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

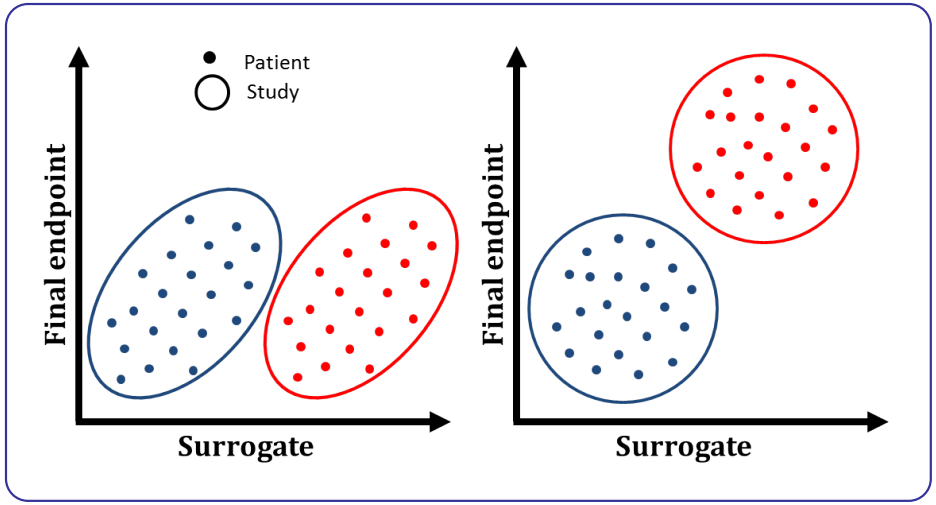
- However, a **surrogate endpoint** could be used as primary endpoint in early development, and no or limited data are collected on the clinical endpoint of interest

$\Rightarrow$ General methodology to predict the success of a future trial from surrogate endpoints

Introduction (2/2)

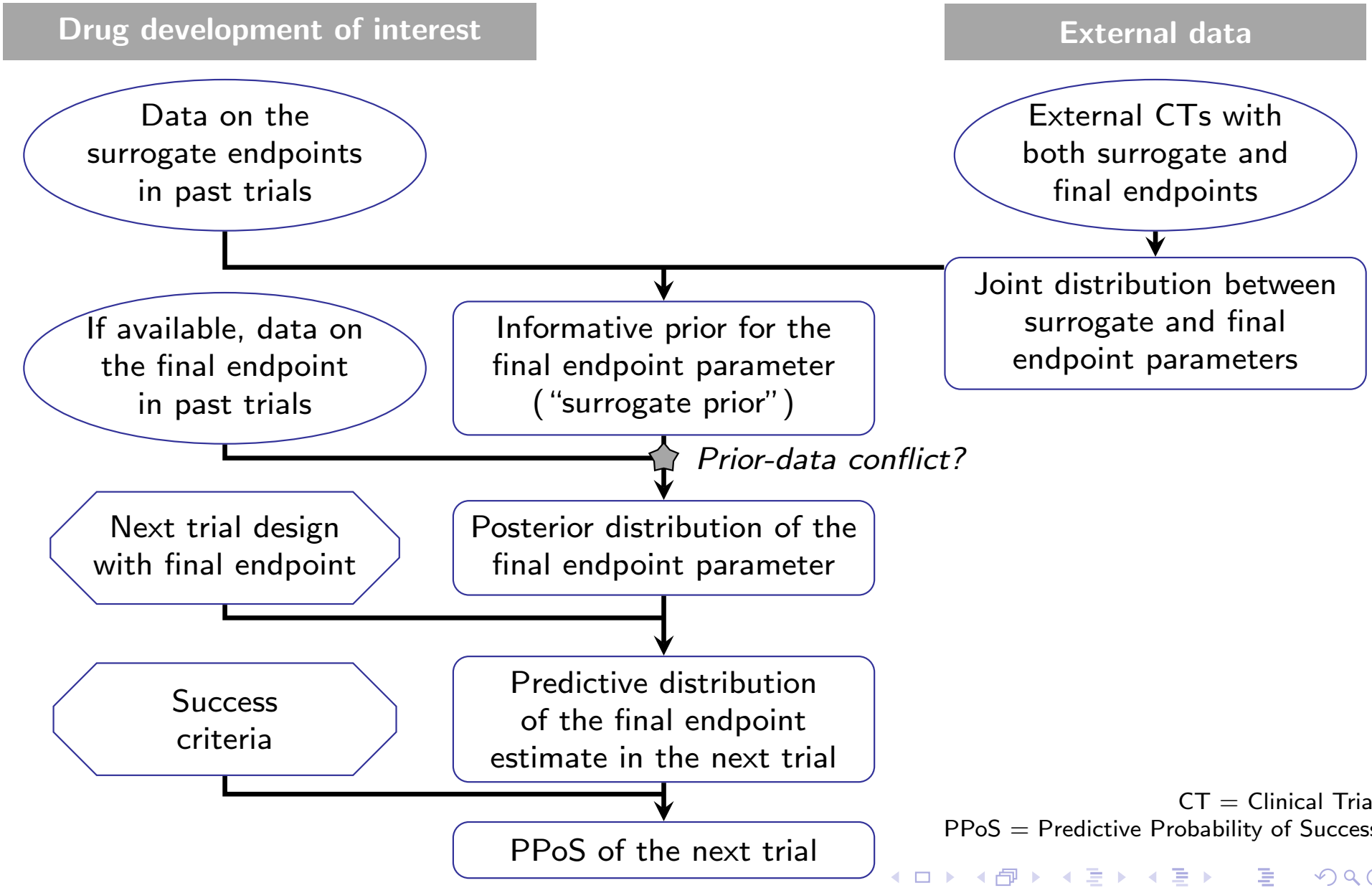
- Terminology used in this presentation
  - **Surrogate endpoint**: marker used in early phase as a measure of the treatment effect
  - **Final endpoint**: clinical endpoint of interest (accepted for confirmatory phase from a regulatory perspective)

- "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
  - $\Rightarrow$ **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



CT = Clinical Trial
PPoS = Predictive Probability of Success

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

Phase II trial (completed)
Experimental arm vs Control arm
N/arm = 100
Primary (surrogate):
Relapse rate at 1 year

Secondary (final):
Disability progression at 2 years

Next trial design with final endpoint

Success criteria

Phase III trial (planned)
Experimental arm vs Control arm
N/arm = 337
Primary (final):
Disability progression at 2 years

