Leverage existing evidence: Evidence, eminence and extrapolation

Gerald Hlavin [1]

joint work with

Franz König [2] Martin Posch [2] Christoph Male [2] Peter Bauer [2]

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Disclaimer

The opinions expressed in this presentation are the presenter's own and do not reflect the view of the Main Association of Austrian Social Security Institutions.

Drugs and Biologics for the Paediatric Population in the EU

Because of ethical concerns and practical reasons, for many years drugs and biologics were primarily evaluated in adults, resulting in ...

- ... off label use in children of medicines that were authorised for adults;
- ... empirically selected doses based on the weight of the child;
- ... potential exposure of children to unsafe and/or ineffective treatments.

$\Rightarrow$ European Paediatric Regulation in 2007

The Paediatric Investigation Plan (PIP)

- Plan for pharmaceutical and clinical development in children
- Proposed by the company
- At the end of phase I of adult development
- Agreed, or refused by the Paediatric Committee (PDCO) of the EMA
- Legally binding
- Later modifications possible if requested by the company

EMA/PDCO/367243/2015
London, 14 August 2015

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-001461-PIP02-14

Scope of the application

Active substance(s):

Acotiamide

Condition(s):

Treatment of functional dyspepsia

Pharmaceutical form(s):

Coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Zeria Pharmaceutical Co Ltd

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Zeria Pharmaceutical Co Ltd submitted for agreement to the European Medicines Agency on 7 November 2014 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 16 December 2014.

Supplementary information was provided by the applicant on 20 May 2015. The applicant proposed modifications to the paediatric investigation plan.

Development of EMA Guidance on Extrapolation

- Framework to specify the requirements for the amount and type of data to be generated in the paediatric population making best use of all available information.
- March 2013 Concept Paper
- April 1, 2016 Draft Reflection Paper

1 April 2016
EMA/199678/2016

Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

Draft agreed by Biostatistics Working Party	March 2016
Draft agreed by Modelling and simulation group	March 2016
Draft agreed by PKWP	March 2016
Draft agreed by Scientific Advice Working Party	March 2016
Draft Adopted by PRAC	17th March 2016
Draft Adopted by PDCO	31st March 2016
Draft Adopted by CHMP	31st March 2016

Definition and Rationales for Extrapolation

"Extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product (...)"

Rationales

- Avoid unnecessary studies
  For ethical reasons and efficient resource allocation
- Optimising decision making when patients are scarce
  To make use of all available information

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A Quantitative Concept for Extrapolation

Evidence, Eminence and Extrapolation
G Hlavin, F König, C Male, M Posch, P Bauer
Statistics in Medicine 35, 2117-2132, 2016
http://dx.doi.org/10.1002/sim.6865 (open-access).

Research Article

Statistics in Medicine

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6865

Evidence, eminence and extrapolation

Gerald Hlavin,[a*†] Franz Koenig,[a] Christoph Male,[b] Martin Posch[a] and Peter Bauer[a]

A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in small populations such as paediatric populations or orphan indications. Different levels of extrapolation from a larger population to smaller target populations are widely used for supporting decisions in this situation. There are guidance documents in drug regulation, where a weakening of the statistical rigour for trials in the target population is mentioned to be an option for dealing with this problem. To this end, we propose clinical trials designs, which make use of prior knowledge on efficacy for inference. We formulate a framework based on prior beliefs in order to investigate when the significance level for the test of the primary endpoint in confirmatory trials can be relaxed (and thus the sample size can be reduced) in the target population while controlling a certain posterior belief in effectiveness after rejection of the null hypothesis in the corresponding confirmatory statistical test. We show that point-priors may be used in the argumentation because under certain constraints, they have favourable limiting properties among other types of priors. The crucial quantity to be elicited is the prior belief in the possibility of extrapolation from a larger population to the target population. We try to illustrate an existing decision tree for extrapolation to paediatric populations within our framework. © 2016 The Authors. *Statistics in Medicine* Published by John Wiley & Sons Ltd.

Keywords: small population; extrapolation; prior belief; adjustment of the significance level; reduction of sample size

1. Introduction

One of the most challenging tasks in medicine is clinical research in children. In the following paper, we look at drug development in the paediatric population. For decades, it has been criticized that most medicines have not been authorized for the use in children. Off-label use based on the individual responsibility of the treating paediatrician is often the only way how children can benefit from medicines that are only authorized for adults [1]. This relies on the questionable assumption, that children are small adults. There exist several reasons for such a development: clinical research in children is a sensitive area involving emotional and ethical challenges, methodological challenges, for example, the small numbers of children that can be recruited into trials, and on the other hand increased costs that may not be compensated by economic returns if the treated disease is rare in children. In order to improve the situation, new legal requirements have been created in the USA [2, 3] and in the European Union (EU) [4, 5]. Essentially, these require companies to agree a plan for developing a medicine in children with the regulatory authorities before authorization in adults. If studies in children performed according to the agreed plan are submitted and lead to authorization in children, patent exclusivity is prolonged as a reward for the extra effort of the drug developer.

The scope of such a paediatric investigation plan (PIP) may reach from a full programme (including pre-clinical research, pharmacokinetics, pharmacodynamics, dose finding studies and two fully powered pivotal phase III studies) for diseases only existing in childhood at the upper end of the spectrum and, for example, a single (pharmacokinetic) case series in children on the lower end of the spectrum. The latter situation is obviously based on the assumption that data and results from adult patients can be

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How to Specify the Level of Evidence for Trials in Children?

- Consider the setting where a PIP is specified (and data of pivotal trials in adults are not yet available).
- Under the assumptions that
  - results from adult trials can be extrapolated to a certain extent to children and
  - the drug will be approved for adults (based on pivotal trials)

  can we relax the standard significance level for pivotal trials in children?
- How to choose the relaxed significance level?

  When 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.

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Confidence in Efficacy in Adults

What is the probability that the drug is effective in adults, given a successful adult development program?

Probability of effect in adults, given a successful Phase 3

$$1 - \gamma_a = \frac{(1-\beta_a)(1-r_a)}{(1-\beta_a)(1-r_a)+\alpha r}$$

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Significance level of adult development program

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- Significance level of adult development program
- Power of adult development program

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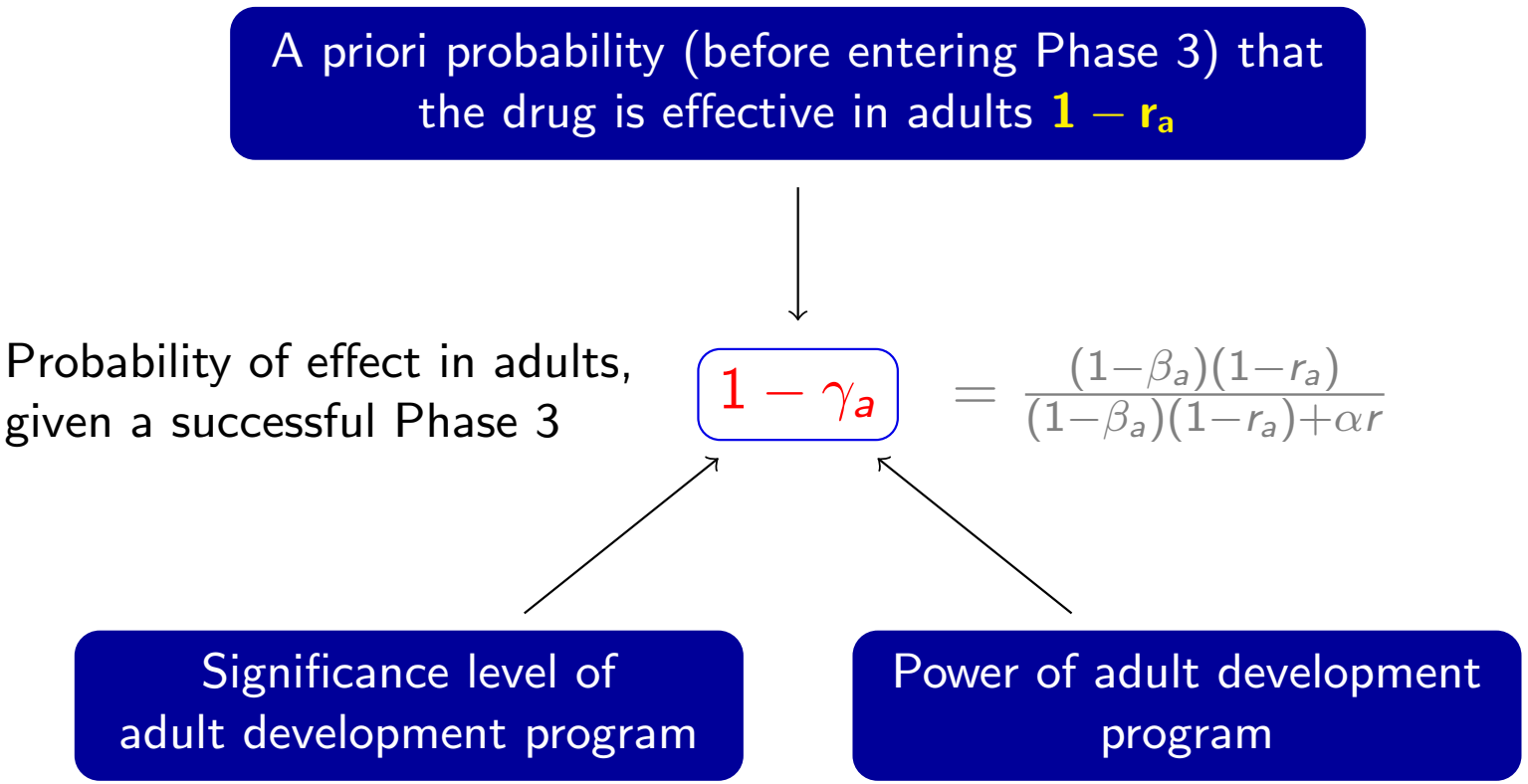

The confidence for efficacy in adults

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

$1 - \gamma_a = 0.973$ 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%.

