Sample Size Derivation for Composite Binary Endpoints Accounting for Departures of the Anticipated Values

Marta Bofill Roig
Guadalupe Gómez Melis

Primary Composite Endpoints

Efficacy endpoints

The primary endpoint measures the clinical evidence in a clinical trial.

Composite Endpoint

Combination of several responses into a unique variable.

- More information.
- Power might be increased.

Challenges in the design of clinical trials with Composite Endpoints:

- How to specify the expected treatment effect.
- How to determine the required sample size.
- How to easily compute the effect and sample size.

TACTICS-TIMI 18 trial[1]

Invasive strategy (Intervention) versus Conservative strategy (Control)

Events of interest	**Binary Response**
Death or myocardial infarction ε_1	X_1
Rehospitalization ε_2	X_2
Composite event $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$

[1] Cannon, CP, et al. (2001). The New England Journal of Medicine.

TACTICS-TIMI 18 trial[1]

Invasive strategy (Intervention) versus Conservative strategy (Control)

Events of interest	**Binary Response**	**Probabilities**	**Effect**
Death or myocardial infarction ε_1	X_1		
Rehospitalization ε_2	X_2		
Composite event $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$\delta_* = p_*^{(1)} - p_*^{(0)}$

[1] Cannon, CP, et al. (2001). The New England Journal of Medicine.

TACTICS-TIMI 18 trial[1]

Invasive strategy (Intervention) versus Conservative strategy (Control)

Events of interest	Binary Response	Probabilities	Effect
Death or myocardial infarction ε_1	X_1		
Rehospitalization ε_2	X_2		
Composite event $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$\delta_* = p_*^{(1)} - p_*^{(0)}$

Sample size formula needs the anticipation of the composite parameters $(p_*^{(0)}, \delta_*)$:

$$n = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

[1] Cannon, CP, et al. (2001). The New England Journal of Medicine.

Planning TACTICS-TIMI 18 trial based on TIMI IIIB and VANQWISH[2]

Sample size formula

$$n = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

TIMI IIIB at 6 weeks of follow-up:

- Death or myocardial infarction
- Positive exercise test

VANQWISH at 12 months of follow-up:

- Death or myocardial infarction

[2] Cannon, CP, et al. (1998). American Journal of Clinical Oncology.

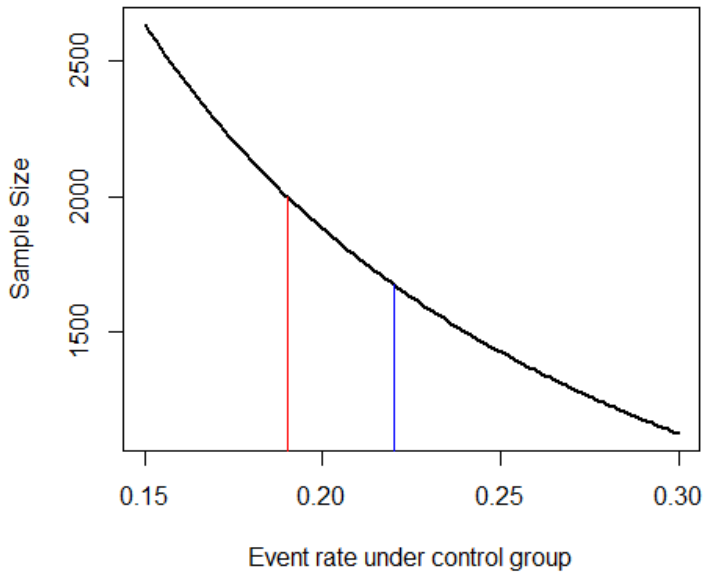
Planning TACTICS-TIMI 18 trial based on TIMI IIIB and VANQWISH[2]

Sample size formula

$$n = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

TIMI IIIB at 6 weeks of follow-up:

- Death or myocardial infarction
- Positive exercise test



VANQWISH at 12 months of follow-up:

- Death or myocardial infarction

TACTICS-TIMI 18 ($\alpha = 0.05$, $1 - \beta = 0.8$):

- Planned sample size:

  For given $p_*^{(0)} = 0.22$, TACTICS-TIMI 18 recruited $n = 1720$ patients to detect $\delta_* = -0.055$.

- Sample size based on observed values:

  For given $p_*^{(0)} = 0.19$, $n = 2000$ patients should be recruited to detect $\delta_* = -0.055$.

[2] Cannon, CP, et al. (1998). American Journal of Clinical Oncology.

Aims of the talk

1. Composite parameters from its margins
2. Sample size derivation based on the composite components
3. Software free tool: CompARE

Using **CompARE**[3] to design trials with composite endpoints

CompARE : Binary Endpoints

Endpoint 1:

Probability under control group:

Point value

Anticipated value:

0.095

Effect measure:

Risk Difference

Risk Difference:

-0.022

Endpoint 2:

Probability under control group:

Point value

Anticipated value:

0.137

Effect measure:

Risk Difference

Risk Difference:

-0.027

Home | Composite Endpoint Characteristics | ARE method | Effect Size | Sample Size | Loss in power | Sample Size derivation based on bands | Help

CE CHARACTERISTICS

OBTAIN THE EVENT RATES OF THE COMPOSITE ENDPOINT AND STUDY THE DEGREE OF ASSOCIATION

EFFECT SIZE

COMPUTE THE TREATMENT EFFECT IN DIFFERENT EFFECT MEASURES

SAMPLE SIZE

CALCULATE THE REQUIRED SAMPLE SIZE

ARE METHOD

CHOOSE WHICH IS THE BEST SUITED PRIMARY ENDPOINT FOR YOUR TRIAL

GO TO COMPARE HOME-PAGE

[3] https://cinna.upc.edu/compare/

Composite parameters from its margins

Composite Binary Endpoint from its margins

Event	Binary Response	Probabilities	Risk difference
ε_1	X_1	$(p_1^{(0)}, p_1^{(1)})$	$\delta_1 = p_1^{(1)} - p_1^{(0)}$
ε_2	X_2	$(p_2^{(0)}, p_2^{(1)})$	$\delta_2 = p_2^{(1)} - p_2^{(0)}$
$\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$\delta_* = p_*^{(1)} - p_*^{(0)}$

