



# Predictive probability of success using surrogate endpoints

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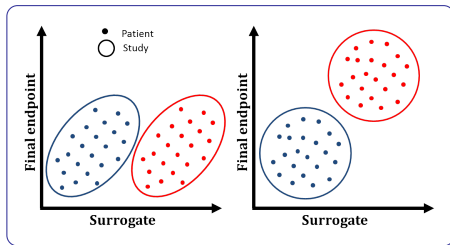
# Introduction (1/2)

- The **Predictive Probability of Success (PPoS)** of a future clinical trial is a key quantitative tool for decision-making in drug development  
*Spiegelhalter et al., 1986 ; O'Hagan et al., 2005 ; Gasparini et al., 2013*
- Derived from prior knowledge and available evidence
- Typically, available evidence = accumulated data on the **clinical endpoint of interest** in previous clinical trials
- However, a **surrogate endpoint** could be used as primary endpoint in early development, and no or limited data are collected on the clinical endpoint of interest

⇒ **General methodology to predict the success of a future trial from surrogate endpoints**

# Introduction (2/2)

- Terminology used in this presentation
  - **Surrogate endpoint:** marker used in early phase as a measure of the treatment effect
  - **Final endpoint:** clinical endpoint of interest (accepted for confirmatory phase from a regulatory perspective)
- “A correlate does not a surrogate make” Fleming and DeMets, 1996
  - A relationship between endpoints estimated from a single trial is insufficient to support predictions across trials
  - It focuses on the patient level association, while we are interested in the relationship between treatment effects on the endpoints at the trial level
  - ⇒ **Meta-analytic approaches** have been proposed to overcome this issue

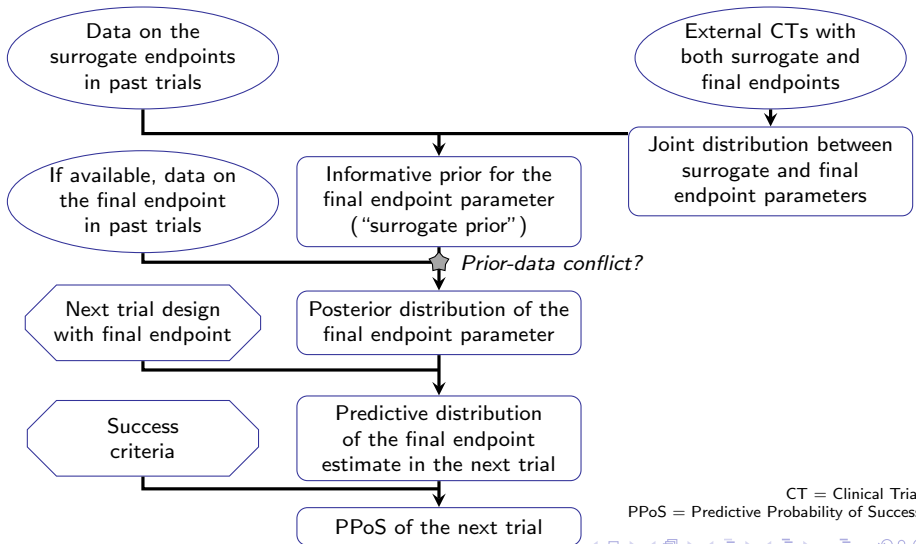


Daniels and Hughes, 1997 ; Buyse *et al.*, 2000 ; Gail *et al.*, 2000 ; Baker and Kramer, 2003 ; Burzykowski *et al.*, 2005 ; Buyse *et al.*, 2016 ; Alonso *et al.*, 2017

# Proposed approach

## Drug development of interest

## External data



# Motivating example

Fictive but realistic case-study in Multiple Sclerosis

## Drug development of interest

Data on the surrogate endpoints in past trials

If available, data on the final endpoint in past trials

Next trial design with final endpoint

Success criteria

### Phase II trial (completed)

Experimental arm vs Control arm

$N/\text{arm} = 100$

Primary (surrogate):  
Relapse rate at 1 year

Secondary (final):  
Disability progression at 2 years

### Phase III trial (planned)

Experimental arm vs Control arm

$N/\text{arm} = 337$

Primary (final):  
Disability progression at 2 years

Success:  $p\text{-value} < 2.5\%$   
(one-sided)