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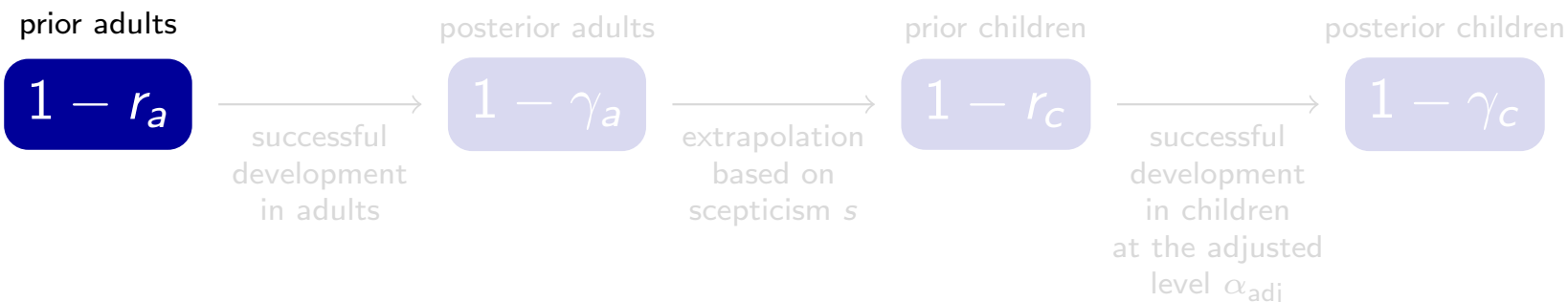

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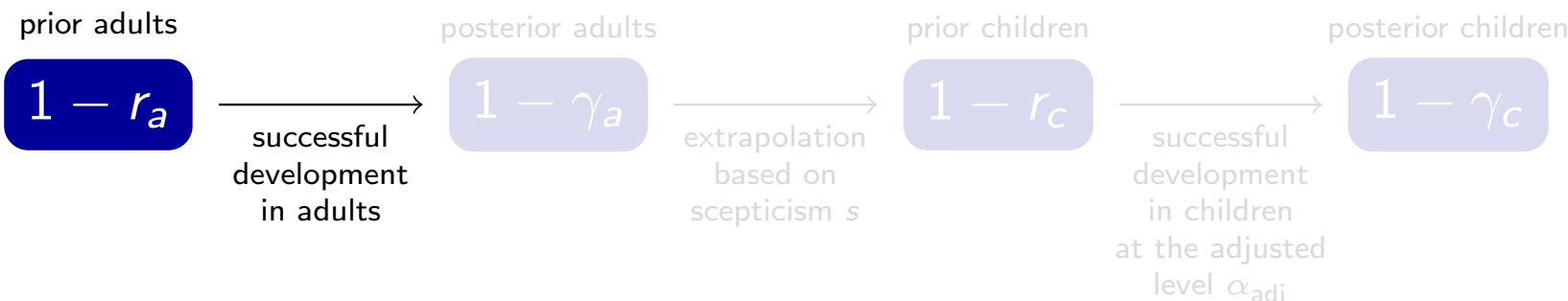

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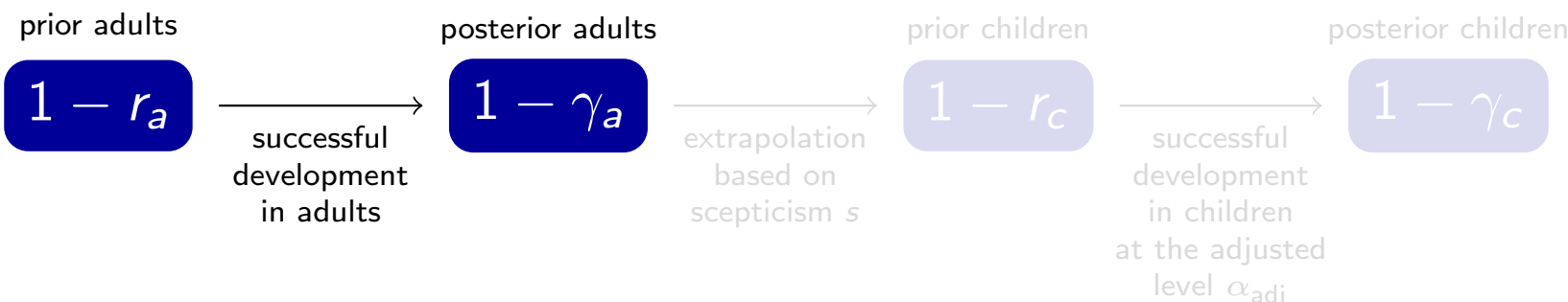


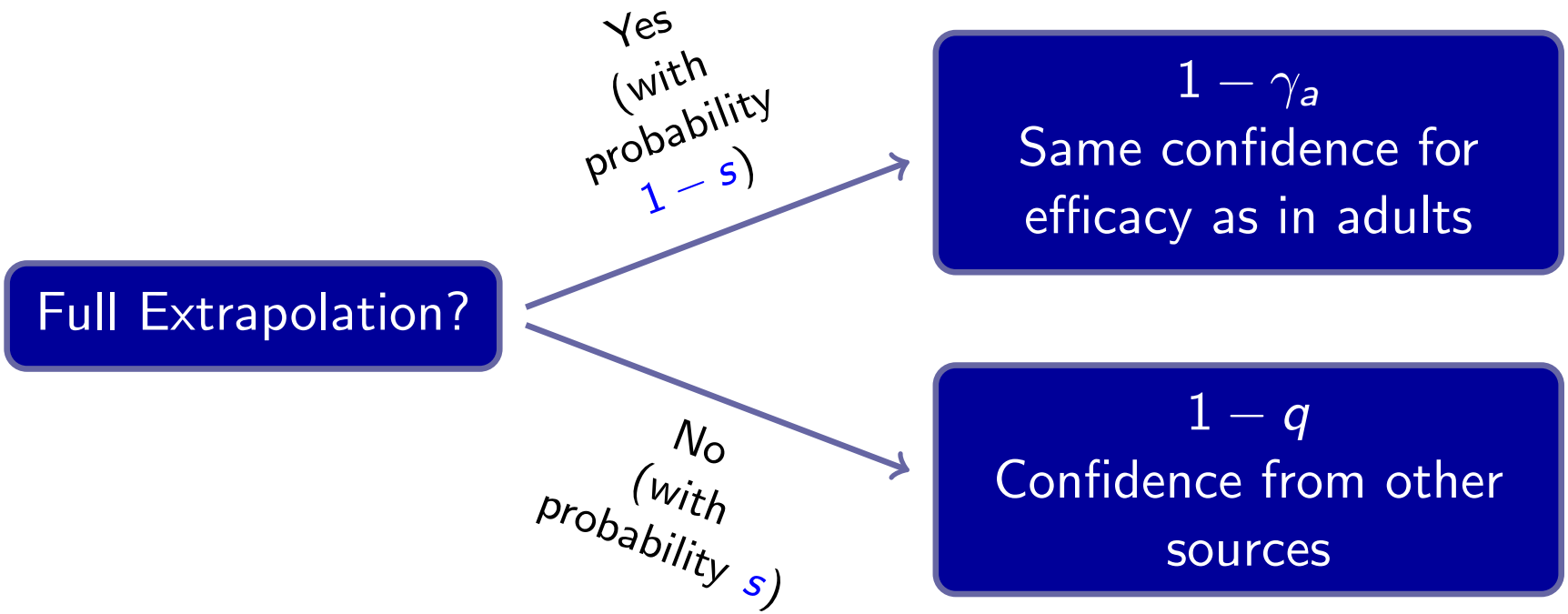
Extrapolation from Adults to Children

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

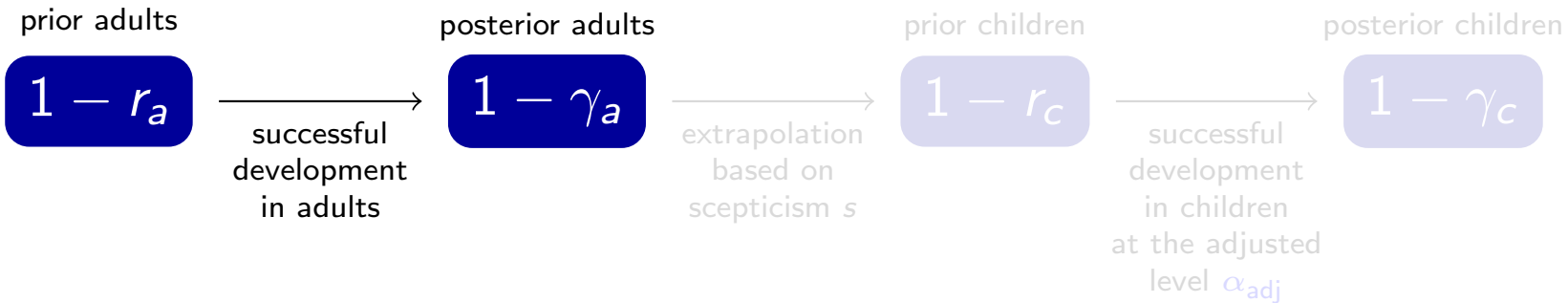


The overall early confidence for efficacy in children conditional on a future successful drug development in adults is

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

Conditional future confidence for efficacy in children

conditional on a successful drug development in children at level α_{adj}



Which significance level α_{adj} do we need to apply in children to achieve the same confidence for efficacy for children as for adults?