Composite Binary Endpoint from its margins

Event	Binary Response	Probabilities	Risk difference
ε_1	X_1	$(p_1^{(0)}, p_1^{(1)})$	$\delta_1 = p_1^{(1)} - p_1^{(0)}$
ε_2	X_2	$(p_2^{(0)}, p_2^{(1)})$	$\delta_2 = p_2^{(1)} - p_2^{(0)}$
$\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$\delta_* = p_*^{(1)} - p_*^{(0)}$

Probability of ε_* (Bahadur's Theorem[4]):

$$p_*^{(i)} = 1 - (1 - p_1^{(i)})(1 - p_2^{(i)}) - \rho^{(i)} \sqrt{p_1^{(i)} p_2^{(i)} (1 - p_1^{(i)})(1 - p_2^{(i)})}$$

[4] Bahadur, RR (1961). Stanford University Press. 158–168.

Composite Binary Endpoint from its margins

Event	Binary Response	Probabilities	Risk difference
ε_1	X_1	$(p_1^{(0)}, p_1^{(1)})$	$\delta_1 = p_1^{(1)} - p_1^{(0)}$
ε_2	X_2	$(p_2^{(0)}, p_2^{(1)})$	$\delta_2 = p_2^{(1)} - p_2^{(0)}$
$\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$\delta_* = p_*^{(1)} - p_*^{(0)}$

Probability of ε_* (Bahadur's Theorem[4]):

$$p_*^{(i)} = 1 - (1 - p_1^{(i)})(1 - p_2^{(i)}) - \rho^{(i)} \sqrt{p_1^{(i)} p_2^{(i)} (1 - p_1^{(i)})(1 - p_2^{(i)})}$$

Risk difference for ε_*[5]:

$$\delta_* = \delta_1 q_2^{(0)} + \delta_2 q_1^{(0)} - \delta_1 \delta_2 + \rho^{(0)} \sqrt{p_1^{(0)} p_2^{(0)} q_1^{(0)} q_2^{(0)}} - \rho^{(1)} \sqrt{p_1^{(1)} p_2^{(1)} q_1^{(1)} q_2^{(1)}}$$

where $q_k^{(0)} = 1 - p_k^{(0)}$, $k = 1, 2$.

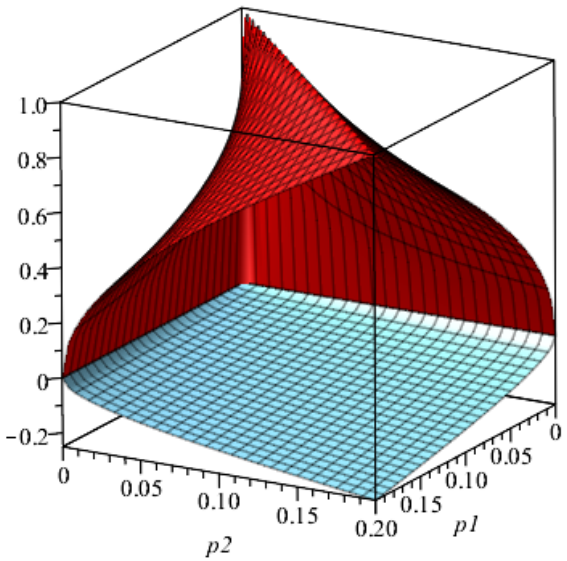
[4] Bahadur, RR (1961). Stanford University Press. 158–168.

[5] Bofill M, Gómez G (2018). Sample size derivation for composite binary endpoints. *Submitted*.

Bounds for Pearson's correlations[6] $\rho^{(0)}$, $\rho^{(1)}$

Given marginal parameters $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ the correlations for each group $\rho^{(0)}$, $\rho^{(1)}$ are bounded:

$$-1 \leq B_L^{(i)}(\theta) \;\leq\; \rho^{(i)} \;\leq\; B_U^{(i)}(\theta) \leq 1$$

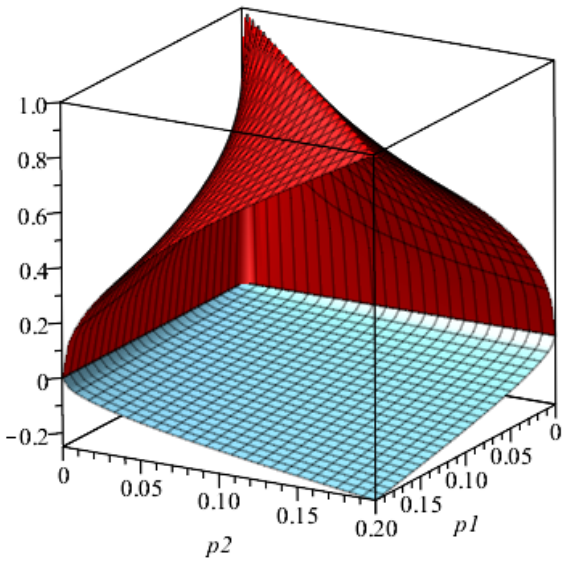


[6] Sozu T, Sugimoto T and Hamasaki T. (2010). *Statistics in Medicine*.