## External data

External CTs with both surrogate and final endpoints

**19 clinical trials  
(5 multi-arm)**  
with both endpoints evaluated

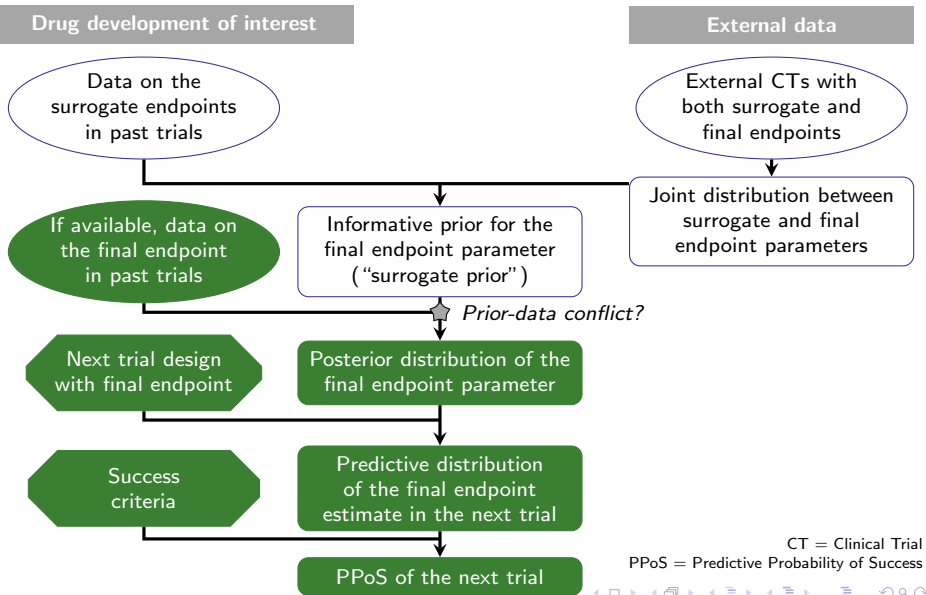
Pozzi *et al.*, 2016

Bujkiewicz *et al.*, 2016

Sormani *et al.*, 2010

# Without considering the surrogate endpoint... (1/2)

PPoS based on the final endpoint only (reminders)



CT = Clinical Trial  
PPoS = Predictive Probability of Success

# Without considering the surrogate endpoint... (2/2)

PPoS based on the final endpoint only (reminders)

## Disability progression at 2 years

Results of the Phase II trial  
at the time of the main analysis

	$\hat{\theta} (\sigma)$
N/arm	10
log(RR) (SE)	-0.386 (0.646)

Vague prior  $\pi_{\theta}^V(\cdot): \theta \sim N(\theta_0, \sigma_0^2)$

Posterior  $g_{\theta}^V(\cdot): \theta \sim N(\theta_p, \sigma_p^2)$

Predictive  $h_{\hat{\theta}_f}^V(\cdot): \hat{\theta}_f \sim N(\theta_p, \sigma_p^2 + \sigma_f^2)$

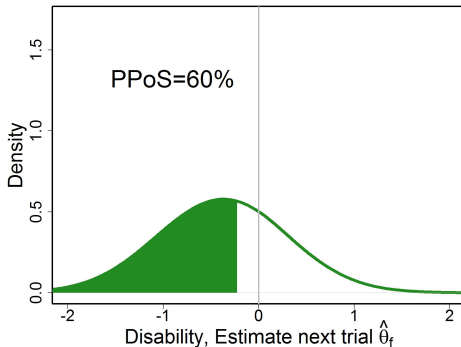
$$PPoS^V = P(\hat{\theta}_f < z_{\alpha} \sigma_f^2) = \int_{u < z_{\alpha} \sigma_f^2} h_{\hat{\theta}_f}^V(u) du$$

The prediction variance depends on:

- The precision of the evidence on the final endpoint
- The precision planned in the future trial on the final endpoint