Conditional future confidence for efficacy in children

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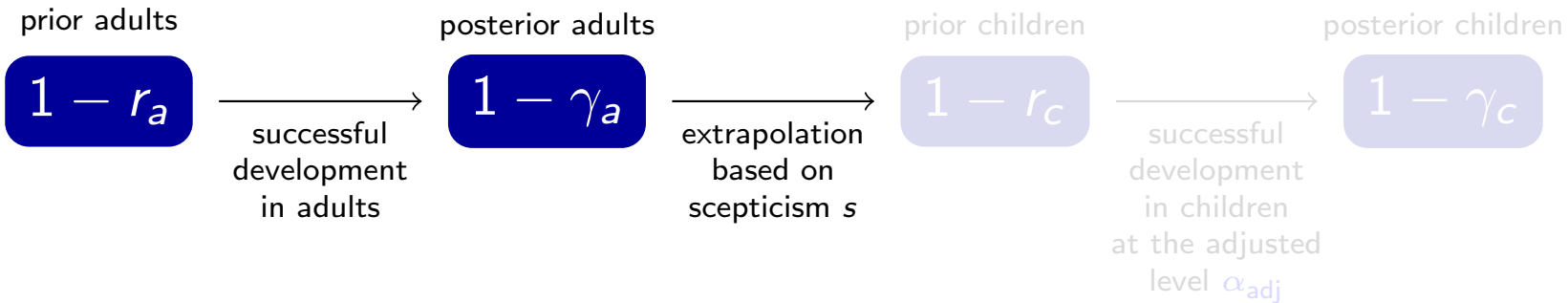

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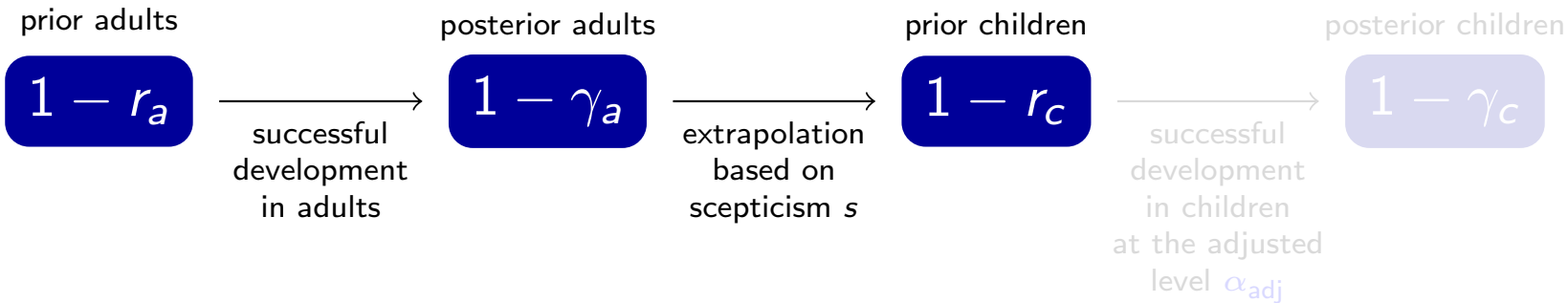

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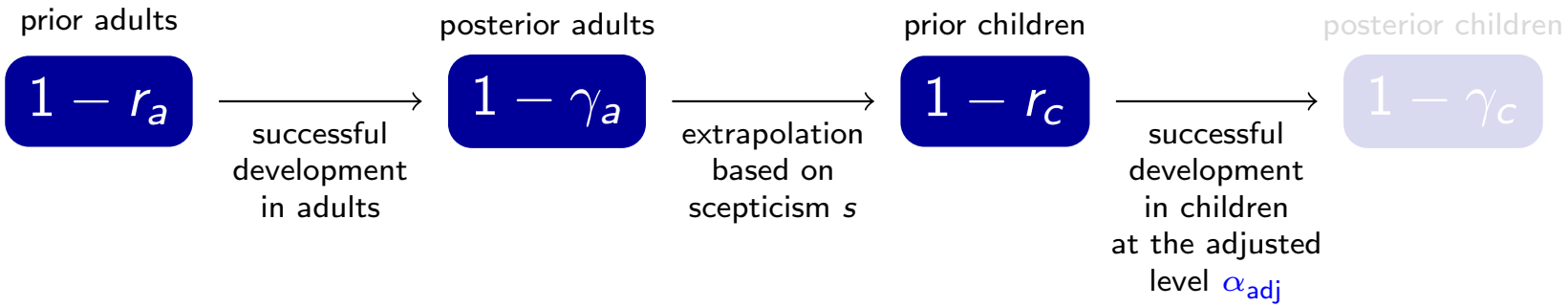

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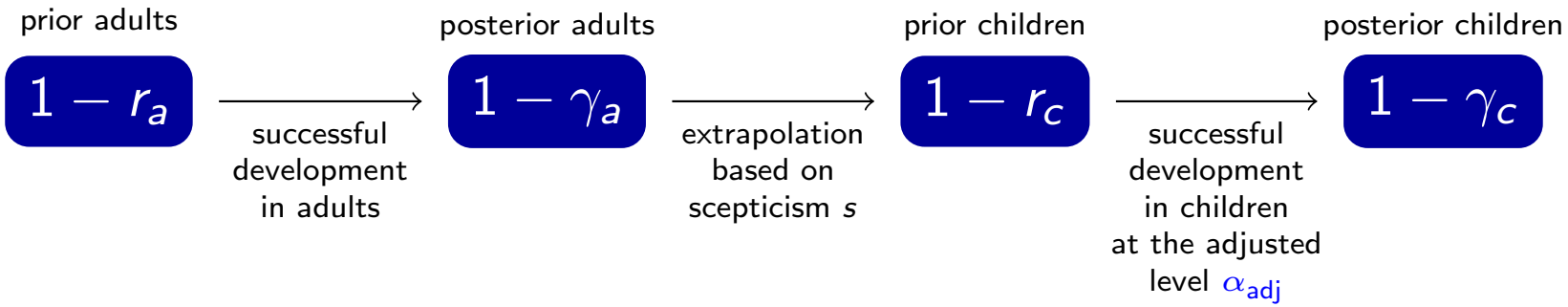

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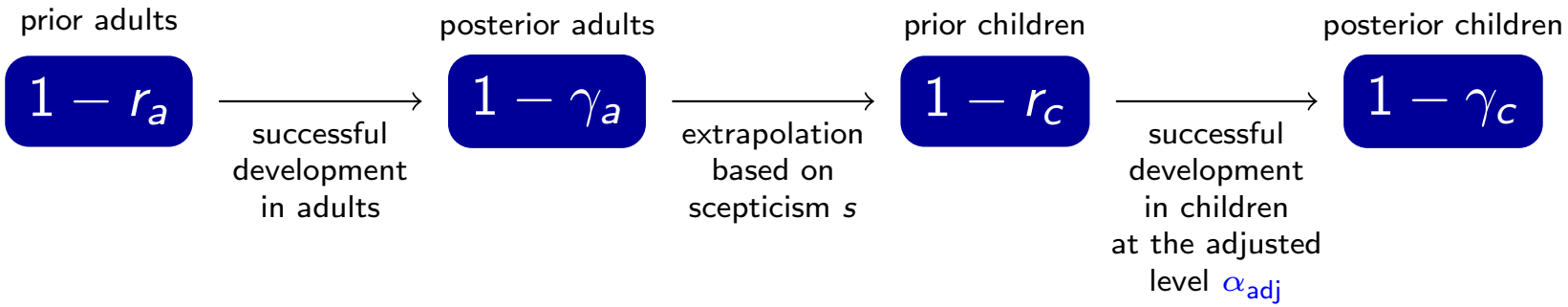