Bounds for Pearson's correlations[6] $\rho^{(0)}$, $\rho^{(1)}$

Given marginal parameters $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ the correlations for each group $\rho^{(0)}$, $\rho^{(1)}$ are bounded:

$$-1 \leq B_L^{(i)}(\theta) \leq \rho^{(i)} \leq B_U^{(i)}(\theta) \leq 1$$



Assuming $\rho^{(0)} = \rho^{(1)}$, the common correlation ρ is bounded:

$$B_L(\theta) = \max\{B_L^{(0)}(\theta), B_L^{(1)}(\theta)\} \leq \rho \leq B_U(\theta) = \min\{B_U^{(0)}(\theta), B_U^{(1)}(\theta)\}$$

[6] Sozu T, Sugimoto T and Hamasaki T. (2010). *Statistics in Medicine*.

Composite parameters when $\rho^{(0)} = \rho^{(1)}$ given $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$

The probability of observing ε_* decreases as the correlation ρ increases.

$$p_*^{(i)} = 1 - (1 - p_1^{(i)})(1 - p_2^{(i)}) - \rho\sqrt{p_1^{(i)} p_2^{(i)} (1 - p_1^{(i)})(1 - p_2^{(i)})}$$

Composite parameters when $\rho^{(0)} = \rho^{(1)}$ given $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$

The probability of observing ε_* decreases as the correlation ρ increases.

$$p_*^{(i)} = 1 - (1 - p_1^{(i)})(1 - p_2^{(i)}) - \rho\sqrt{p_1^{(i)} p_2^{(i)} (1 - p_1^{(i)})(1 - p_2^{(i)})}$$

The effect on the composite endpoint decreases as the correlation ρ increases.

$$\delta_* = \delta_1 q_2^{(0)} + \delta_2 q_1^{(0)} - \delta_1 \delta_2 + \rho\left(\sqrt{p_1^{(0)} p_2^{(0)} q_1^{(0)} q_2^{(0)}} - \sqrt{p_1^{(1)} p_2^{(1)} q_1^{(1)} q_2^{(1)}}\right)$$

Composite parameters when $\rho^{(0)} = \rho^{(1)}$ given $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$

The probability of observing ε_* decreases as the correlation ρ increases.

$$p_*^{(i)} = 1 - (1 - p_1^{(i)})(1 - p_2^{(i)}) - \rho\sqrt{p_1^{(i)} p_2^{(i)} (1 - p_1^{(i)})(1 - p_2^{(i)})}$$

The effect on the composite endpoint decreases as the correlation ρ increases.

$$\delta_* = \delta_1 q_2^{(0)} + \delta_2 q_1^{(0)} - \delta_1 \delta_2 + \rho\left(\sqrt{p_1^{(0)} p_2^{(0)} q_1^{(0)} q_2^{(0)}} - \sqrt{p_1^{(1)} p_2^{(1)} q_1^{(1)} q_2^{(1)}}\right)$$

TACTICS-TIMI 18: Plausible values for the composite parameters $(p_*^{(0)}, \delta_*)$

Marginal parameters	$p_1^{(0)} = 0.095$, $p_2^{(0)} = 0.137$	$\delta_1 = -0.022$, $\delta_2 = -0.027$
Correlation bounds ($\rho = \rho^{(0)} = \rho^{(1)}$)	$B_L(\theta) = -0.10$	$B_U(\theta) = 0.80$
Composite Endpoint $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$0.14 \leq p_*^{(0)} \leq 0.23$	$-0.05 \leq \delta_* \leq -0.03$

Sample size derivation based on the composite components

Sample Size for Composite Binary Endpoints

Testing problem:

$$\mathcal{H}_* : \quad \begin{cases} H_0 : & \delta_* = 0 \\ H_1 : & \delta_* < 0 \end{cases}$$

Sample Size for composite endpoints:

$$n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho) = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

Sample Size for Composite Binary Endpoints

Testing problem:

$$\mathcal{H}_* : \begin{cases} H_0 : & \delta_* = 0 \\ H_1 : & \delta_* < 0 \end{cases}$$

Sample Size for composite endpoints:

$$n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho) = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

Sample size derivation based on marginal components

In practice

- we have prior information on the marginal effects (δ_1, δ_2) and event rates $(p_1^{(0)}, p_2^{(0)})$
- the correlation ρ is usually unknown and difficult to anticipate.

Sample Size based on components information

Sample size behavior given $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$:

The sample size for fixed θ **increases** and **is bounded** with respect to ρ: [5]

$$n(\theta, B_L(\theta)) \leq n(\theta, \rho) \leq n(\theta, B_U(\theta))$$

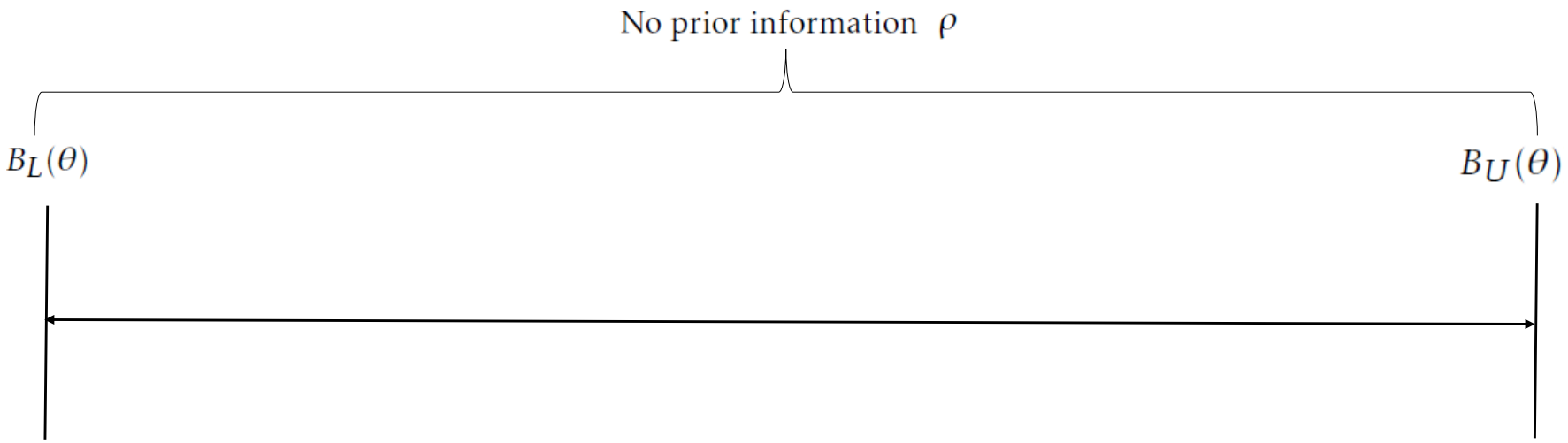
Sample size strategy:

- When the correlation value is unknown $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$
- Accounting for deviations from the anticipated event rates $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$.

[5] Bofill M, Gómez G (2018). Sample size derivation for composite binary endpoints. *Submitted*.

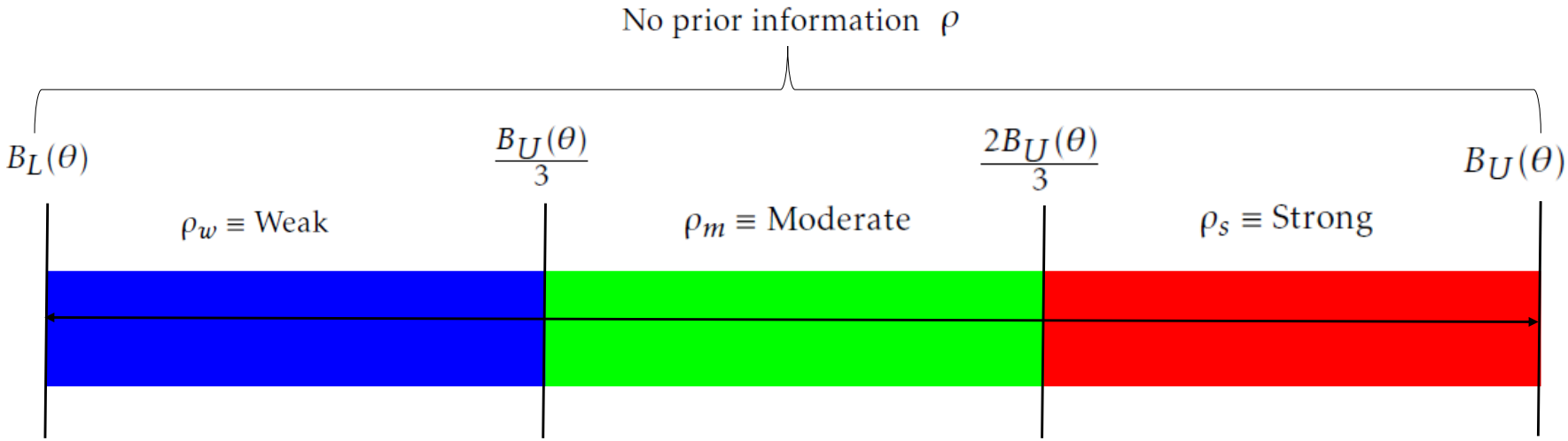
Sample size strategy for fixed $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ and unknown ρ

STEP (I): Define correlation categories and compute their corresponding bounds



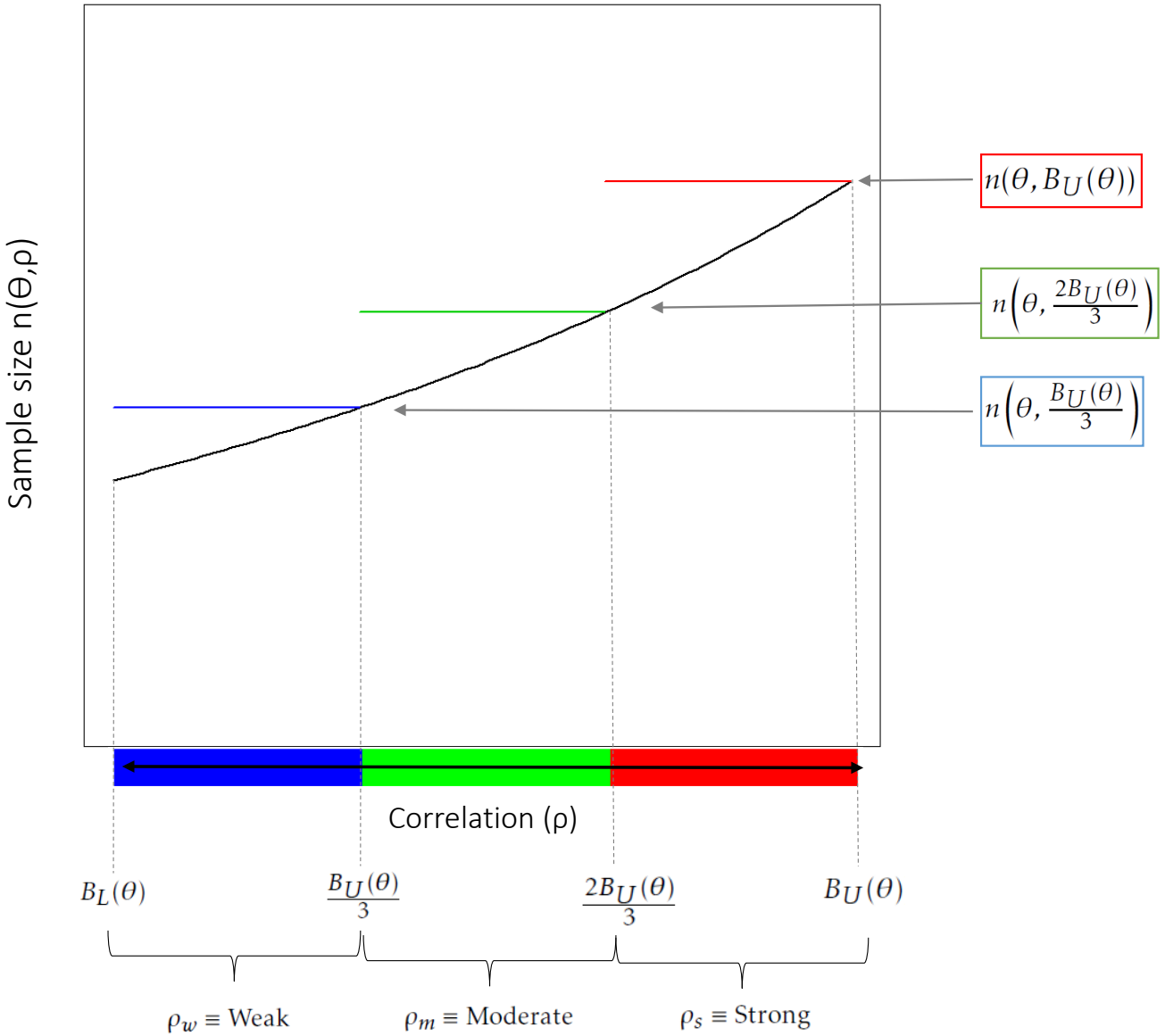
Sample size strategy for fixed $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ and unknown ρ

