# How to weigh the strength of prior information and clarify the expected level of evidence?

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September 30, 2015, EMA, London







This work has received funding the European Union's 7th Framework Programme for research, technological development and demonstration under the grant agreement IDEAL (602552). M Posch was supported by grant agreement ASTERIX (603160).

#### The Paediatric Investigation Plan

REGULATION (EC) No. 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL (+ AMENDMENT)

- A plan for registering the drug in children (PIP) has to be provided to regulators already after early phases of adult drug development.
- How to specify the amount of information required in the paediatric population?
- How do extrapolation assumptions impact on the requirements for the PIP?
- Under the assumption that the drug will be approved for adults (based on pivotal trials in adults) can we relax the standard significance level for pivotal trials in children?

At the time of approving the drug for children, our confidence in the efficacy of the drug in children should be not less than the confidence in the efficacy of the drug in adults. What is the probability that the drug is effective in adults, given a successful adult development program?



## How to determine the prior probability for efficacy $1 - r_a$ ?

- Elicitation from expert knowledge
- Estimation from historic Phase 3 success rates

#### Estimation of $1 - r_a$ based on historic success rates

- In oncology, 40% of new compounds entering Phase 3 are proven to be effective.<sup>1</sup>
- Under the assumption that the success rate is based on developments with two pivotal trials at overall level  $0.025^2$  and power 80%

$$1 - r_a = 0.5$$

<sup>1</sup>Hay et al. Clinical development success rates for investigational drugs. Nature biotechnology 2014;

Given a prior belief  $1 - r_a = 0.5$  the confidence in efficacy conditional on a future successful adult development program is:

 $1-\gamma_{\rm a}=0.973$  if a single trial at level 0.025 and power 90% is performed

 $1 - \gamma_a = 0.9992$  if two trials are performed such that the overall level is  $0.025^2$  and overall power is 80%.



What is the confidence for efficacy in children conditional on a future successful drug development in adults?

- Let the Scepticism s denote the probability that efficacy in adults *cannot* be extrapolated to children.
  - With probability 1 s the confidence in efficacy in adults directly transfers to efficacy in children.
  - With probability *s* extrapolation cannot be applied and the confidence for efficacy in children needs to rely on other sources.

#### Early Confidence for Efficacy in Children

... conditional on a future successful drug development in adults



The overall early confidence for efficacy in children conditional on a future successful drug development in adults is

$$1 - r_c = (1 - s)(1 - \gamma_a) + s(1 - q)$$

#### Conditional future confidence for efficacy in children

conditional on a successful drug development in children at level  $lpha_{\mathrm{adj}}$ 



Which significance level  $\alpha_{adj}$  do we need to apply in children to achieve the same confidence (conditional on a positive paediatric development) for efficacy for the vulnerable paediatric population as for adults, s.t.

$$1 - \gamma_c = \frac{(1 - \beta)(1 - r_c)}{(1 - \beta)(1 - r_c) + \alpha_{adj}r_c} = 1 - \gamma_a \quad ?$$

## The significance level $lpha_{\mathsf{adj}}$ depending on the Scepticism s



## The significance level $\alpha_{adi}$ depending on the Scepticism s



- Power for the paediatric study
- Confidence in efficacy in  $1 - \gamma_a = 0.973$
- confidence in efficacy in

## The significance level $\alpha_{\rm adj}$ depending on the Scepticism s



- Power for the paediatric study  $1 \beta = 0.8$
- Confidence in efficacy in adults  $1 \gamma_a$
- Targeted confidence in efficacy in children  $1 - \gamma_c = 0.973$
- Assumed probability of efficacy without extrapolation 1 - q = 0

## The significance level $\alpha_{\rm adj}$ depending on the Scepticism s



- Power for the paediatric study  $1 \beta = 0.8$
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- Targeted confidence in efficacy in children

 $1 - \gamma_c$ 

 Assumed probability of efficacy without extrapolation 1 - q = 0

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- Targeted confidence in efficacy in children  $1 - \gamma_c = 0.973$
- Assumed probability of efficacy without extrapolation 1 - q

# Case Study Humira

- 2003 registration of Adalimumab at the EMA for moderate and severe active rheumatoid arthritis in adult patients.
- 2008 registration for juvenile ideopathic arthritis based on a single randomized withdrawal study in paediatric patients:
  - Primary outcome measure: proportion of patients who had a disease flare during the 32 week double-blind phase
  - Significance level: 0.05 (two-sided). Power: 0.8 for a 40 % difference between treatments.
  - In the population of primary interest a p-value of p = 0.03 for the primary outcome measure has been observed.
- The committees concerned agree that a single successful confirmatory study would be sufficient for registration.