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

External data

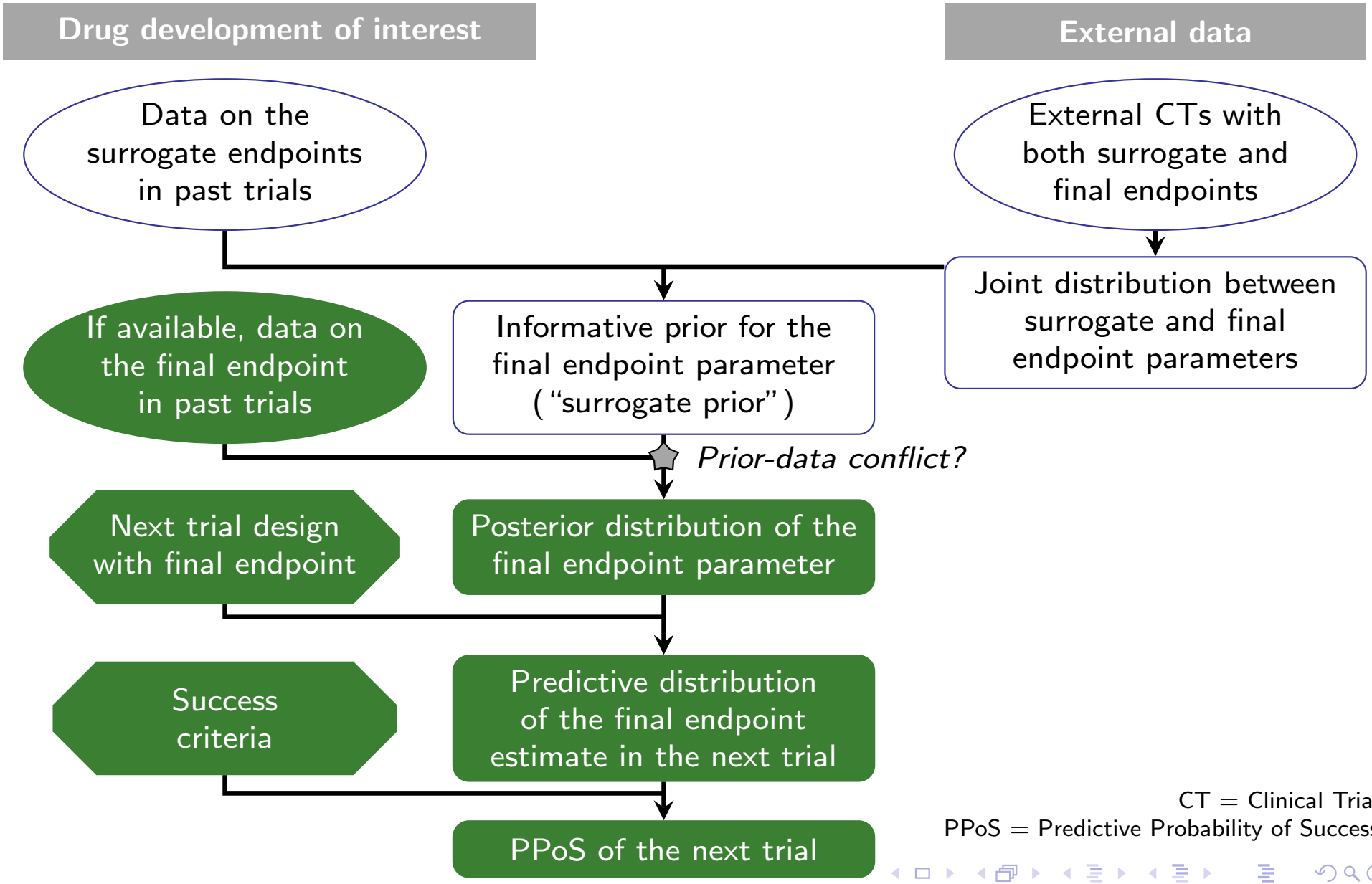
External CTs with both surrogate and final endpoints

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
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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

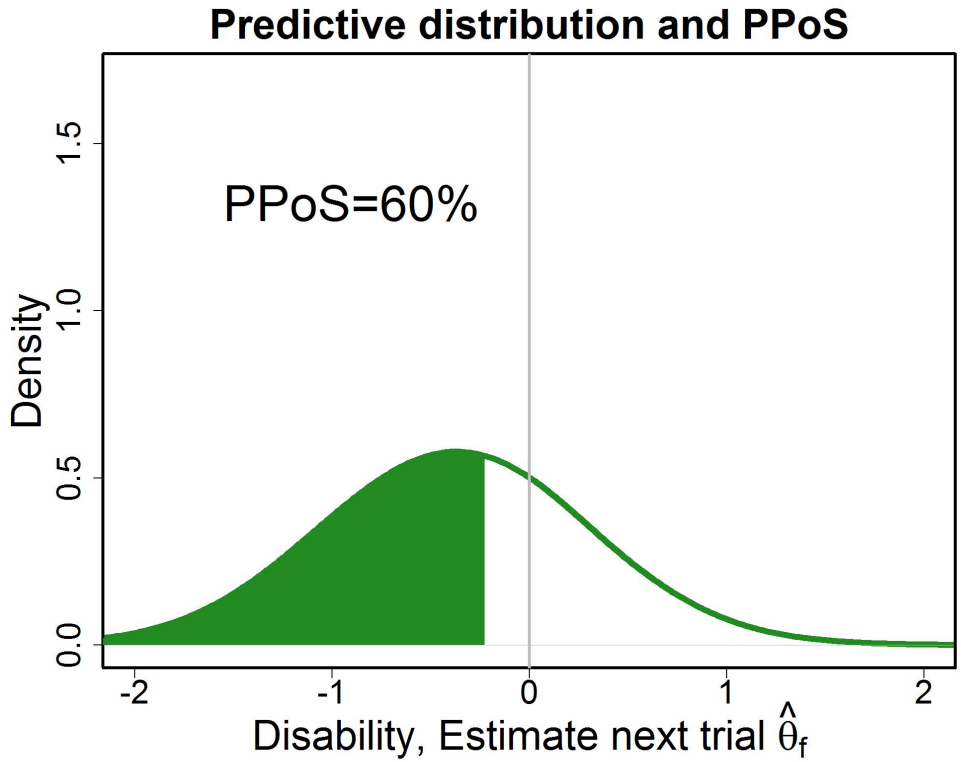
	$\hat{\theta}$ (σ)
N/arm	10
log(RR) (SE)	-0.386 (0.646)

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

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

The **prediction variance** depends on:

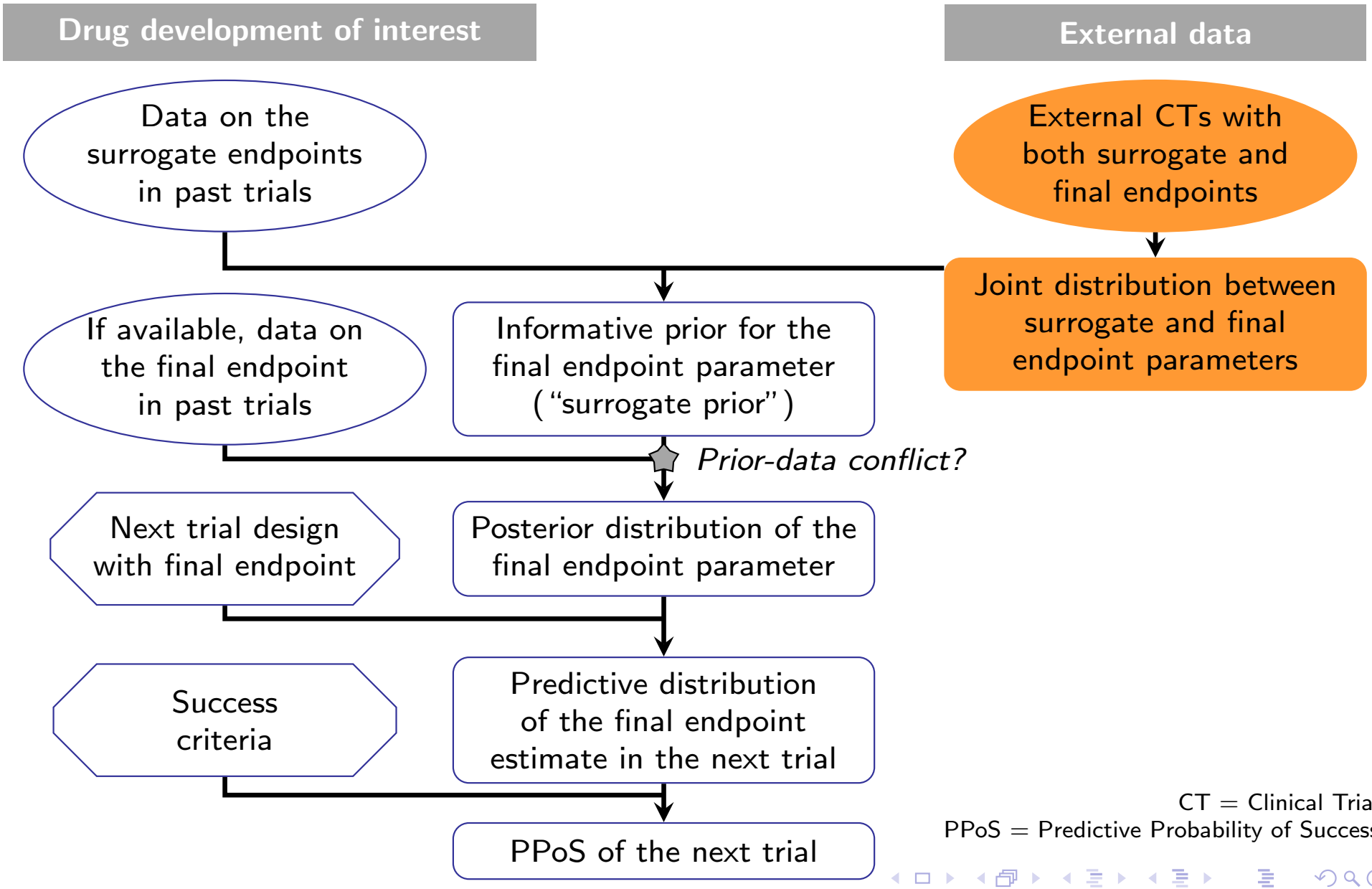
- The precision of the evidence on the final endpoint
- The precision planned in the future trial on the final endpoint