STEP (I): Define correlation categories and compute their corresponding bounds



Sample size strategy for fixed $\theta = (p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ and unknown ρ

STEP (II): Calculate the maximum sample size value in each correlation category



Using **CompARE** to compute the sample size when ρ is unknown

Endpoint 1:

Probability under control group:

Point value

Anticipated value:

0.095

Effect measure:

Risk Difference

Risk Difference:

-0.022

Endpoint 2:

Probability under control group:

Point value

Anticipated value:

0.137

Effect measure:

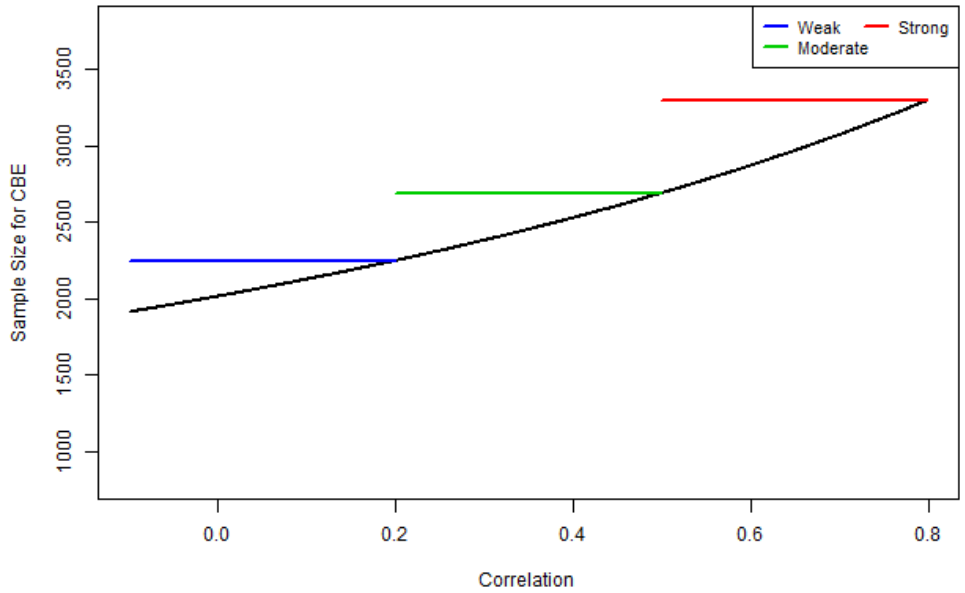
Risk Difference

Risk Difference:

-0.027

Sample size when the correlation value is not known

Weak	Moderate	Strong
2,247	2,690	3,299



Sample Size accounting for deviations from the anticipated event rates

Sample size strategy:

- when the correlation is unknown and the anticipated event rates may be misspecified $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$.

Sample Size accounting for deviations from the anticipated event rates

Sample size strategy:

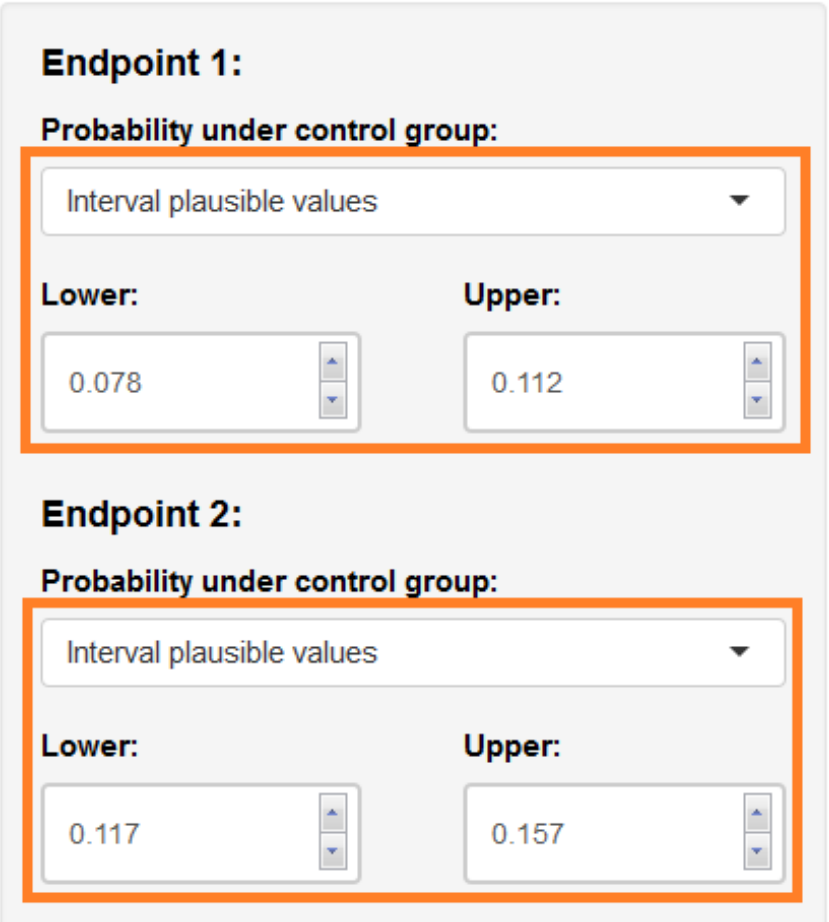
- when the correlation is unknown and the anticipated event rates may be misspecified $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$.

