses are tested in an a priori order at the full alpha level (same as fixed sequence procedure)
- The difference of the fallback procedure from the fixed sequence test is that the full alpha of 0.05 is split for endpoints in a pre-specified order (based on the clinical relevance) and the hypotheses in late order can still be tested (but with different alpha levels) if the previous hypothesis is not rejected.

Initial



Note: Green = rejection

- In contrast to the fixed sequence procedure, the fallback procedure tests all hypotheses in the pre-specified sequence even if the initial hypotheses are not rejected

CHW Statistic

- Use CHW statistic with pre-specified weighting of data from each stage (Cui, Hung & Wang, 1999)
- The CHW statistic is

$$Z^*_{j,CHW} = \frac{\sqrt{w^{(1)}}Z^{*(1)} + \sqrt{w^{(2)}}Z^{*(2)} + \cdots + \sqrt{w^{(j)}}Z^{*(j)}}{\sqrt{w^{(1)} + w^{(2)} + \cdots + w^{(j)}}}$$

- This statistic is asymptotically normally distributed with mean

$$E(Z^*_{j,CHW}) = \frac{\delta \sum_{l=1}^{j} \sqrt{w^{(l)}\, I^{*(l)}}}{\sqrt{\sum_{l=1}^{j} \sqrt{w^{(l)}}}}$$

and unit variance, where $I^{*(l)}$ is the incremental information at look l

- Cui, Hung and Wang (1999) and Lehmacher and Wassmer (1999) have shown that

$$P_0\left(\bigcup_{j=1}^{K} \left|Z^*_{j,CHW}\right| \geq b_j\right) = \alpha$$

- Note: If no sample size change, then $Z^*_{j,CHW} = Z^*_{j,Wald}$

Conditional Power Calculations

- Adaptive sample size changes are commonly driven by conditional power or the probability, given the current data, of attaining statistical significance by the end of the study
- Suppose we are at some look $L < K$ and the observed value of the test statistic is z_L. Conditional power for a given value of δ and total sample size n_K^* is defined as

$$CP_\delta(z_L, n_K^*) = P_\delta\{ \cup_{j=L+1}^{K} (Z_{j,CHW}^* \geq b_j \mid z_L) \}$$

- One may use either the value of δ specified at the design stage or the value $\hat{\delta}_L$ estimated at look L in the above expression for CP

References about SSR Methodology

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