Adaptive Levels of Evidence

An extrapolation framework to specify requirements for drug development in children

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joint work with

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Workshop European Medicines Agency
March 29, 2017

This work has received funding from 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).

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 (...)"

Draft Reflection paper on extrapolation of efficacy and safety in paediatric medicine development, EMA, 2016

Rationales

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  For ethical reasons and efficient resource allocation
- Optimising decision making when patients are scarce
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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).
- Can we relax the standard significance level for pivotal trials in children, taking into account that
  - the drug will have been approved for adults (based on pivotal trials) and
  - results from future adult trials can be extrapolated to a certain extent to children.
- How to choose the relaxed significance level?

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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
- Power of adult development program

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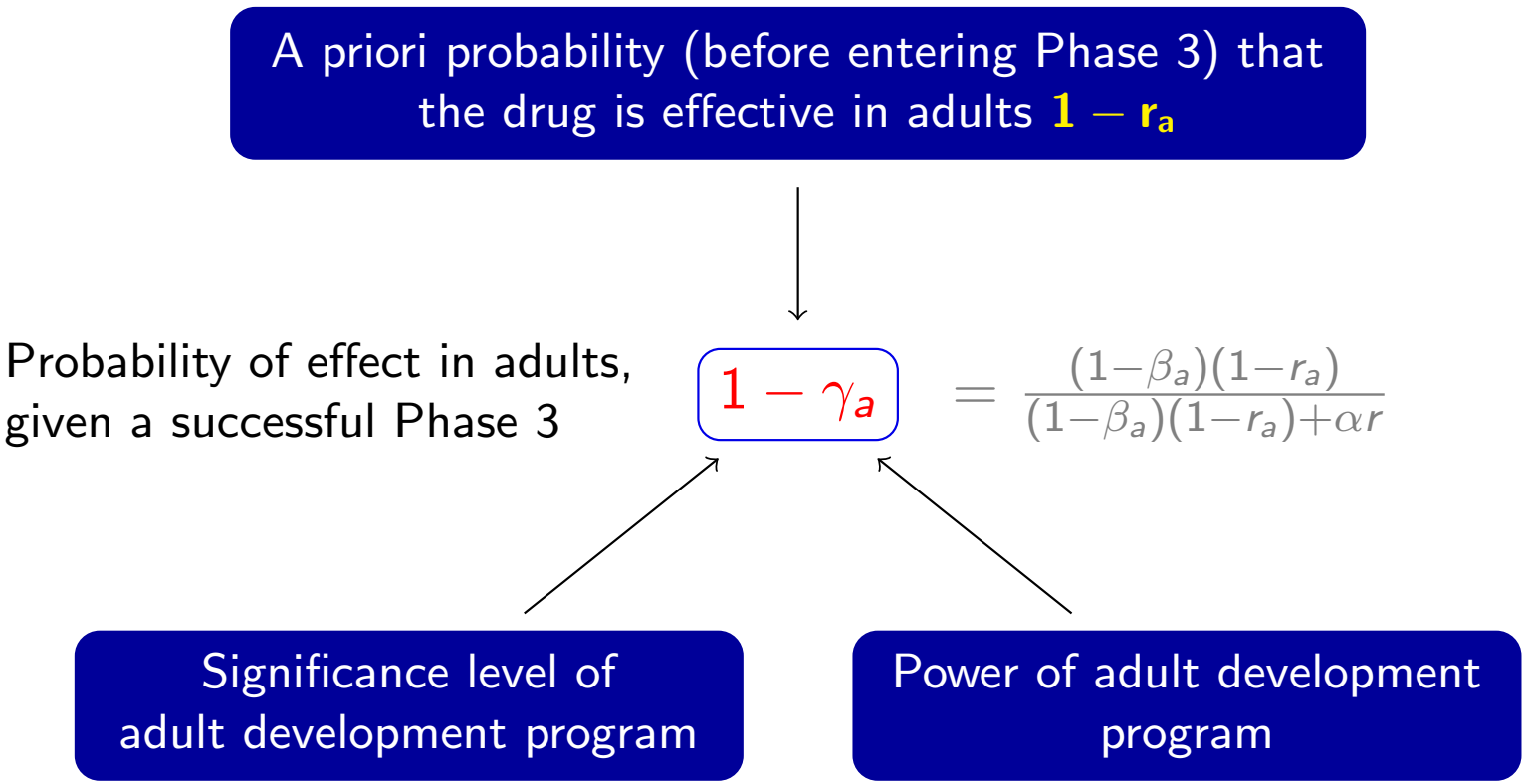

How to determine the prior probability for efficacy $1 - r_a$?