Intervals of plausible values for the event rates:

- $I_1 = \left[\underline{p_1^{(0)}}, \overline{p_1^{(0)}}\right]$ for the event rate $p_1^{(0)}$.
- $I_2 = \left[\underline{p_2^{(0)}}, \overline{p_2^{(0)}}\right]$ for the event rate $p_2^{(0)}$.

TACTICS-TIMI 18:

- Event rates: $p_1^{(0)} = 0.095$ and $p_2^{(0)} = 0.137$.



Sample Size accounting for deviations from the anticipated event rates

Sample size strategy:

- Accounting for deviations from the anticipated event rates $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$.

How can we calculate the required sample size based on I_1 and I_2 for given (δ_1, δ_2) and ρ?

Sample Size accounting for deviations from the anticipated event rates

Sample size strategy:

- Accounting for deviations from the anticipated event rates $\rightarrow n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$.

How can we calculate the required sample size based on I_1 and I_2 for given (δ_1, δ_2) and ρ?

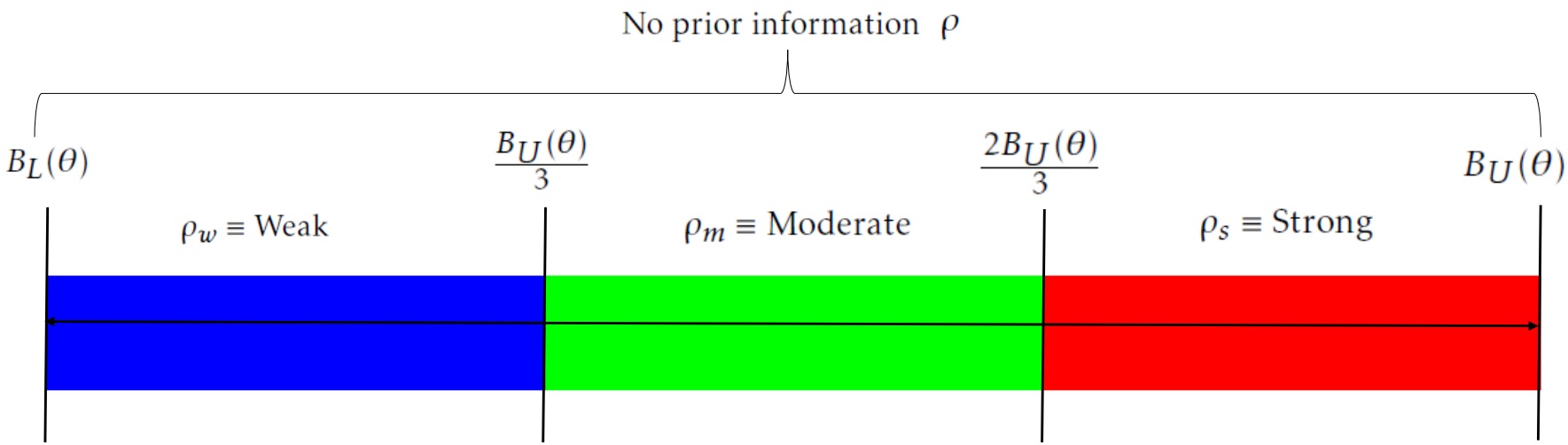
Sample size behavior according to the intervals I_1 and I_2 for fixed (δ_1, δ_2) and ρ

Sample size **bounds** given I_1 and I_2:

$$n\left(\underline{p_1^{(0)}}, \underline{p_2^{(0)}}, \delta_1, \delta_2, \rho\right) \leq n(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho) \leq n\left(\overline{p_1^{(0)}}, \overline{p_2^{(0)}}, \delta_1, \delta_2, \rho\right)$$