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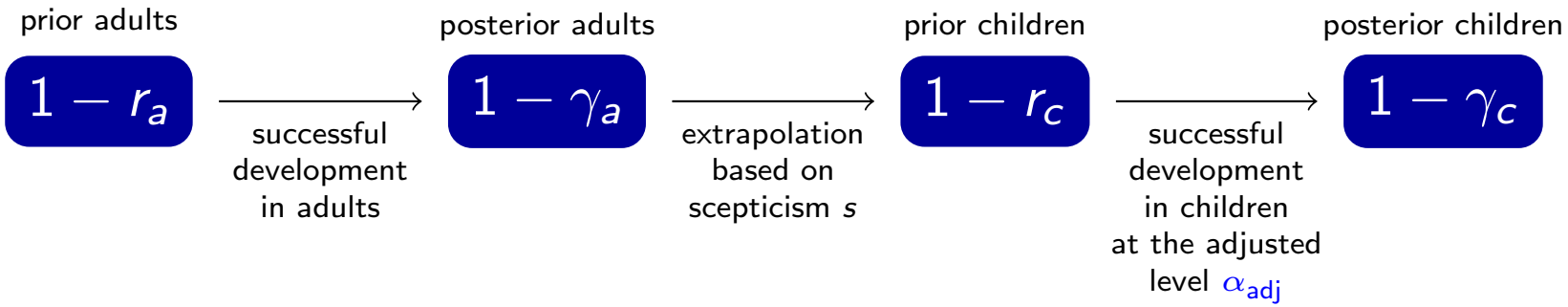

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$$1 - \gamma_a =$$

confidence efficacy adults

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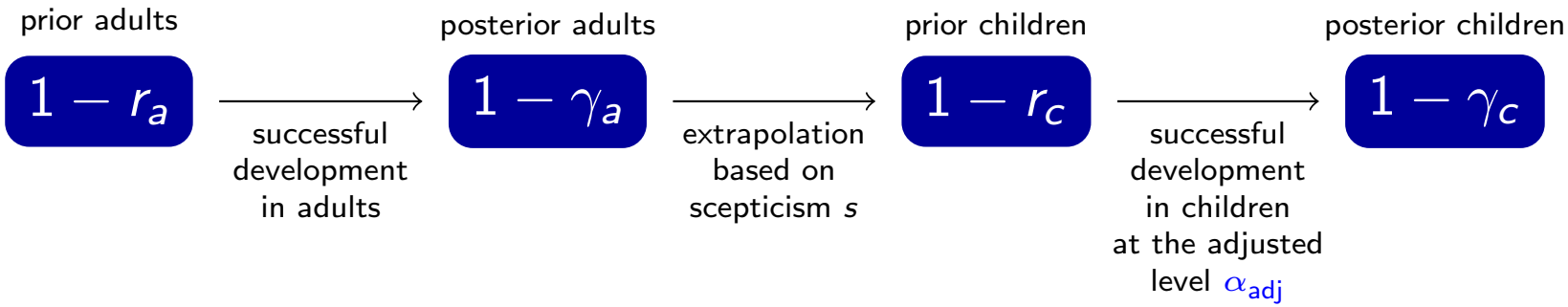

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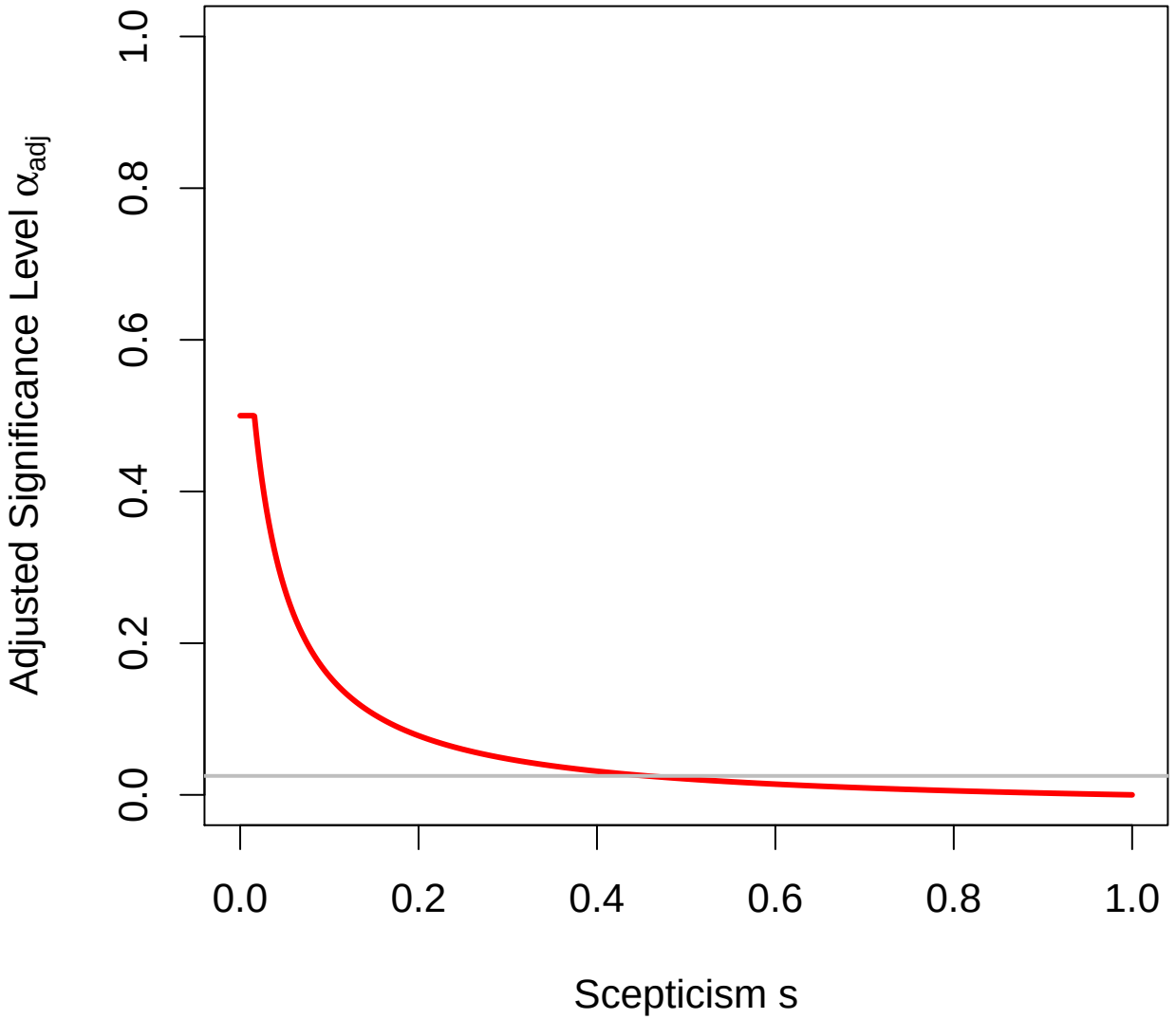
$$\underbrace{1 - \gamma_a}_{\substack{\text{confidence} \\ \text{efficacy adults}}} = \frac{(1 - \beta_c)(1 - r_c)}{(1 - \beta_c)(1 - r_c) + \alpha_{adj} r_c} := \underbrace{1 - \gamma_c}_{\substack{\text{confidence} \\ \text{efficacy children}}}$$

The significance level α_{adj} depending on the Scepticism s



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

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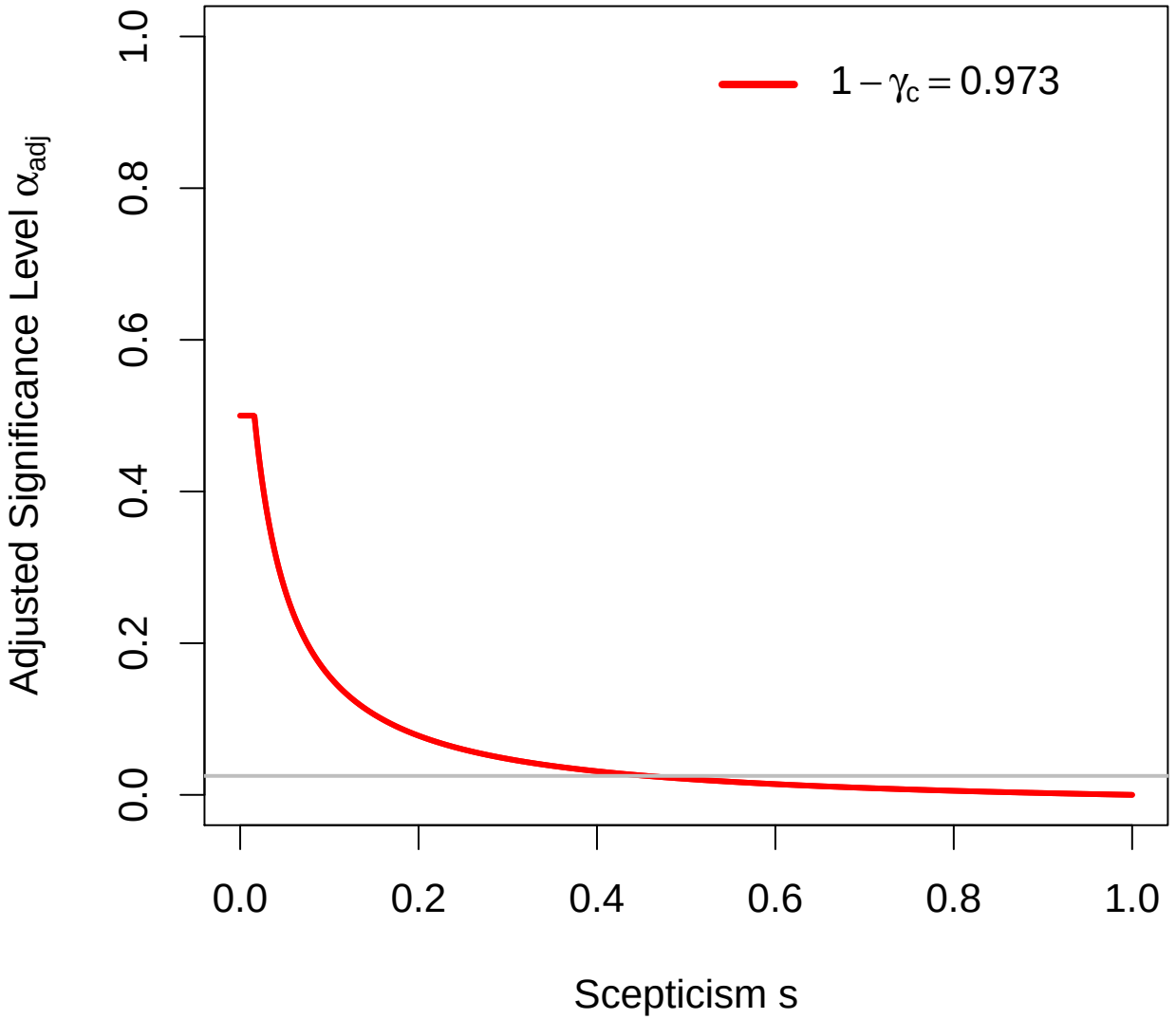