Which scepticism s is compatible with this strategy in our framework?

## Case Study (continued)

What is the maximum Scepticism factor such that only one instead of two pivotal studies at level 0.025 (one-sided) are required to achieve the same final confidence in efficacy as in adults?

Prior Adults $1 - r_{a}$	0.1	0.3	0.5	0.7	0.9
Posterior Adults $1-\gamma_{s}$	.9930	.9982	.9992	.9997	.99999
Maximal Scepticism $s$ $(1 - \gamma_c = 1 - \gamma_a)$	.178	.053	.024	.010	.003
Maximal Scepticism s $(1 - \gamma_c = 0.9992)$	.018	.023	.024	0.025	0.025
Maximal Scepticism s $(1 - \gamma_c = 0.973)$	.467	.469	.470	.470	.470

 $1 - q = 0, 1 - \beta_a = 1 - \beta_c = 0.80$ 

#### Fixing of

- the Scepticism factor *s*.
- the success rate of new compounds in a special class of diseases and compounds or, alternatively the targeted confidence in efficacy in adults  $1 \gamma_a$  given a successful adult development.
- the prior confidence in efficacy in children if extrapolation is not possible (1 q)

## How to quantify Scepticism? A challenge to the Experts.

- In an early stage, when a PIP has to be assessed, often no Phase III data from adult studies are available (as PIPs should be provided as early as possible).
- Therefore, the quantification has to rely on expert opinion concerning the disease, the patient population, the medicinal product, ...
- Specific methods for elicitating prior beliefs in Bayesian statistics may be applied also here.
- Modeling and simulation may give guidance on the translation of treatment effects from adults to children. The scepticism *s* can then quantify the uncertainty of the models.

- Is it reasonable to require confidence levels of 0.9992 (0.973) for drug licensing?
- Is it reasonable to require lower confidence levels in vulnerable populations?
- A fully decision theoretic approach would require to specify overall utility functions accounting for false positive and false negative conclusions, benefits and risks. This would give guidance on the level of confidence  $(1 \gamma_c)$  in efficacy that should be required for children?

## Application in the Regulatory Context

- The environment of extrapolation is likely to change after a PIP has been agreed on in an early phase, when later data from adult studies will become available.
- Requests for modification of an approved PIP is an appropriate way to account for the data in adults.
- If these data become available, other Bayesian approaches may be applied to adaptively modify the pre-planned paediatric development programme.
- The framework formally incorporates prior information and expert knowledge, while still applying frequentist testing albeit at a modified significance level.

Evidence, Eminence and Extrapolation G Hlavin, F König, C Male, M Posch, P Bauer, 2015 (revision submitted) Backup Slides

#### Sample Size Reduction



- Power for the paediatric study  $1 \beta = 0.8$
- Confidence in efficacy in adults

 $1-\gamma_{a}=0.973$ 

• Targeted confidence in efficacy in children  $1 - \gamma_c = 0.973$ 

#### How robust is the determination of $1 - r_a$ ?

Historic Success Rate	$lpha_{historic}$	$1-eta_{historic}$	$1 - r_{a}$
0.4	0.025	0.9	0.43
		0.8	0.48
		0.7	0.56
	0.025 <sup>2</sup>	0.9	0.44
		0.8	0.50
		0.7	0.57
0.3	0.025	0.8	0.35
	0.025 <sup>2</sup>	0.8	0.37

#### Computation of $1 - r_a$

 $1 - r_a$  solves: Historic Success Rate  $= (1 - \beta_{\text{historic}})(1 - r_a) + \alpha_{\text{historic}}r_a$ .

Prior Adults	Significance Level	Power	Posterior Adults
$1 - r_a$	$\alpha_{a}$	$1-eta_{a}$	$1-\gamma_{a}$
0.5	0.025	0.9	0.9730
		0.8	0.9697
		0.7	0.9655
	0.025 <sup>2</sup>	0.9	0.9993
		0.8	0.9992
		0.7	0.9991
0.3	0.025	0.8	0.9320
	0.025 <sup>2</sup>	0.8	0.9982