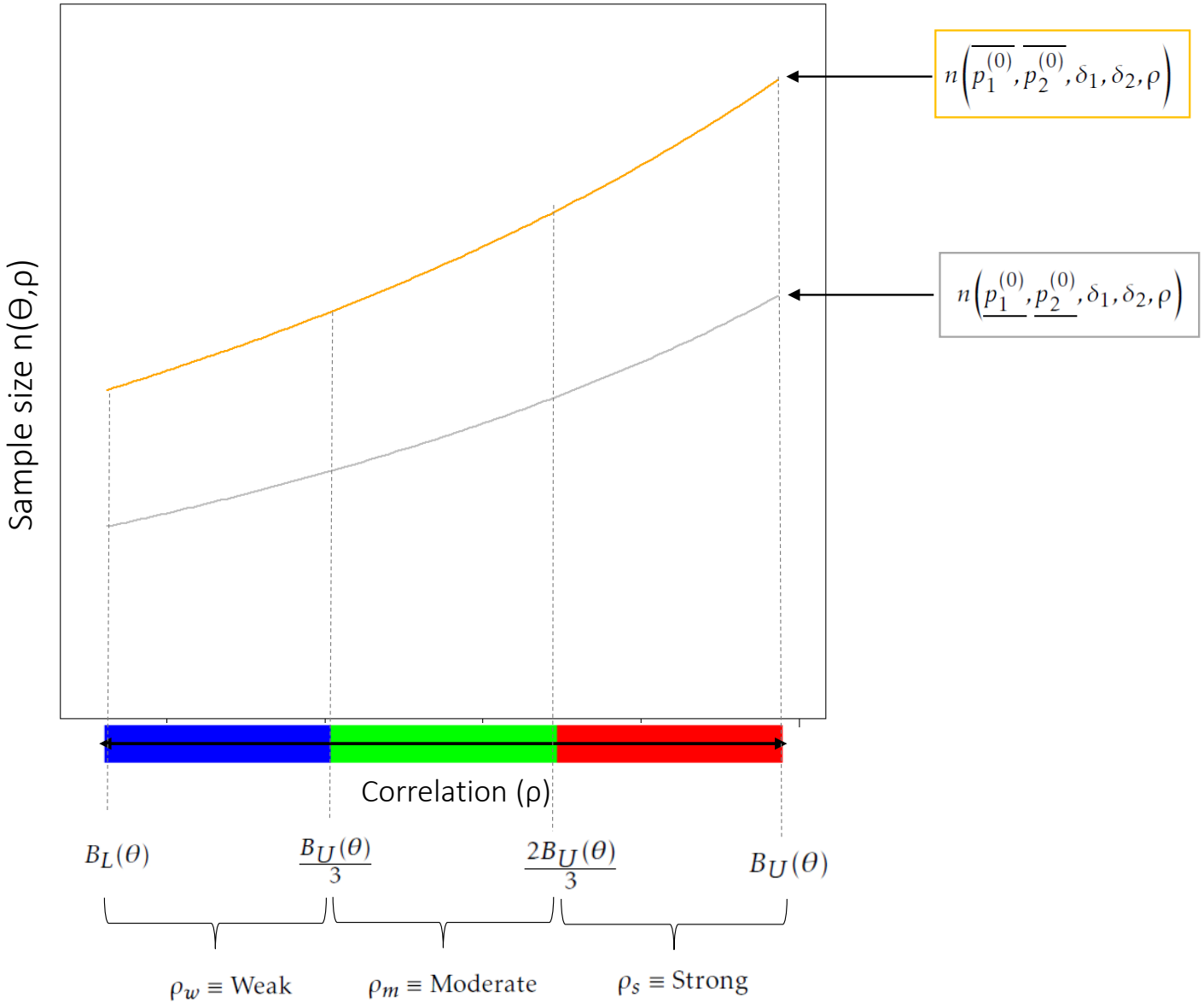
Sample size strategy for fixed $\theta = (I_1, I_2, \delta_1, \delta_2)$ and unknown ρ

STEP (I): Define correlation categories and compute their corresponding bounds



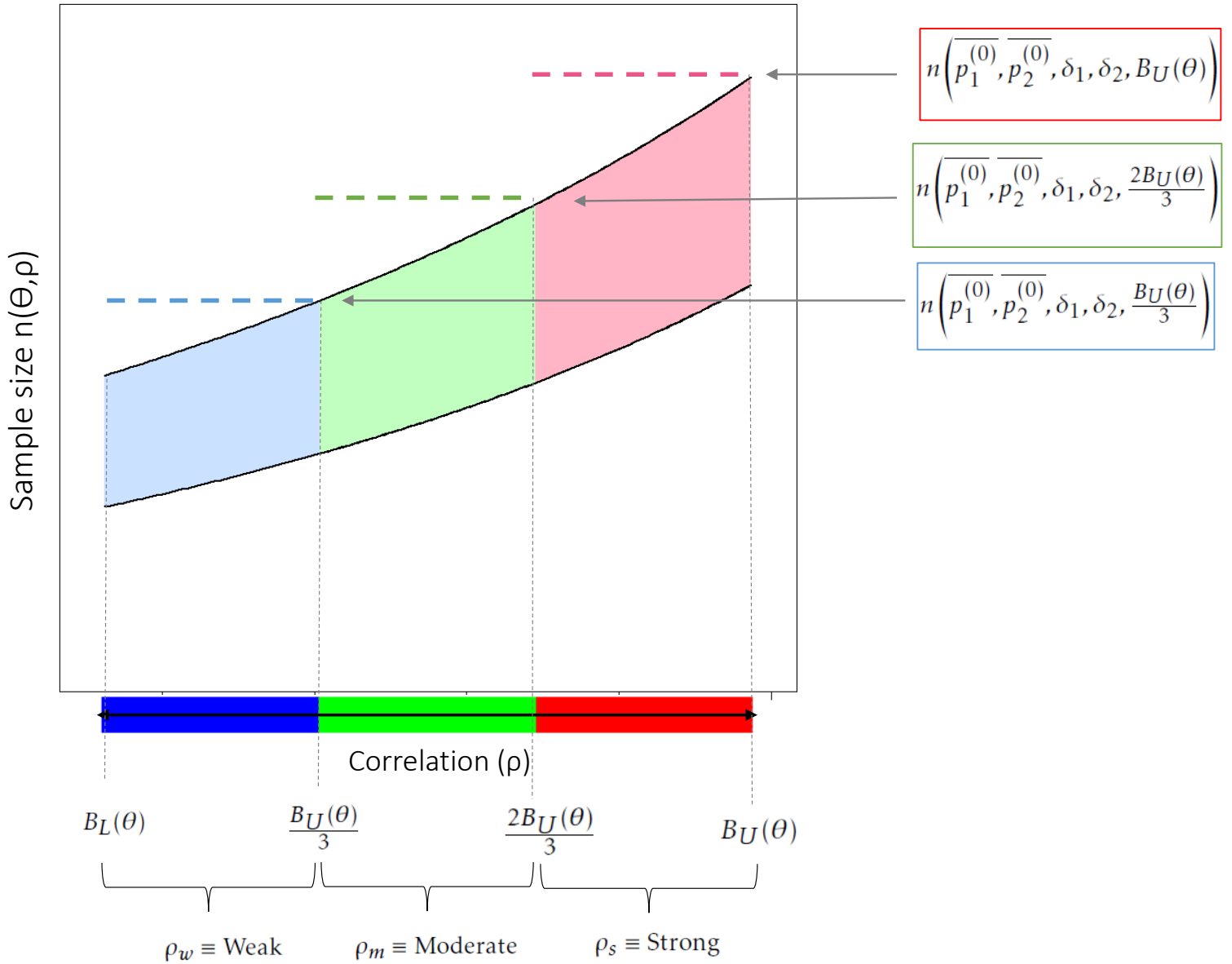
Sample size strategy for fixed $\theta = (I_1, I_2, \delta_1, \delta_2)$ and unknown ρ