RR=Relative Risk
SE=Standard Error

Joint distribution between surrogate and final endpoint parameters

Meta-analytic approach using external CTs (1/2)



CT = Clinical Trial
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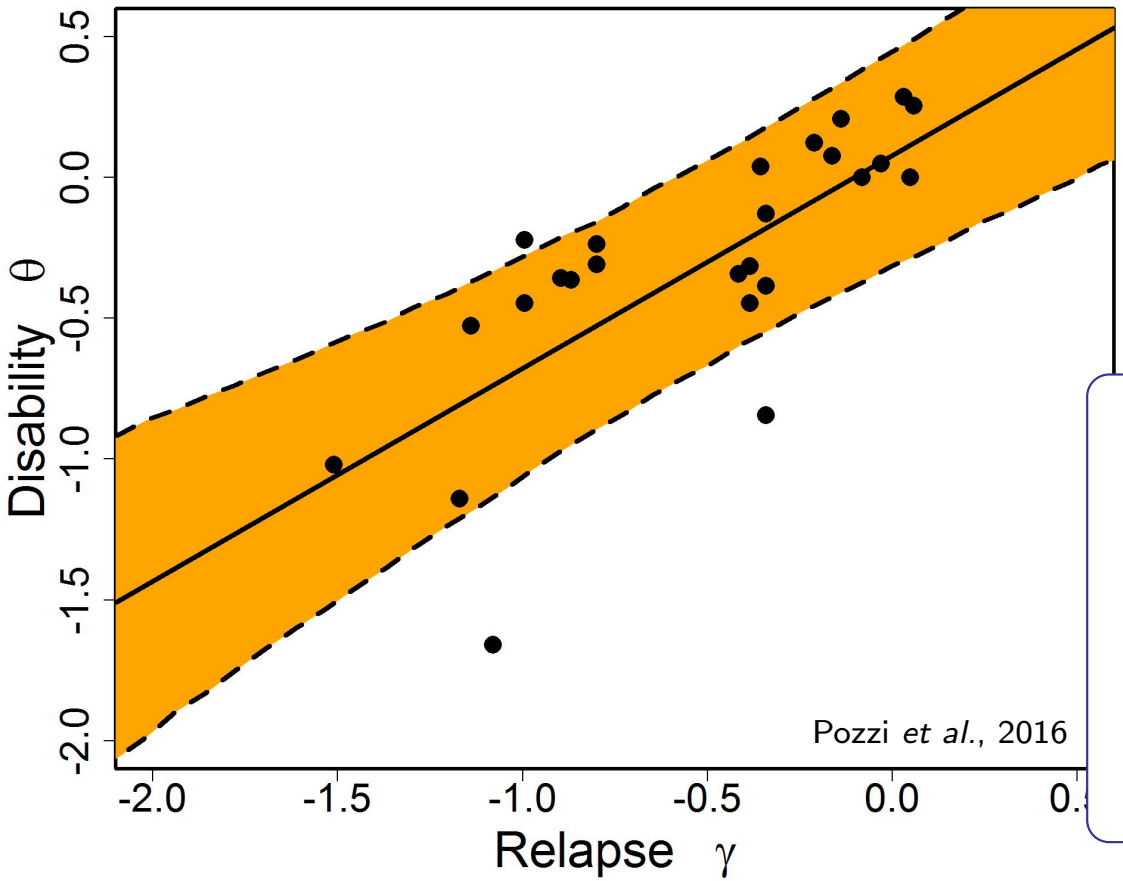
Joint distribution between surrogate and final endpoint parameters
Meta-analytic approach using external CTs (2/2)

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

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



The **precision** of the predictive interval depends on:

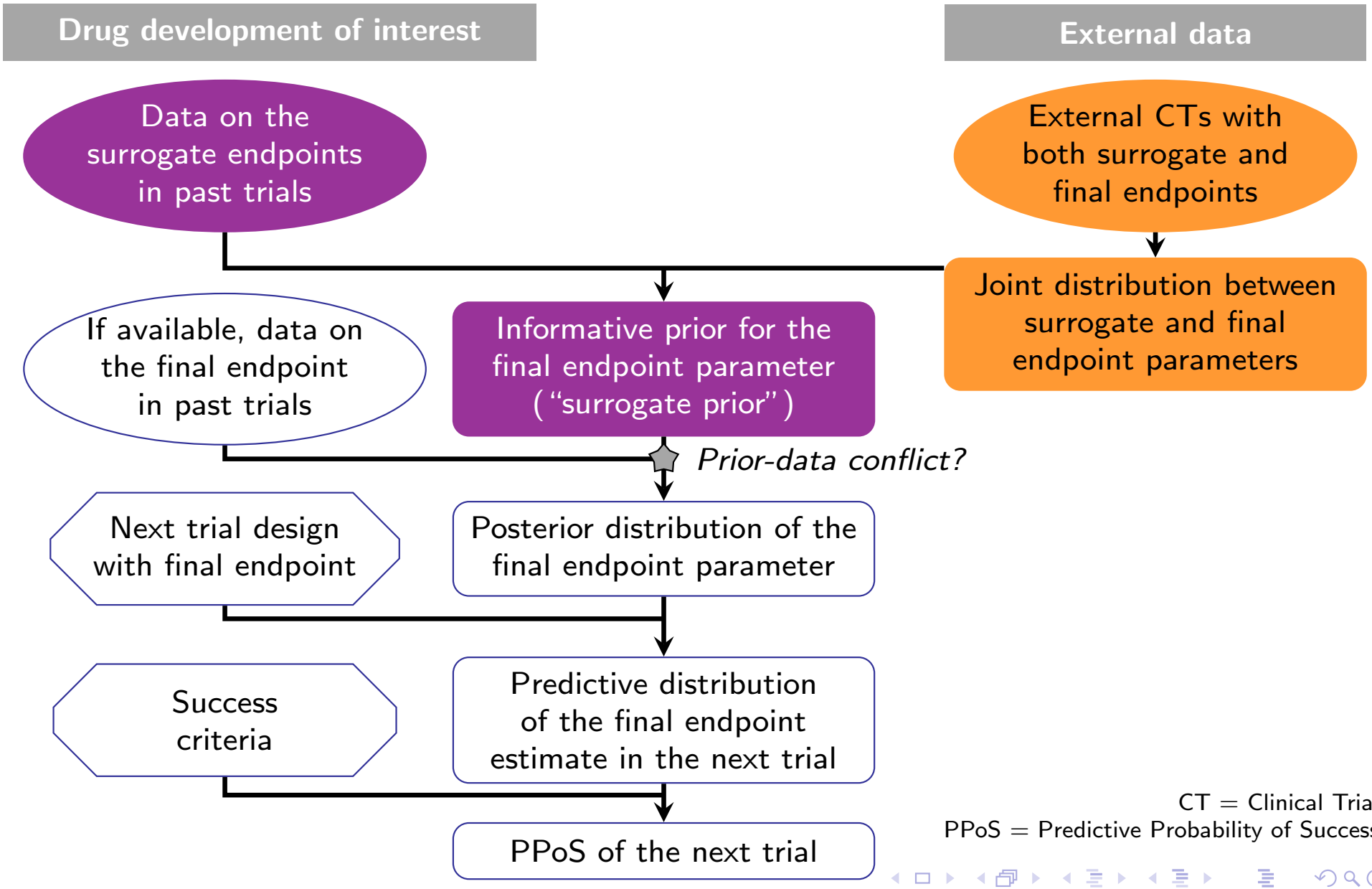
- The variance of the joint post. distribution $f_{a,b,\tau}(\cdot)$: **small if the amount of data in the meta-analysis is large**
- The dependence between the end-points: **τ is small if the surrogate is 'good'**