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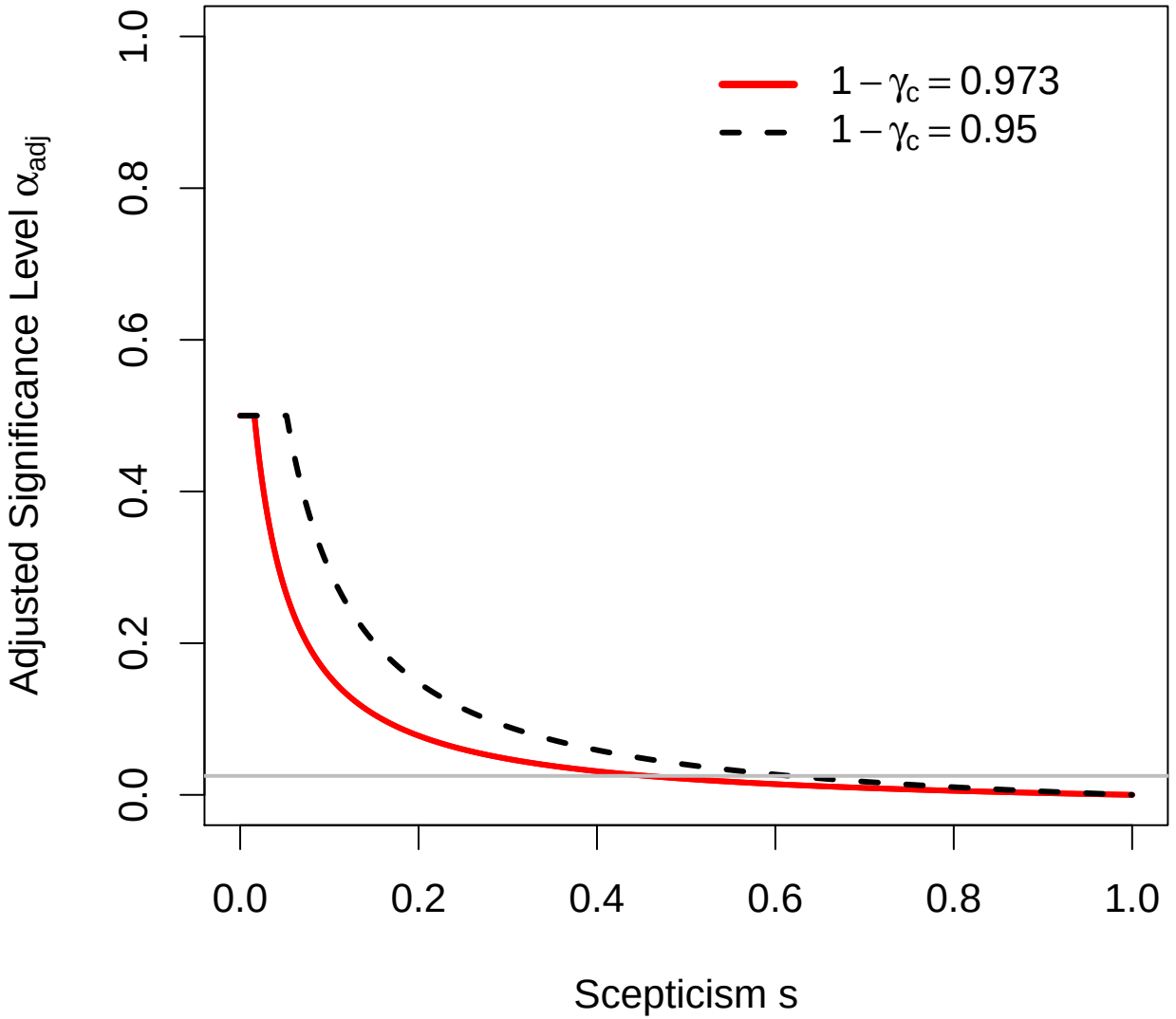

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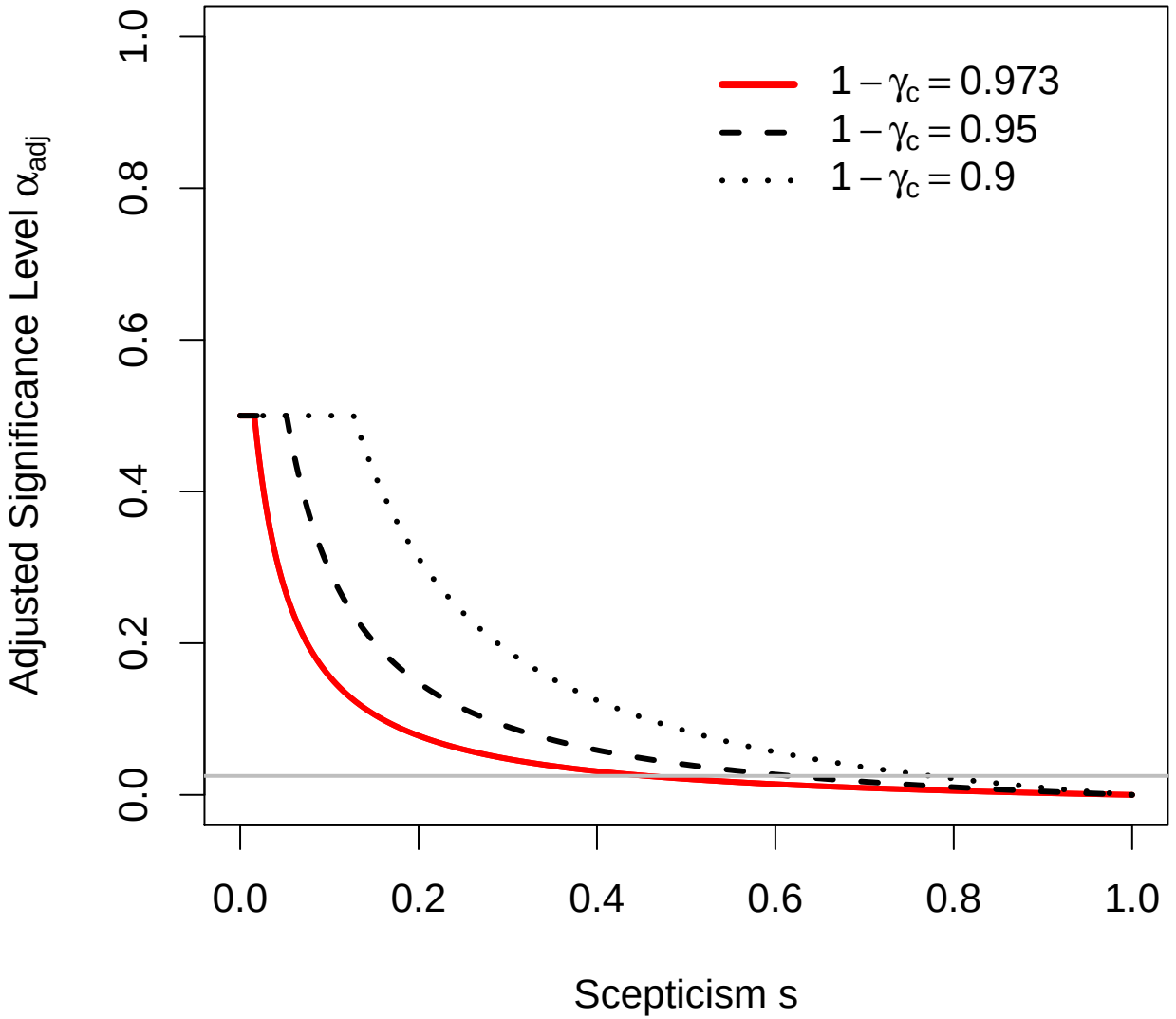