STEP (II): Calculate the maximum sample size value in each correlation category



Sample size strategy for fixed $\theta = (I_1, I_2, \delta_1, \delta_2)$ and unknown ρ

STEP (II): Calculate the maximum sample size value in each correlation category



Using **CompARE** to compute the sample size based on $(I_1, I_2, \delta_1, \delta_2)$ when ρ is unknown

Endpoint 1:

Probability under control group:

Interval plausible values

Lower: 0.078 **Upper:** 0.112

Effect measure:

Risk Difference

Risk Difference:

-0.022

Endpoint 2:

Probability under control group:

Interval plausible values

Lower: 0.117 **Upper:** 0.157

Effect measure:

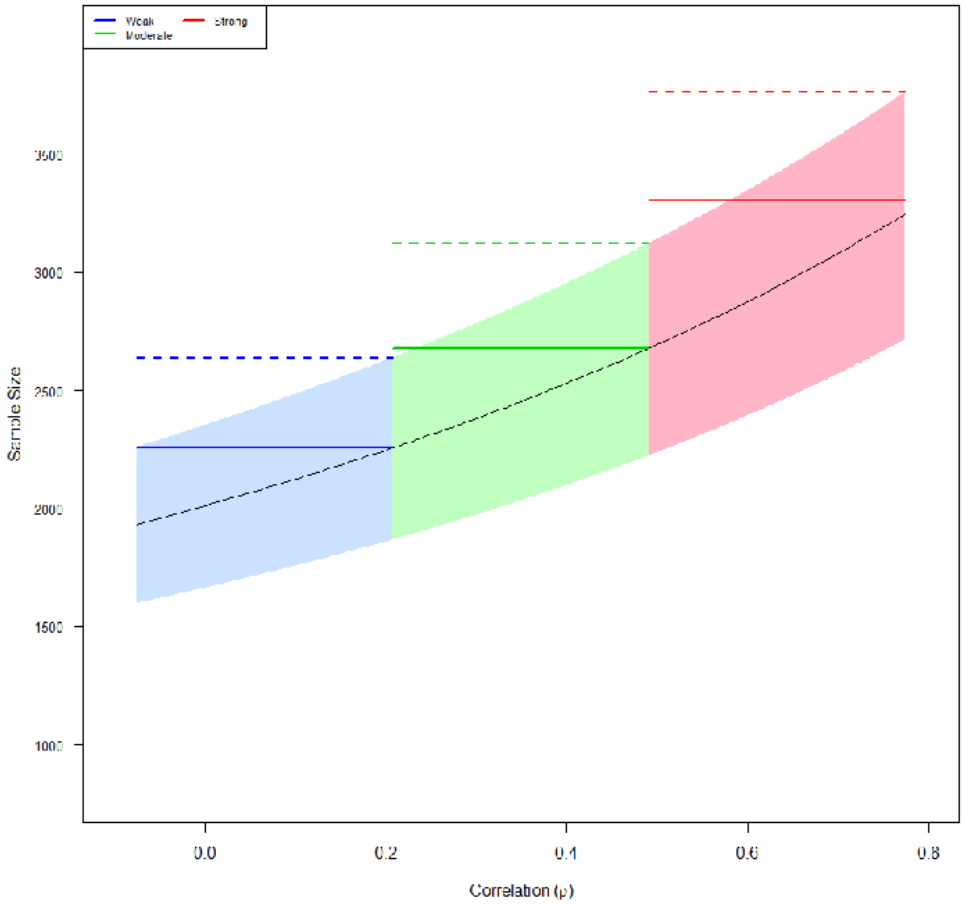
Risk Difference

Risk Difference:

-0.027

Sample Size accounting for departures of the anticipated values

Weak	Moderate	Strong
2.627	3.138	3.824



Concluding remarks and future research

Final remarks

- The correlation value has a great impact on the needed sample size.
- We propose strategies to derive the sample size even if the correlation is not specified and accounting for misspecifications of the anticipated event rates.
- **CompARE** can be used as a tool to calculate the sample size for composite endpoints under different scenarios.

Concluding remarks and future research

Final remarks

- The correlation value has a great impact on the needed sample size.
- We propose strategies to derive the sample size even if the correlation is not specified and accounting for misspecifications of the anticipated event rates.
- **CompARE** can be used as a tool to calculate the sample size for composite endpoints under different scenarios.

Future Research

- Sample size for small samples and for unbalanced designs.
- Different correlation in each treatment group.
- Improving the implementation in the web-platform **CompARE**.

THANK YOU

GRÀCIES ESKERRIK ASKO GRAZAS GRACIAS