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	τ	0.15 [0.05,0.29]

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



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

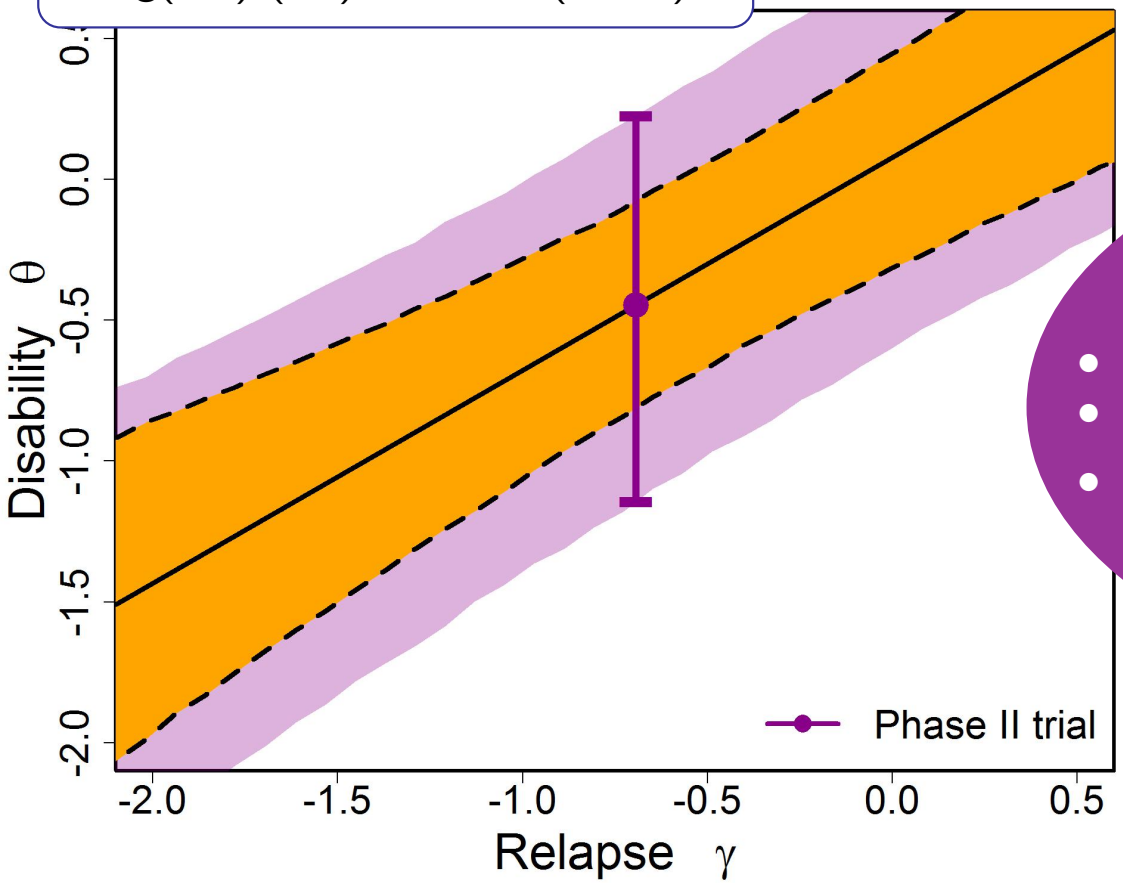
"Surrogate prior"

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

	$\hat{\gamma}$ (δ)
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 $f_{\theta|a,b,\tau}(.)$: $\theta \mid a, b, \tau \sim N(a + b\gamma_p, \tau^2 + b^2\delta_p^2)$
Unconditional distribution $\pi_\theta^S(\cdot)$: $\int f_{\theta|a,b,\tau}(.) f_{a,b,\tau}(x, y, z) d(x, y, z)$



The **precision** of the prediction 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: **δ_p^2 is small if the amount of data on the surrogate is large**

RR=Relative Risk
SE=Standard Error

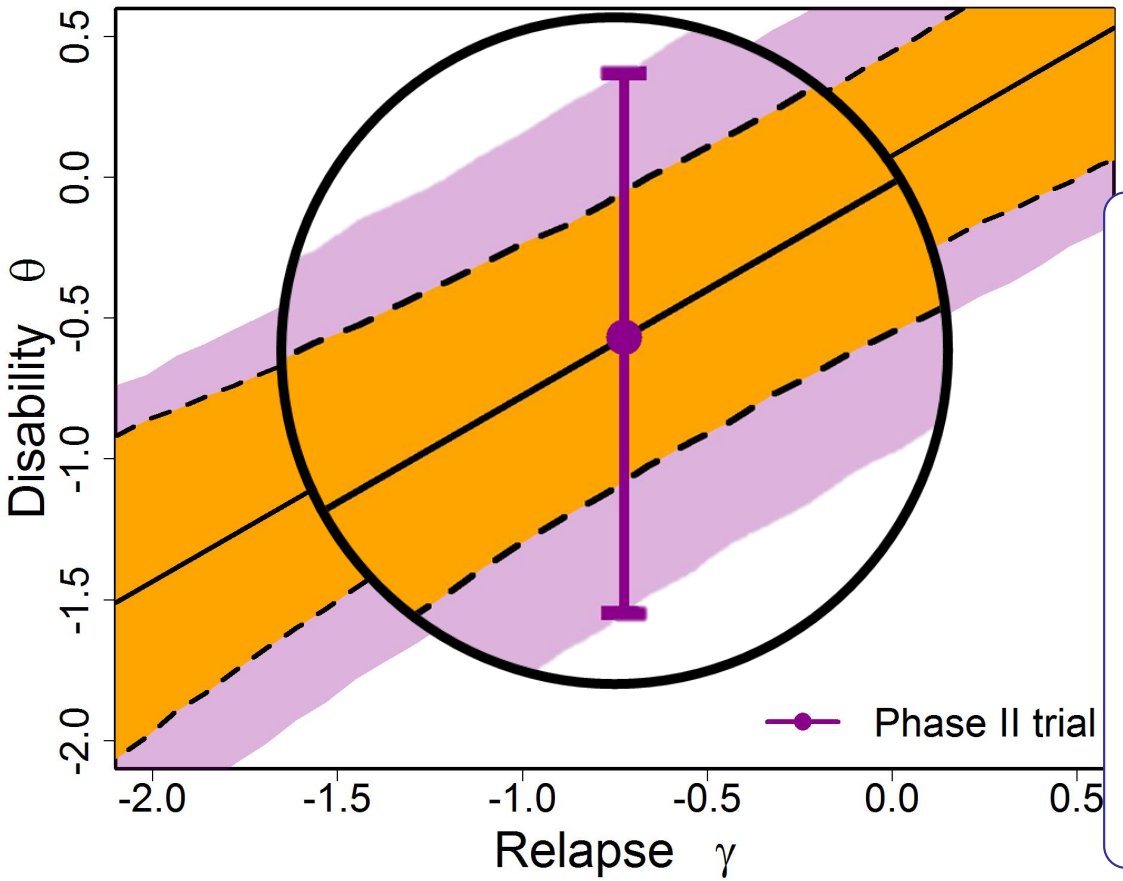
Informative prior for the final endpoint parameter (3/3)
"Surrogate prior"