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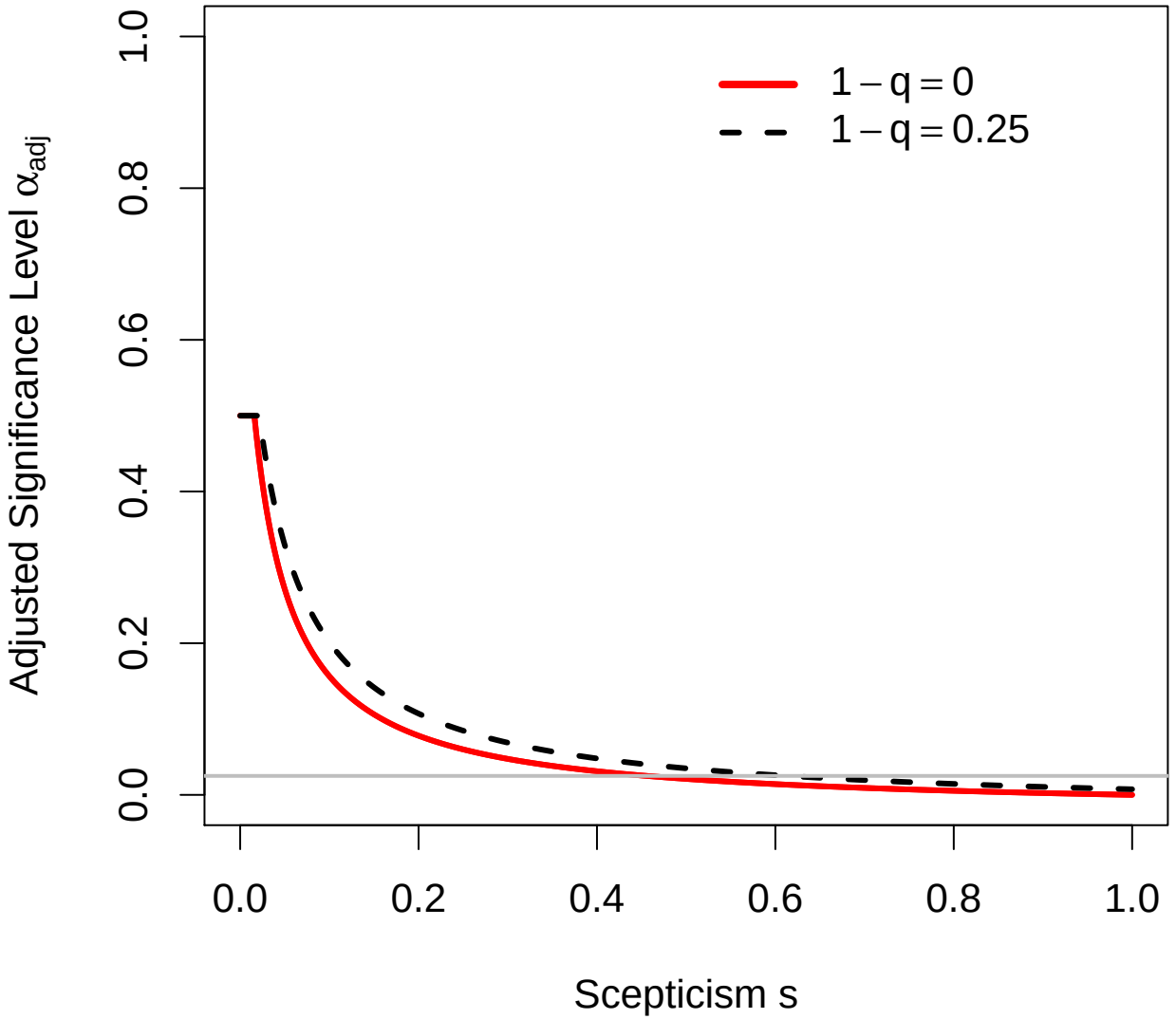

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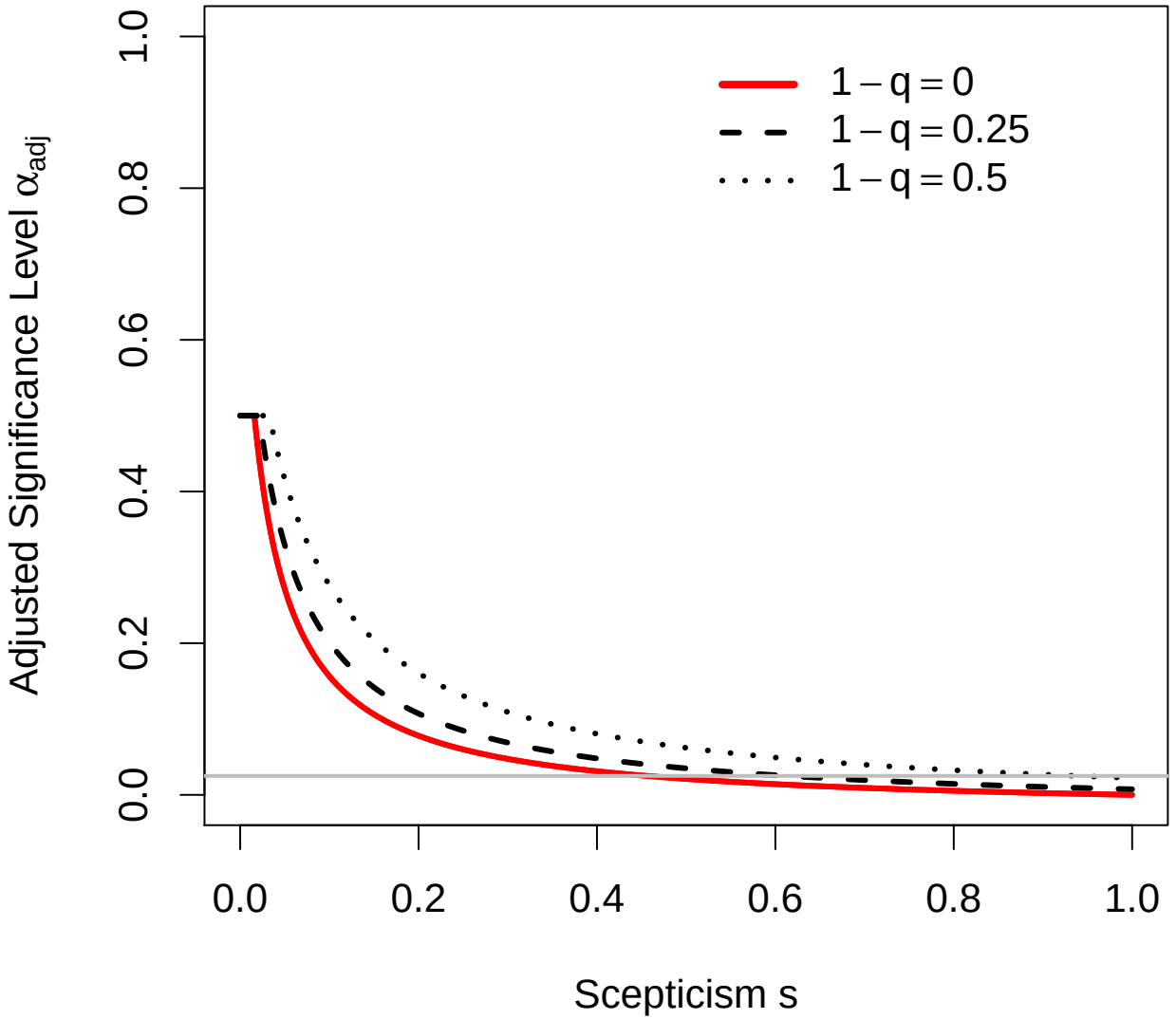