- 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;

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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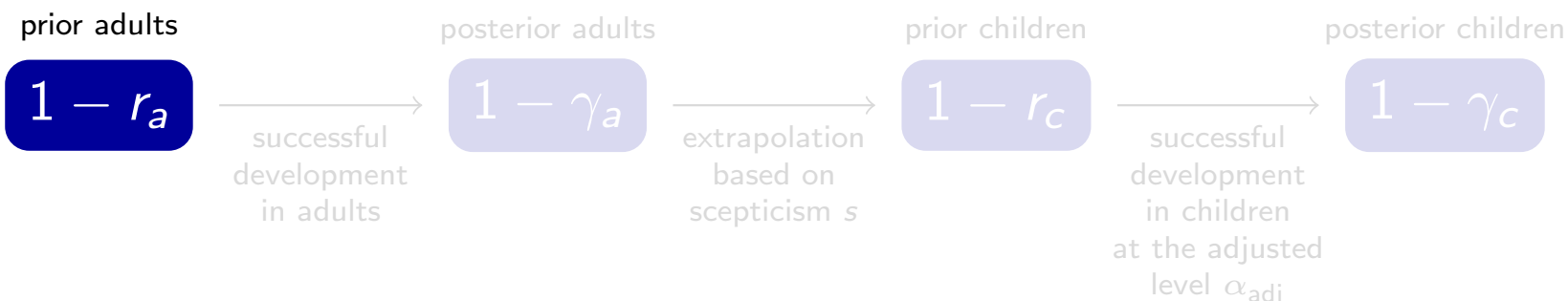

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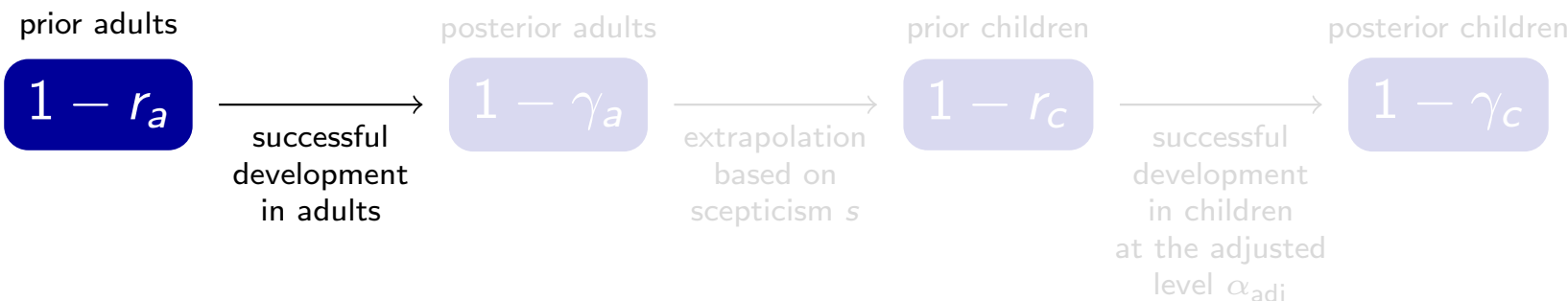

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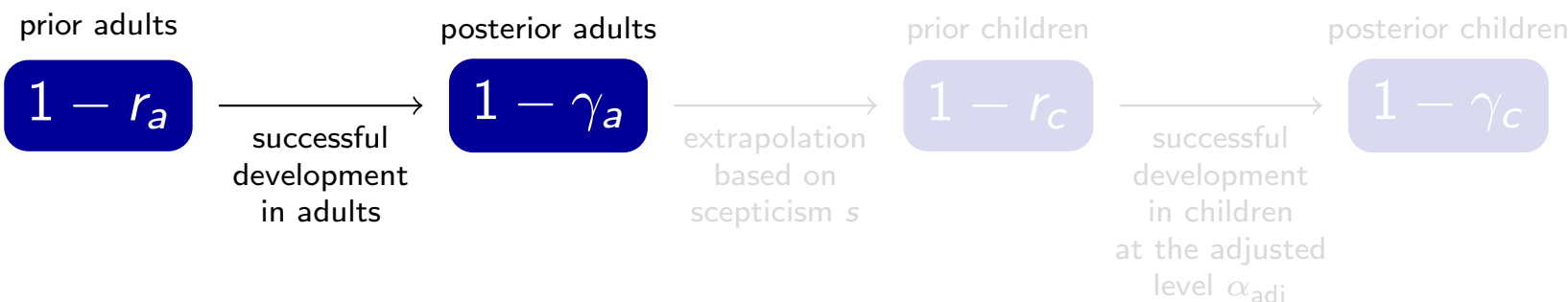