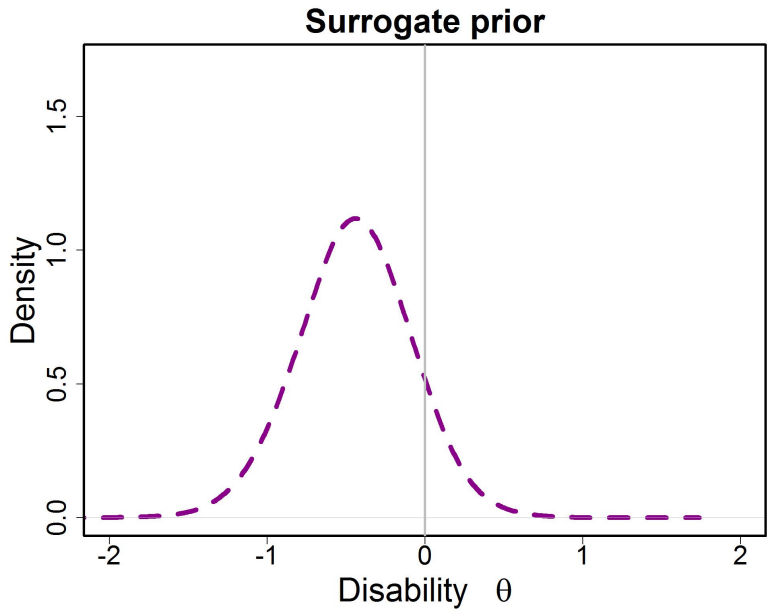
Final endpoint **"Surrogate prior"**:

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

We call this distribution the **"surrogate prior"**

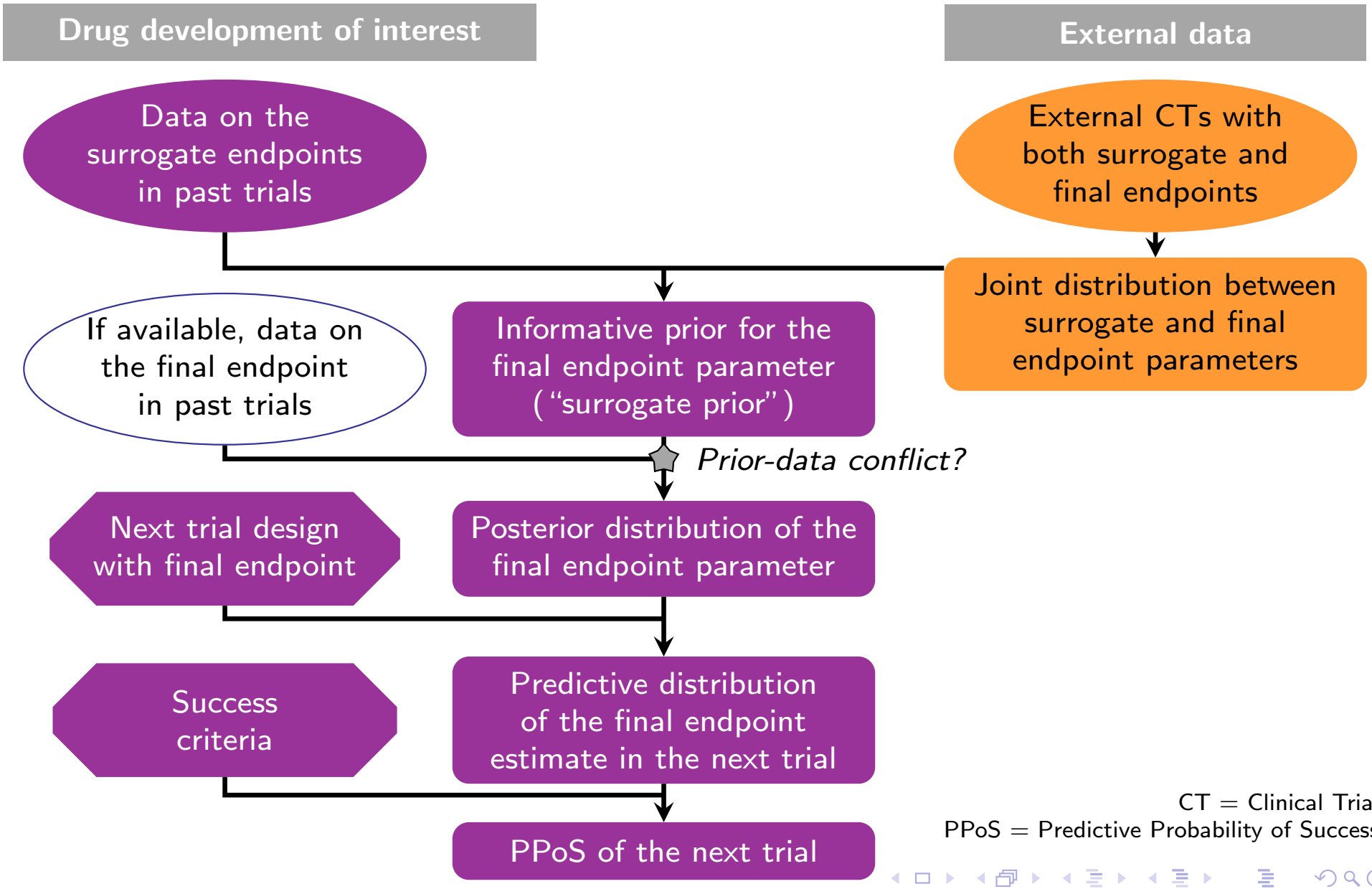
(Distribution derived from data on the surrogate endpoint, to be used as a prior for the final endpoint)