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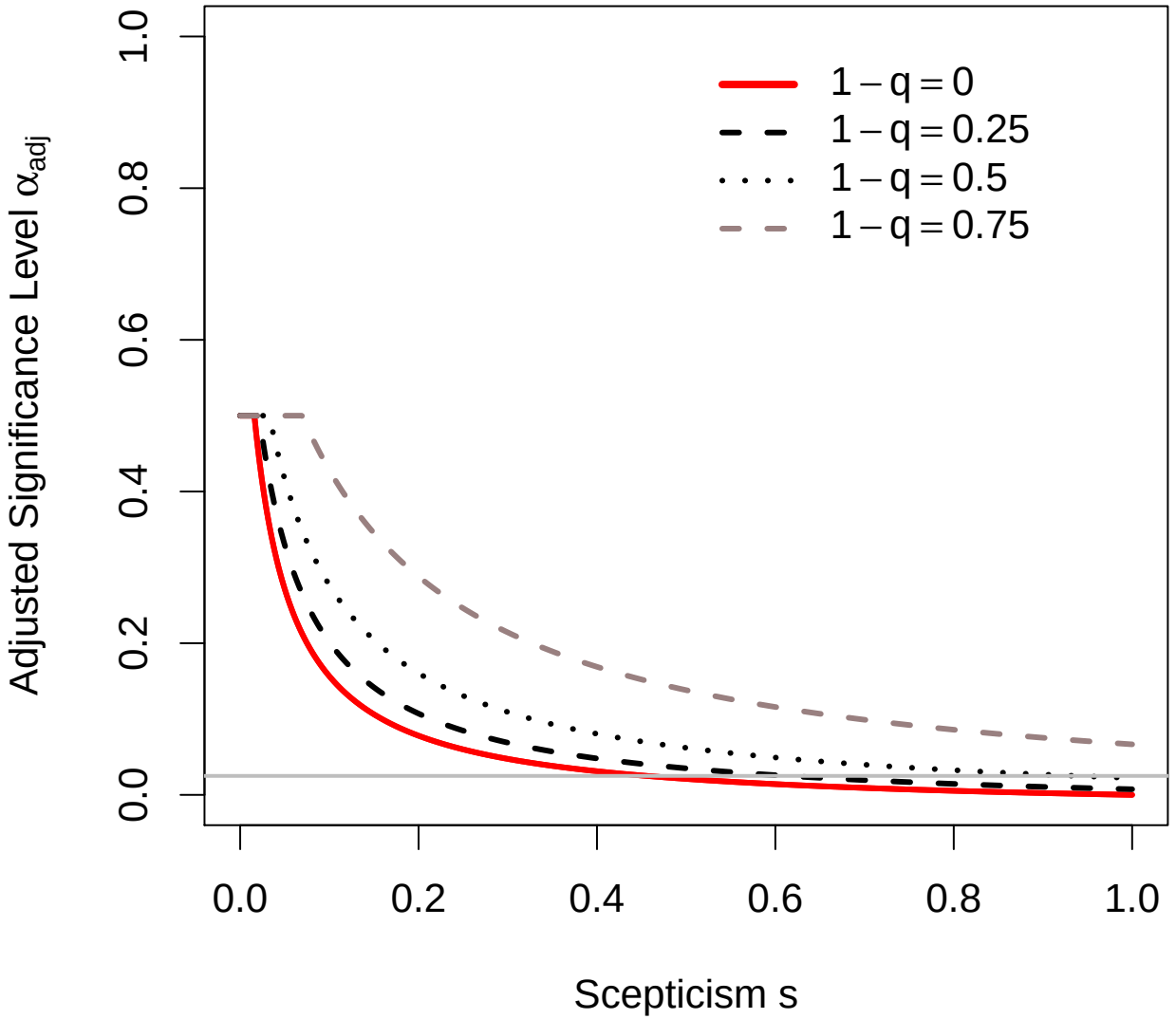

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Hypothetical Case Study: Humira

- 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: 0.025 (one-sided). Power: 0.8 for a 40 % difference between treatments.
  - In the population of primary interest a p-value of $p = 0.015$ for the primary outcome measure has been observed.
- The committees concerned agreed that a single successful confirmatory study would be sufficient for registration.

Which scepticism s is compatible with the strategy to require a single study only?

Case Study (continued)

What is the largest Scepticism factor such that only one pivotal study at level 0.025 (one-sided) is required to achieve the same final confidence in efficacy as in adults?

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

Prior Adults $1 - r_a$	0.1	0.3	0.5	0.7	0.9
Posterior Adults $1 - \gamma_a$	.9930	.9982	.9992	.9997	.9999
Maximum Scepticism s $(1 - \gamma_c = 1 - \gamma_a)$	.178	.053	.024	.010	.003
Maximum Scepticism s $(1 - \gamma_c = 0.973)$	.467	.469	.470	.470	.470

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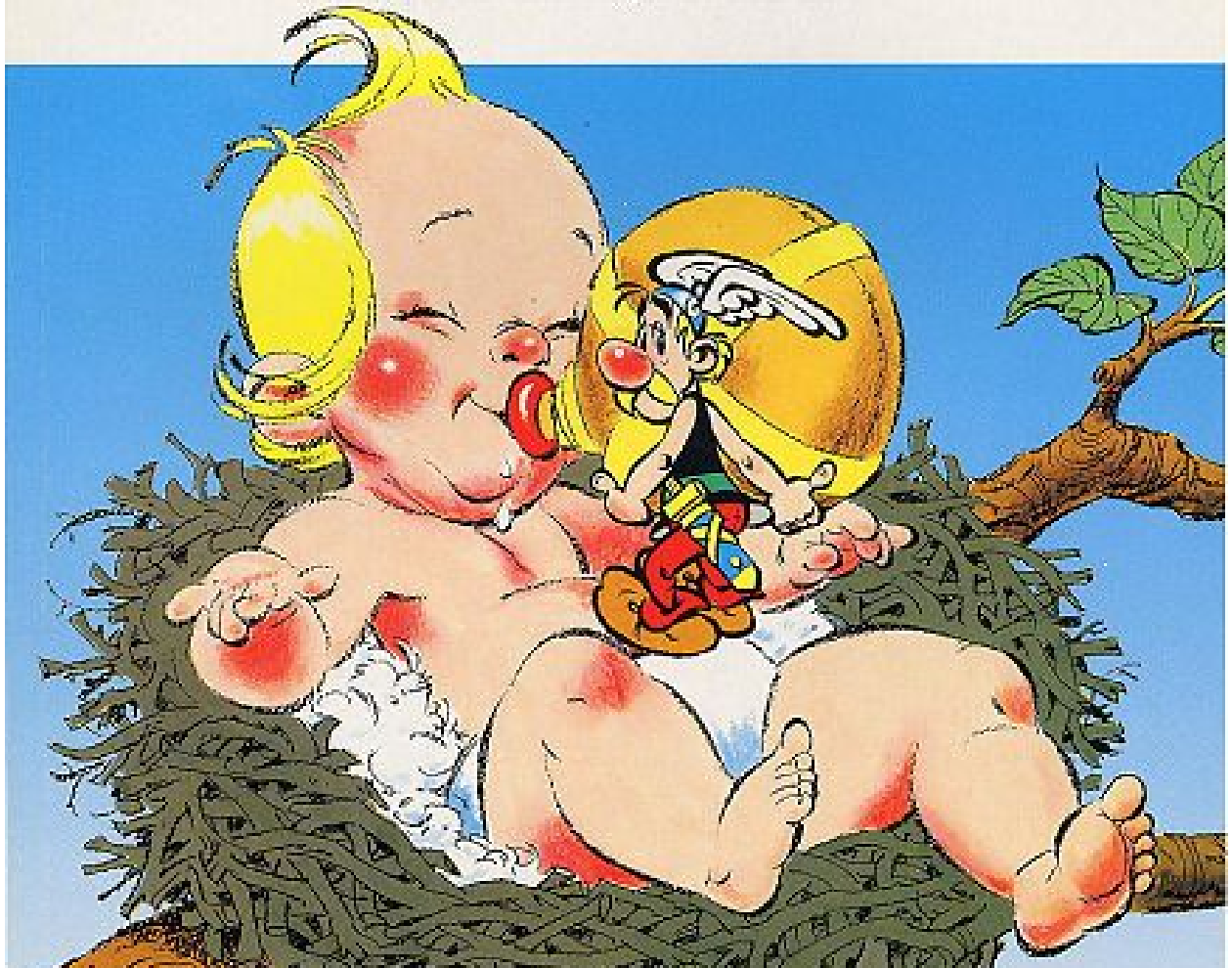
R. GOSCINNY — A. UDERZO

Asterix & Son

Text och teckningar av UDERZO



How to Quantify Scepticism? A Challenge to the Experts.

The elicitation of s will be informed by

- Evidence synthesis concerning the disease, the patient population, the medicinal product, ...
- Modelling and simulation to predict the translation of treatment effects from adults to children.
- Expert opinion

Similarly, the parameters $1 - r_a$ (prior success rate of new compounds in adults) and $1 - q$ (prior confidence in efficacy if extrapolation is not possible) need to be elicited.