RR=Relative Risk  
SE=Standard Error

## Predictive distribution and PPoS



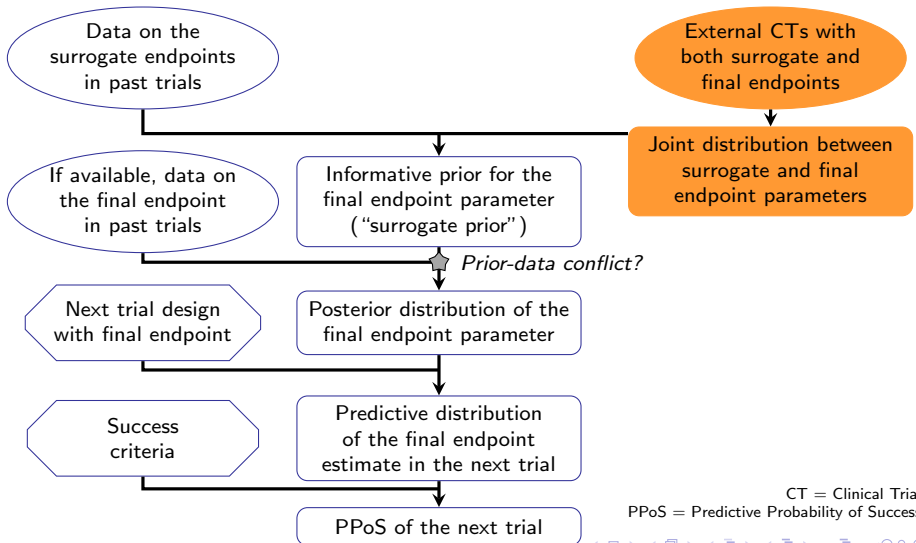
# Joint distribution between surrogate and final endpoint parameters

## Meta-analytic approach using external CTs

(1/2)

Drug development of interest

External data



CT = Clinical Trial  
PPoS = Predictive Probability of Success



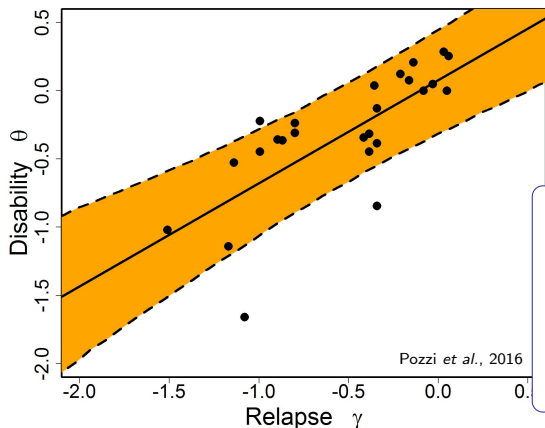
# Joint distribution between surrogate and final endpoint parameters

## Meta-analytic approach using external CTs

(2/2)

Conditional distribution:  $\theta_i \mid \gamma_i, a, b, \tau \sim N(a + b\gamma_i, \tau^2)$

Joint distribution:  $\begin{pmatrix} \hat{\theta}_i \\ \hat{\gamma}_i \end{pmatrix} \mid \gamma_i, a, b, \tau \sim N\left(\begin{pmatrix} a + b\gamma_i \\ \gamma_i \end{pmatrix}, \begin{pmatrix} \sigma_i^2 + \tau^2 & \rho_i \sigma_i \delta_i \\ \rho_i \sigma_i \delta_i & \delta_i^2 \end{pmatrix}\right)$



The **variance** of the joint dist. between endpoints depends on:

- The variance of the joint post. distribution  $f_{a,b,\tau}(\cdot)$ : **small if the amount of data in the meta-analysis is large**
- The dependence between the endpoints:  $\tau$  is **small if the surrogate is 'good'**

### Regression parameters

Posterior means and  
95% credible intervals (CrI)