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

PPoS based on the surrogate endpoint only



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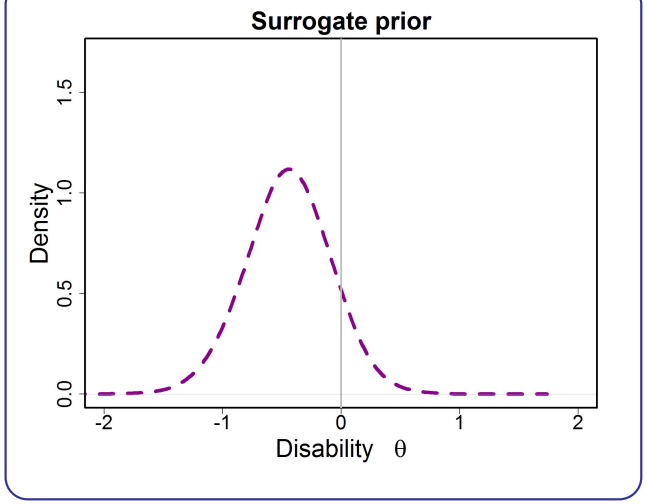
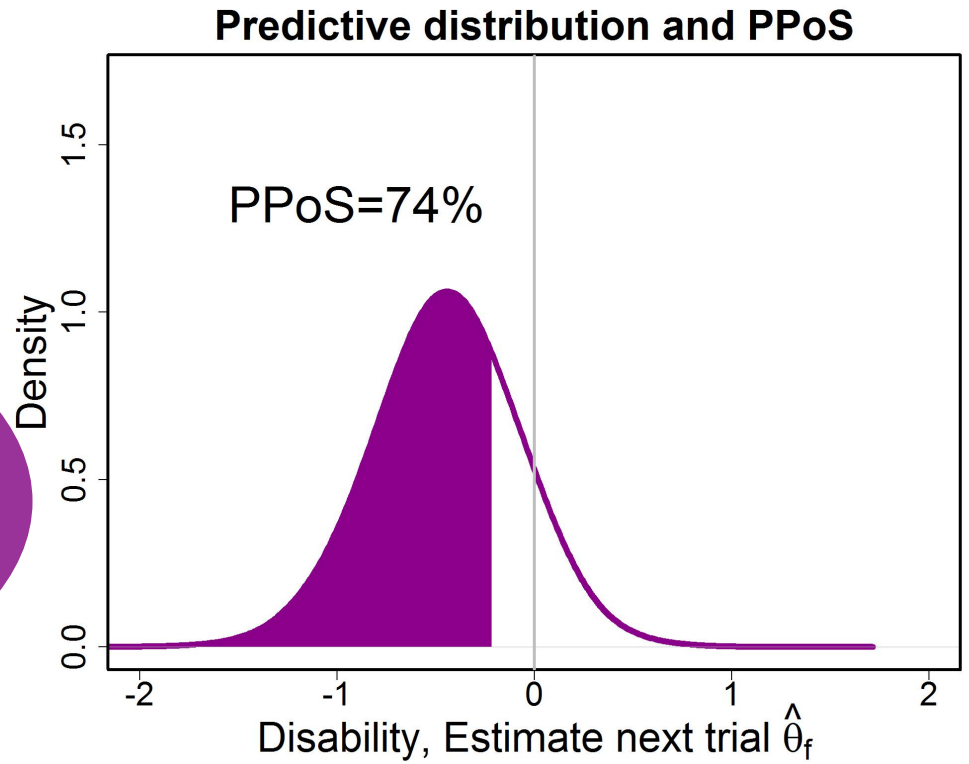
Without considering the data on the final endpoint... (2/2)
PPoS based on the surrogate endpoint only



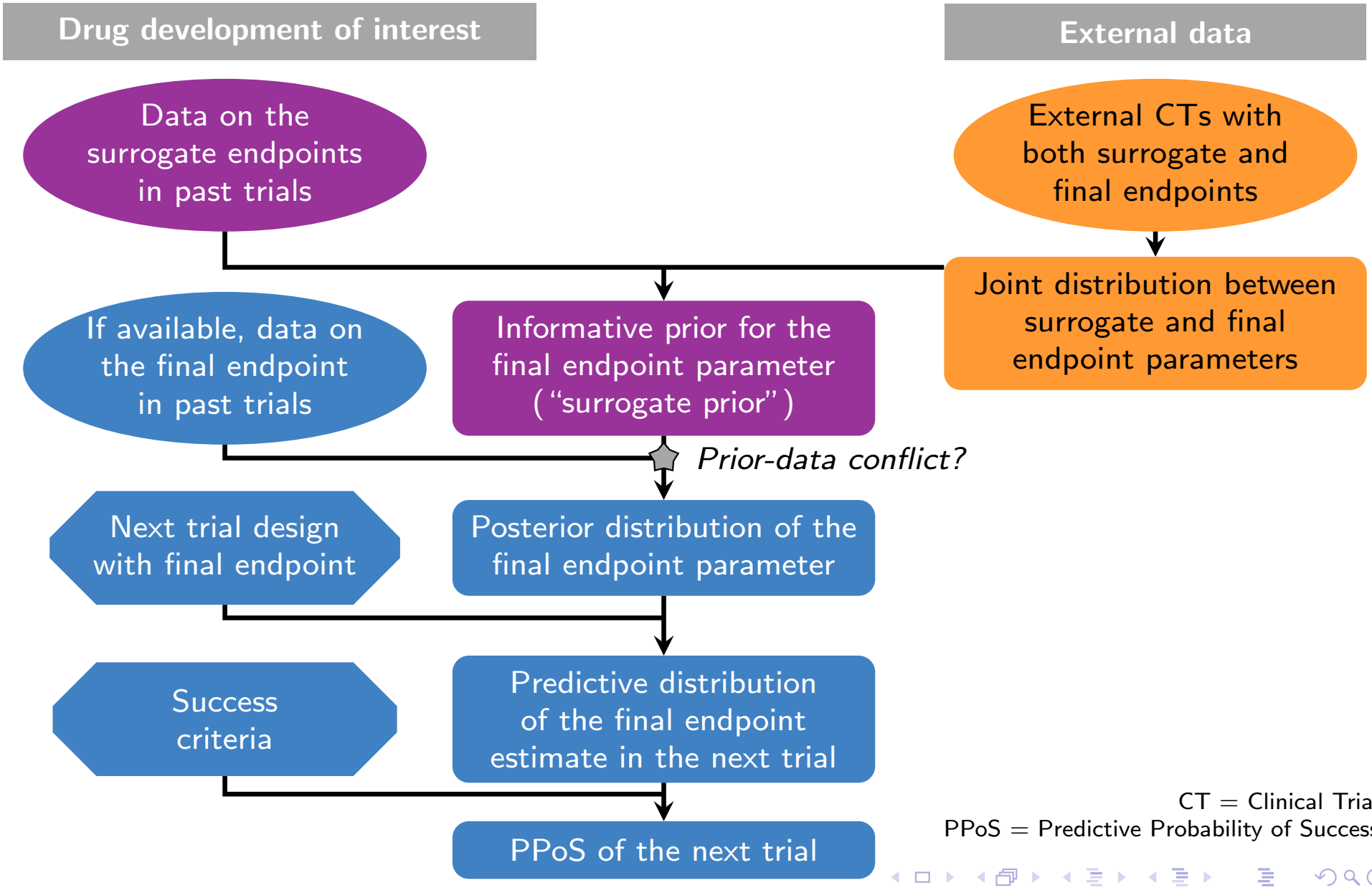
Surrogate prior $\pi_\theta^S(\cdot) = \int f_{\theta|a,b,\tau}(.) f_{a,b,\tau}(x,y,z) d(x,y,z)$
Posterior = prior (no data)
Predictive $h^S_{\hat{\theta}_f}(\cdot) = \int f_{\hat{\theta}_f|\theta=t}(\cdot)\pi_\theta^S(t)dt$
$PPoS^S = \int_{u<z_\alpha\sigma_f^2} h^S_{\hat{\theta}_f}(u)du$

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: **σ_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