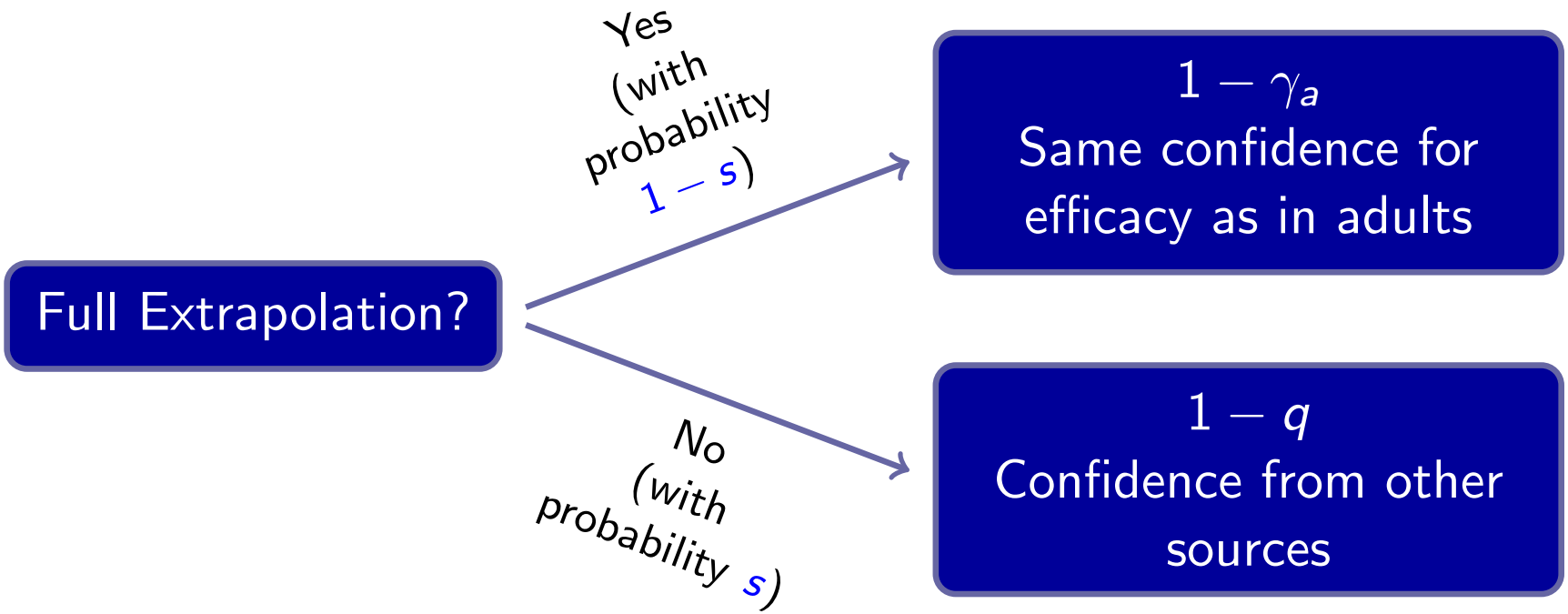
Extrapolation from Adults to Children

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

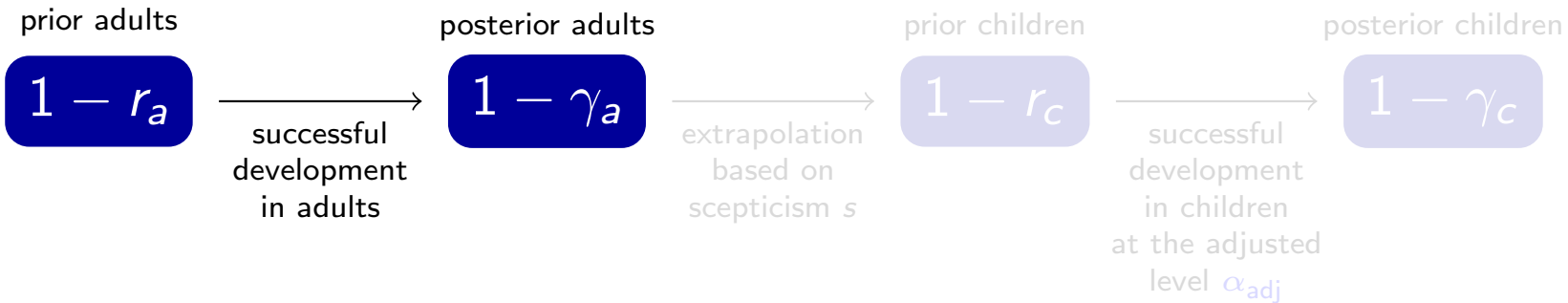


The overall early confidence for efficacy in children conditional on a future successful drug development in adults is

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