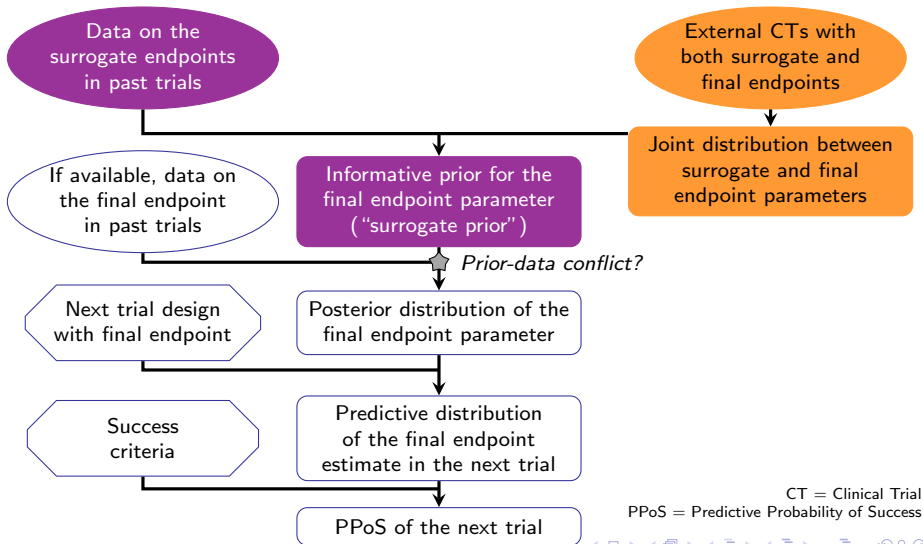
Parameter	Mean [95% CrI]
Intercept $a$	0.08 [-0.10, 0.24]
Slope $b$	0.76 [ 0.47, 1.02]
Error $\tau$	0.15 [ 0.05, 0.29]

# Informative prior for the final endpoint parameter (1/3)

“Surrogate prior”

Drug development of interest

External data



CT = Clinical Trial  
PPoS = Predictive Probability of Success

# Informative prior for the final endpoint parameter (2/3)

“Surrogate prior”

**Relapse rate at 1 year**  
Results of the Phase II trial  
(main analysis)

	$\hat{\gamma}(\delta)$
N/arm	100
log(RR) (SE)	-0.693 (0.397)

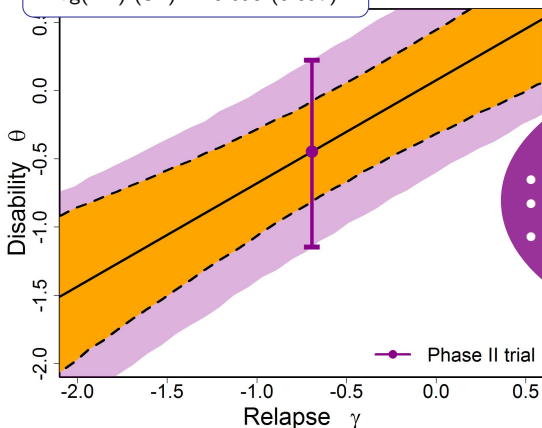
Surrogate endpoint: Vague prior:  $\gamma \sim N(\gamma_0, \delta_0^2)$

Posterior:  $\gamma \sim N(\gamma_p, \delta_p^2)$

Final endpoint:

Conditional distribution  $f_{\theta|a,b,\tau}(\cdot)$ :  $\theta | a, b, \tau \sim N(a + b\gamma_p, \tau^2 + b^2\delta_p^2)$

Unconditional distribution  $\pi_{\theta}^S(\cdot)$ :  $\int f_{\theta|a,b,\tau}(\cdot) f_{a,b,\tau}(x, y, z) d(x, y, z)$



The variance of the unconditional distribution depends on:

- The variance of the joint post. distribution  $f_{a,b,\tau}(\cdot)$
- The dependence between the endpoints
- **The precision of the evidence on the surrogate:  $\delta_p^2$  is small if the amount of data on the surrogate is large**

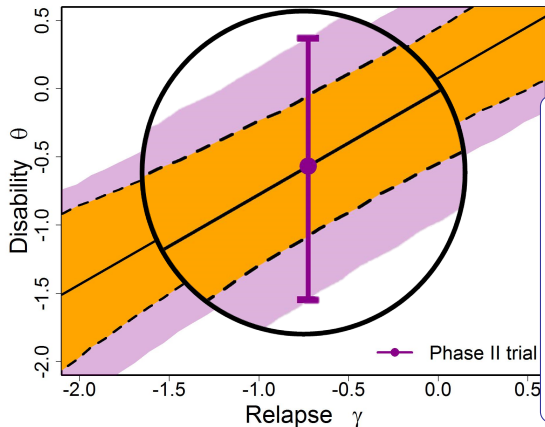
RR=Relative Risk  
SE=Standard Error

# Informative prior for the final endpoint parameter (3/3)

“Surrogate prior”