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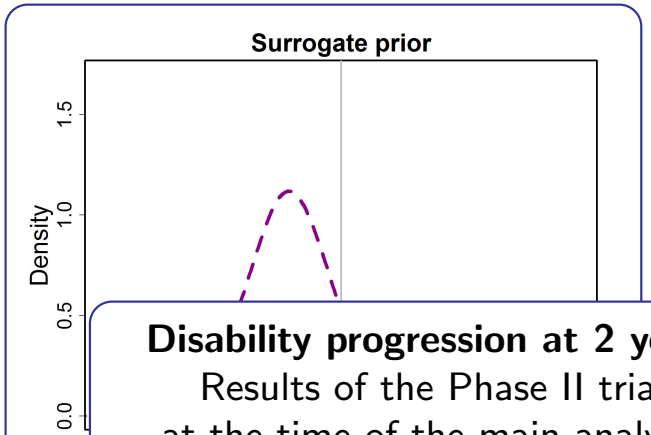
Considering the whole evidence... (2/2)
PPoS based on the surrogate and the final endpoints



Disability progression at 2 years
Results of the Phase II trial
at the time of the main analysis

	$\hat{\theta}$ (σ)
N/arm	10
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Surrogate prior $\pi_\theta^S(\cdot) = \int f_{\theta|a,b,\tau}(.) f_{a,b,\tau}(x,y,z) d(x,y,z)$

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

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

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

The **prediction variance** depends on:

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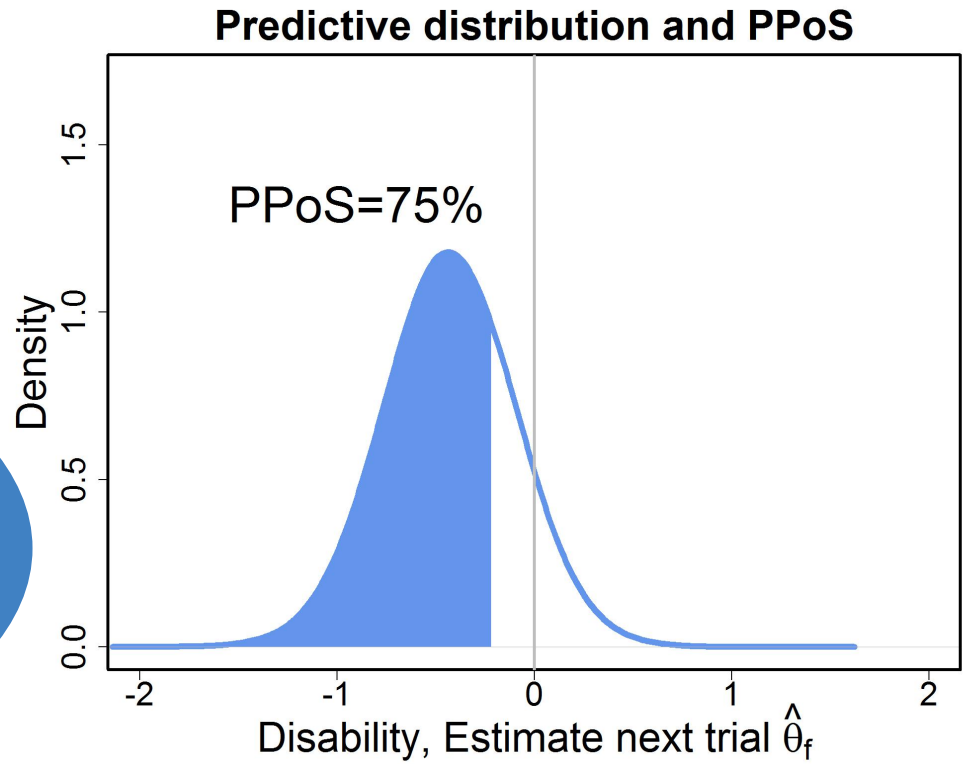
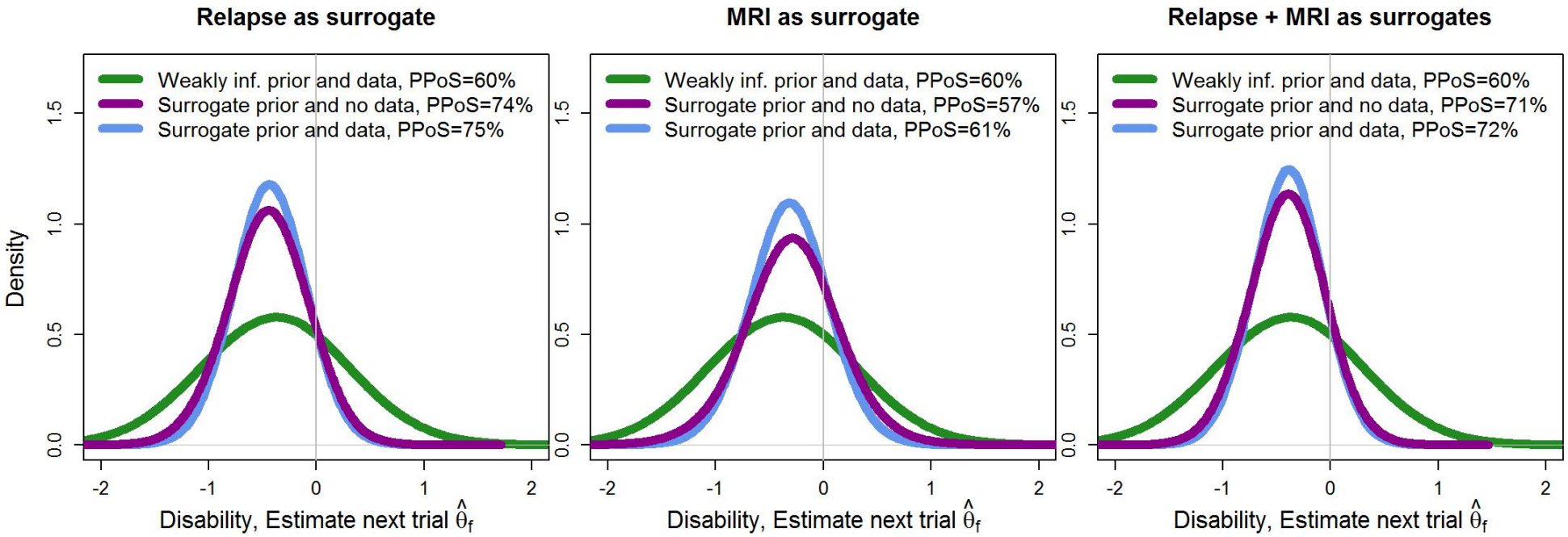
- The precision of the evidence on the surrogate
- The precision of the evidence on the final endpoint
- The precision planned in the future trial on the final endpoint