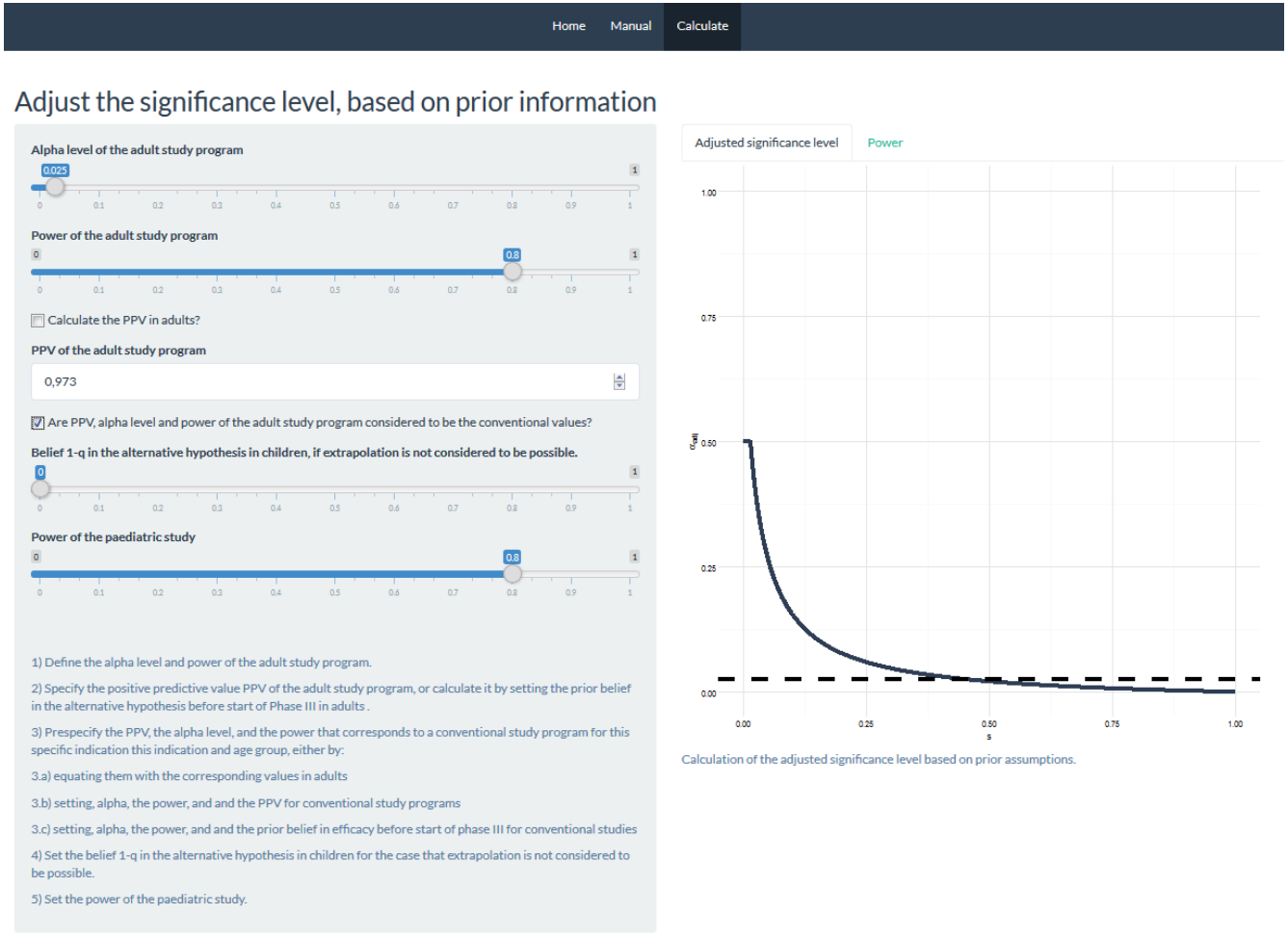
Challenges in a Potential Regulatory Application

- The concept depends on robust evidence synthesis methods to elicit the parameters.
- Results may depend sensitively on the assumptions.
- PIPs agreed on in early phases may need to be modified when data from studies in adults become available. However, modifications of an approved PIP can currently only be requested by applicants.
- If data in adults become available, more sophisticated Bayesian approaches may be applied to adaptively modify the pre-planned paediatric development programme.

How to choose the level of confidence $1 - \gamma_c$?

- 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?
- Should the choice be based on decision theoretic approaches that quantify the costs of false positive and false negative conclusions, benefits and risks?

Online R-Shiny Extrapolation Application



- R-Shiny Extrapolation App (beta-version)
- http://www.ideal-apps.rwth-aachen.de:3838/Extrapolation/

Thank you for your attention!

References

- Hlavin, G., Koenig, F., Male, C., Posch, M., & Bauer, P. (2016). *Evidence, eminence and extrapolation*. Statistics in medicine.
- Bauer, P., & Koenig, F. (2016). *Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children?*. Pharmaceutical Statistics.
- EMA (2012). Human medicines development and evaluation. *Concept paper on extrapolation of efficacy and safety in medicine development.* EMA/129698/2012
- FDA (2003). *Guidance for industry: exposure-response relationships - study design, data analysis, and regulatory applications*
- EMA (2016). *Draft Reflection paper on extrapolation of efficacy and safety in paediatric medicine development*. `http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf`

Backup Slides

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

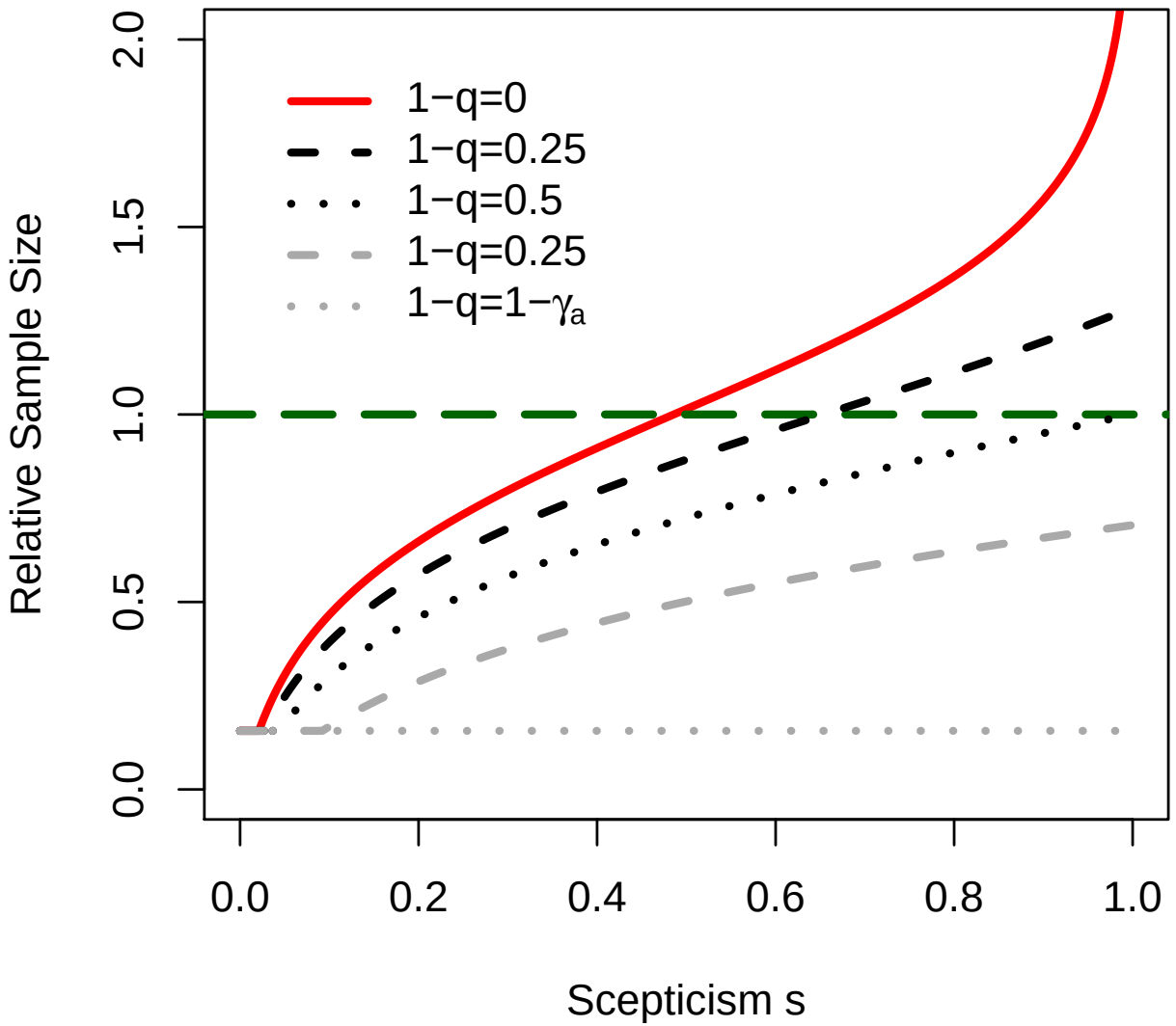
- Elicitation from expert knowledge
- Estimation from historic Phase 3 success rates
  For example:
  - In oncology, 40% of new compounds entering Phase 3 are proven to be effective.[1]
  - Under the assumption that the success rate is based on developments with two pivotal trials at overall level 0.025^2 and power 80% we obtain $1 - r_a = 0.5$.

[1] Hay et al. Clinical development success rates for investigational drugs. Nature biotechnology 2014;

How sensitive does $1 - \gamma_a$ depend on the assumptions?

Prior Adults $1 - r_a$	Significance Level α_a	Power $1 - \beta_a$	Posterior Adults $1 - \gamma_a$
0.5	0.025	0.9	0.9730
		0.8	0.9697
		0.7	0.9655
	0.025^2	0.9	0.9993
		0.8	0.9992
		0.7	0.9991
0.3	0.025	0.8	0.9320
	0.025^2	0.8	0.9982

Sample Size Reduction



- Power for the paediatric study $1 - \beta_c = 0.8$
- Confidence in efficacy in adults $1 - \gamma_a = 0.973$
- Targeted confidence in efficacy in children $1 - \gamma_c = 0.973$