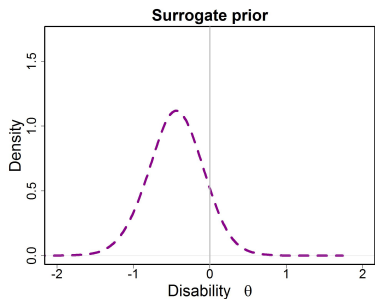
Final endpoint **“Surrogate prior”**:

$$\pi_{\theta}^S(\cdot) = \int f_{\theta|a,b,\tau}(\cdot) f_{a,b,\tau}(x, y, z) d(x, y, z)$$



We call this distribution the **“surrogate prior”**

(Distribution derived from data on the surrogate endpoint, to be used as a prior for the final endpoint)

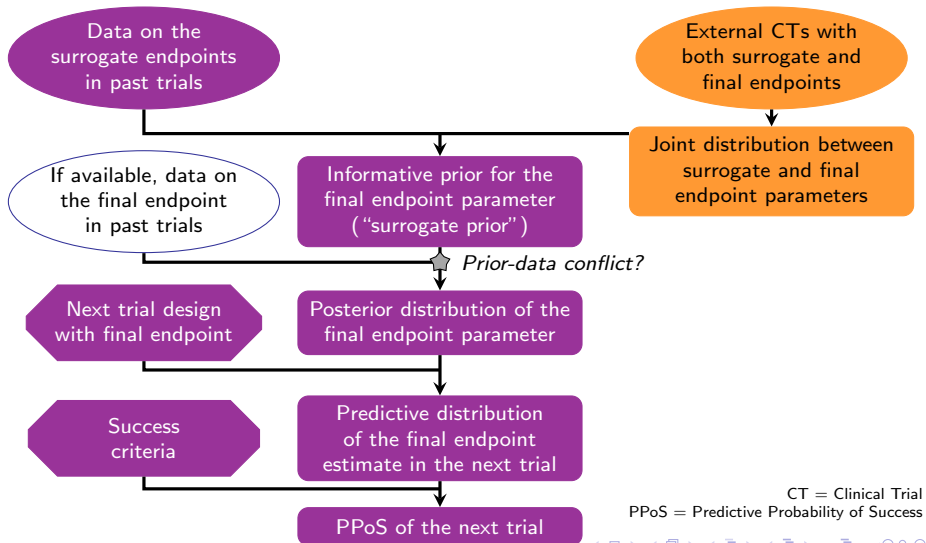


# Without considering the data on the final endpoint... (1/2)

PPoS based on the surrogate endpoint only

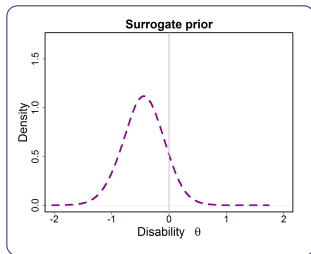
Drug development of interest

External data



# Without considering the data on the final endpoint... (2/2)

## PPoS based on the surrogate endpoint only



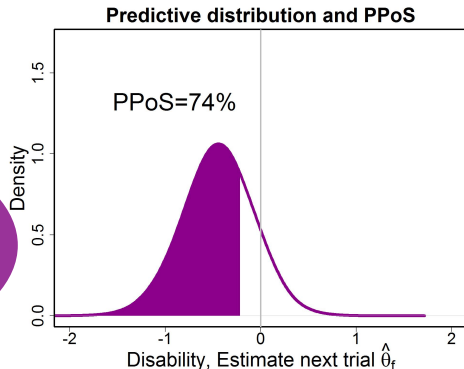
Surrogate prior  $\pi_{\theta}^S(\cdot) = \int f_{\theta|a,b,\tau}(\cdot) f_{a,b,\tau}(x, y, z) d(x, y, z)$   
Posterior = prior (no data)