RR=Relative Risk ; SE=Standard Error

Summary and multiple surrogates



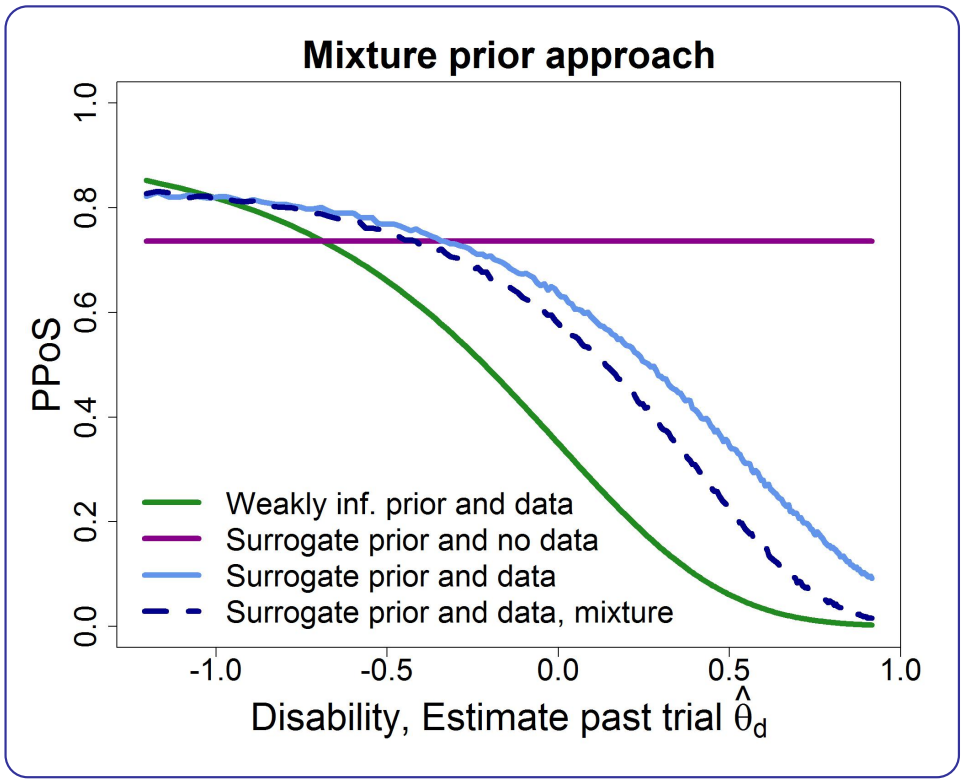
Consistency of the results → Confidence in the decision

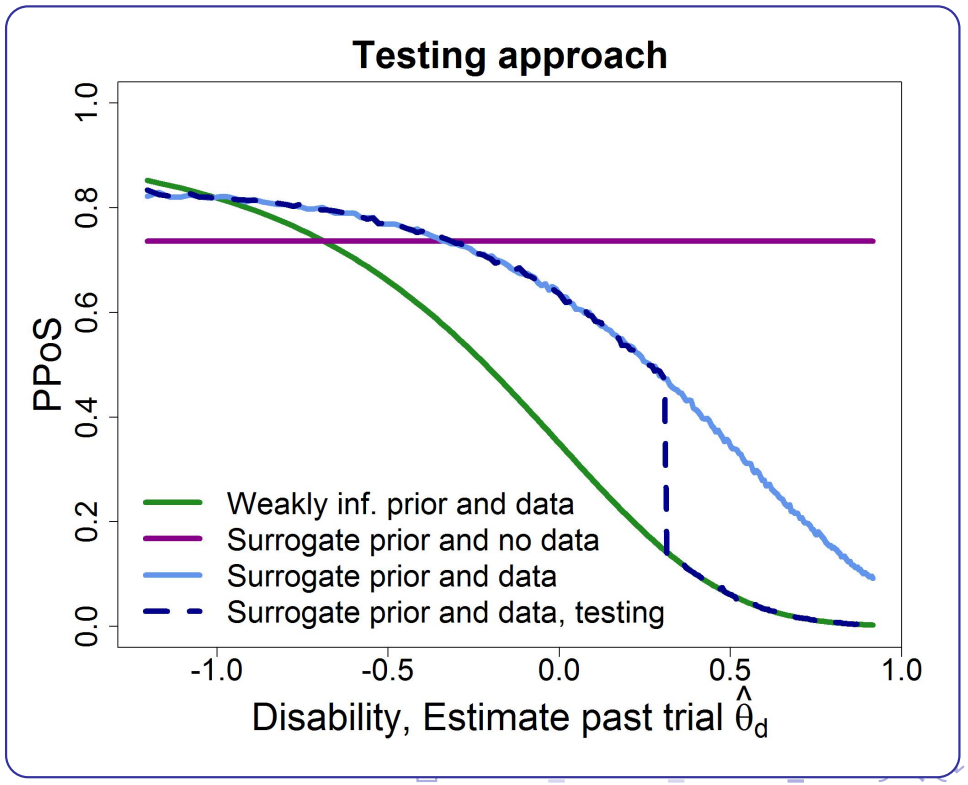
Prior data conflict

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...)

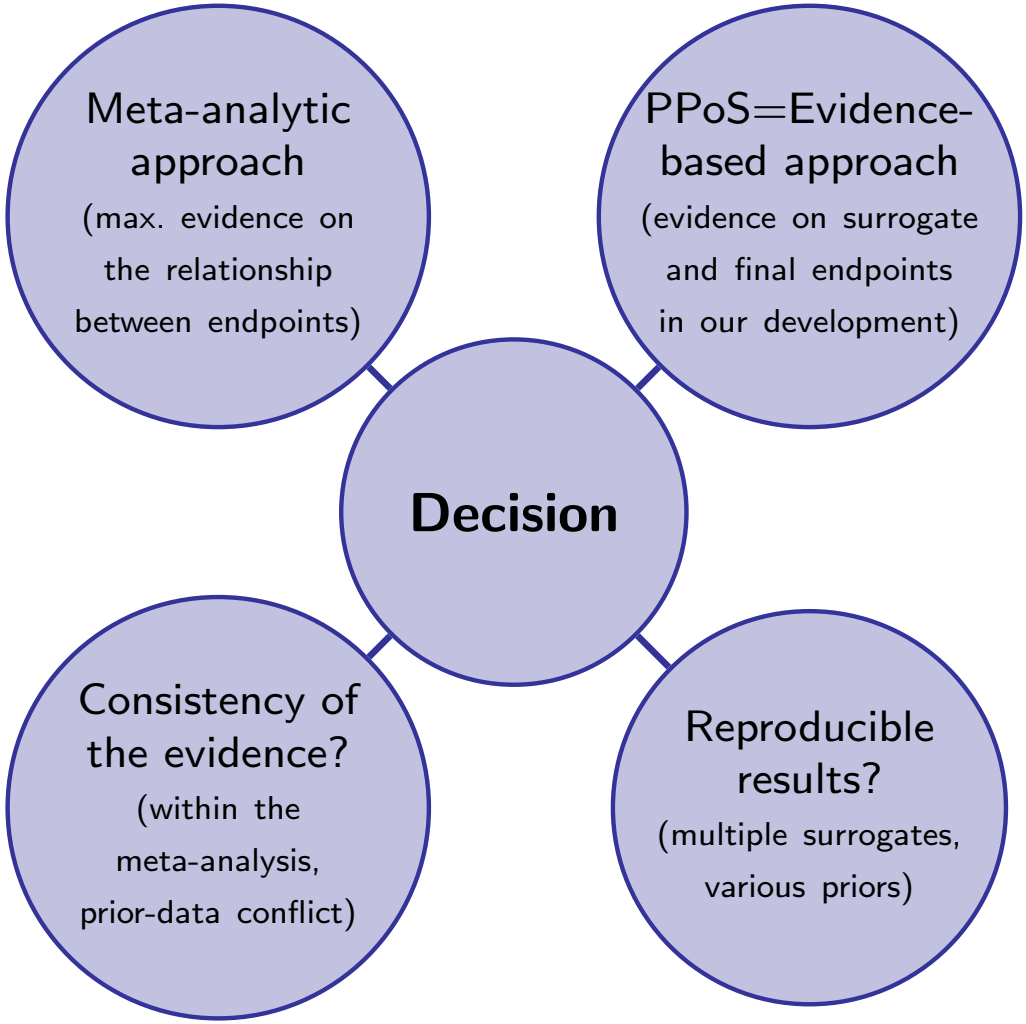
Mutsvari *et al.*, 2016 ; Schmidli *et al.*, 2014 ; Ibrahim *et al.*, 2015





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 $\rightarrow$ more risk when making the decision...



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Thank-you!