Predictive  $h_{\hat{\theta}_f}^S(\cdot) = \int f_{\hat{\theta}_f|\theta=t}(\cdot) \pi_{\theta}^S(t) dt$

$PPoS^S = \int_{u < z_{\alpha} \sigma_{\hat{\theta}_f}^2} h_{\hat{\theta}_f}^S(u) du$

The prediction variance depends on:

- The variance of the joint post. distribution  $f_{a,b,\tau}(\cdot)$
- The dependence between the endpoints
- The precision of the evidence on the surrogate
- The precision planned in the future trial on the final endpoint:  $\sigma_{\hat{\theta}_f}^2$  is small if the planned # of patients / events is large

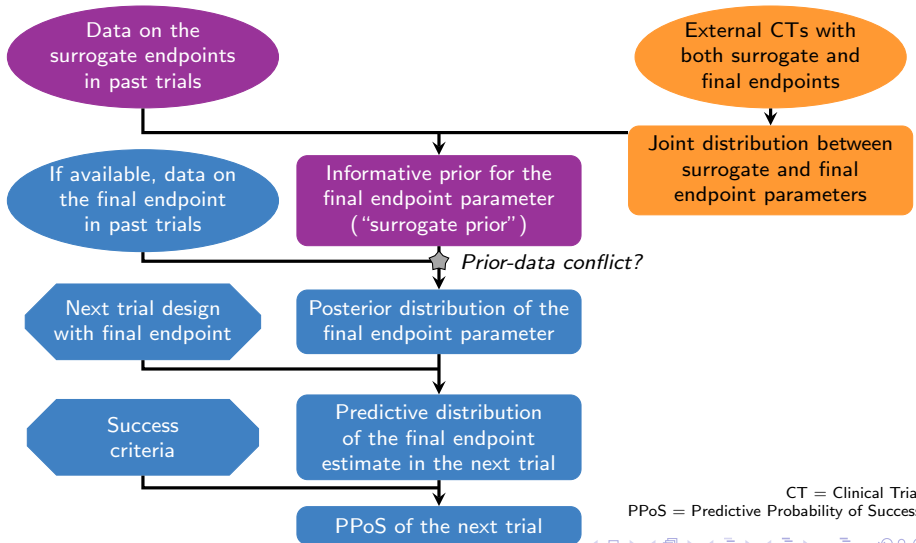


# Considering the whole evidence... (1/2)

## PPoS based on the surrogate and the final endpoints

### Drug development of interest

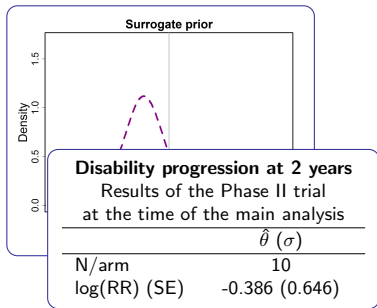
### External data



CT = Clinical Trial  
PPoS = Predictive Probability of Success

# Considering the whole evidence... (2/2)

## PPoS based on the surrogate and the final endpoints



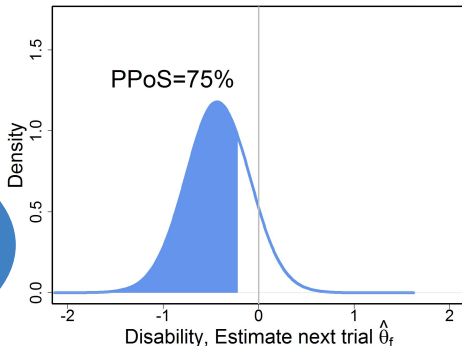
$$\text{Surrogate prior } \pi_{\theta}^S(\cdot) = \int f_{\theta|a,b,\tau}(\cdot) f_{a,b,\tau}(x, y, z) d(x, y, z)$$

$$\text{Posterior } g_{\theta}^S(\cdot) = \frac{f_{\hat{\theta}|\theta}(d) \pi_{\theta}^S(\cdot)}{\int f_{\hat{\theta}|\theta=t}(d) \pi_{\theta}^S(t) dt}$$

$$\text{Predictive } h_{\hat{\theta}_f}^S(\cdot) = \int f_{\hat{\theta}_f|\theta=t}(\cdot) g_{\theta}^S(t) dt$$

$$PPoS^S = \int_{u < z_{\alpha} \sigma_f^2} h_{\hat{\theta}_f}^S(u) du$$

### Predictive distribution and PPoS



The prediction variance depends on:

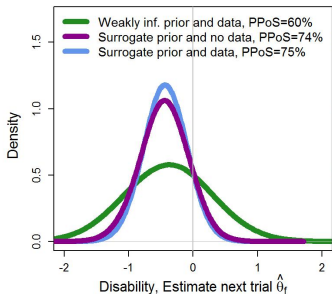
- The variance of the joint post. distribution  $f_{a,b,\tau}(\cdot)$
- The dependence between the endpoints
- The precision of the evidence on the surrogate
- **The precision of the evidence on the final endpoint**
- The precision planned in the future trial on the final endpoint

RR=Relative Risk ; SE=Standard Error

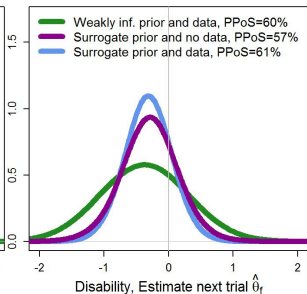


# Summary and multiple surrogates

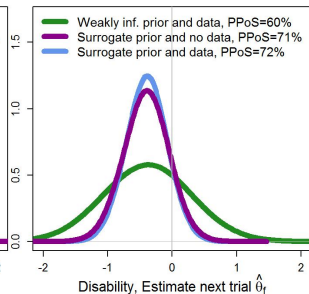
Relapse as surrogate



MRI as surrogate



Relapse + MRI as surrogates



Consistency of the results → Confidence in the decision

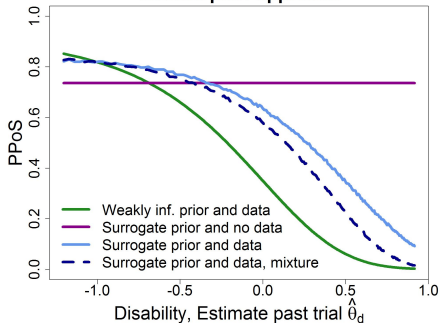
# Prior data conflict

Evidences on the surrogate and the final endpoints may be conflicting...

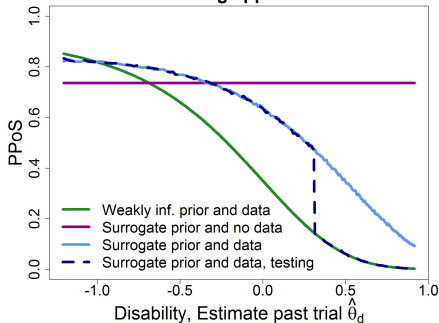
→ Methods for handling **prior-data conflict** could be used (testing approach, mixture/robust prior, power prior...)

Mutsvari *et al.*, 2016 ; Schmidli *et al.*, 2014 ; Ibrahim *et al.*, 2015

### Mixture prior approach



### Testing approach



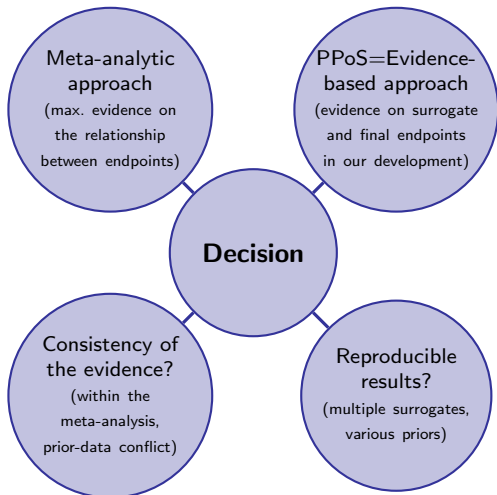
# Concluding remarks

- **General, reliable approach**

- Makes the best use of all the available evidence
- Takes into account all sources of uncertainty
- Consistency and reproducibility assessments are part of the decision-making process
- Could be combined with subjective prior from experts

- **Data demanding**

- Less evidence → more risk when taking the decision...



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# Thank-you!