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?

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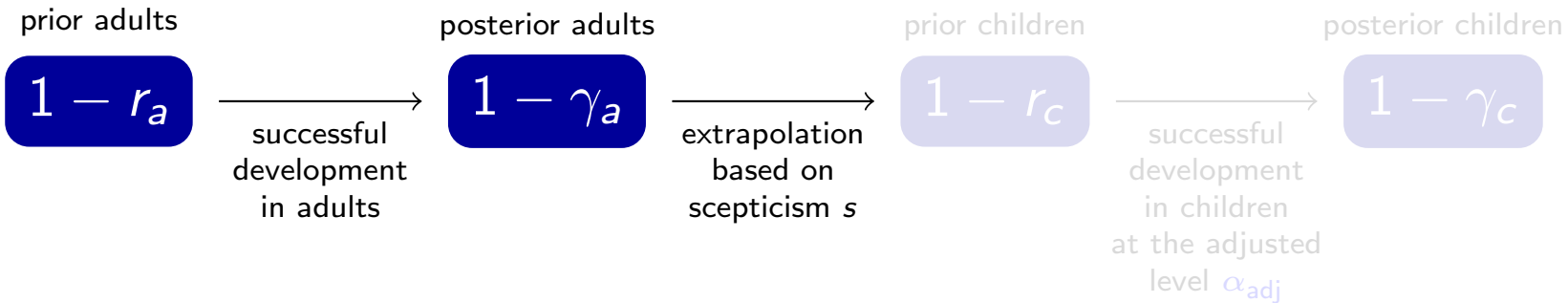

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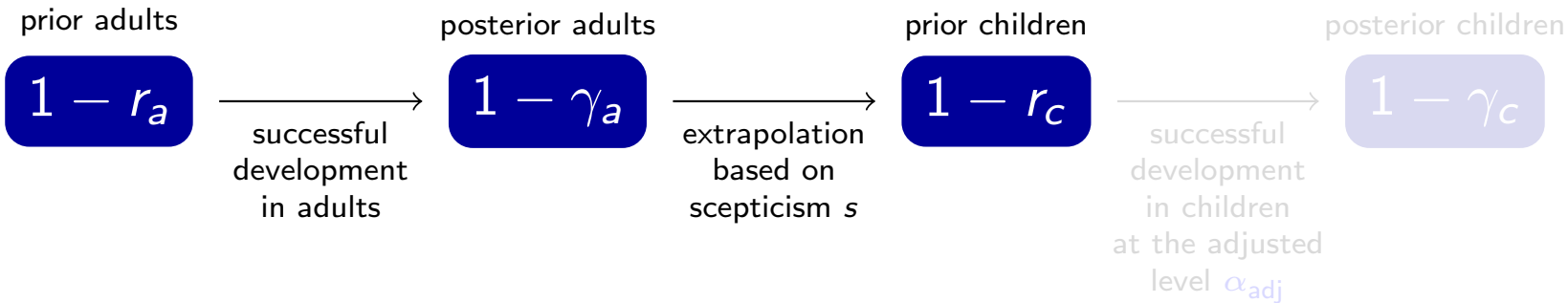

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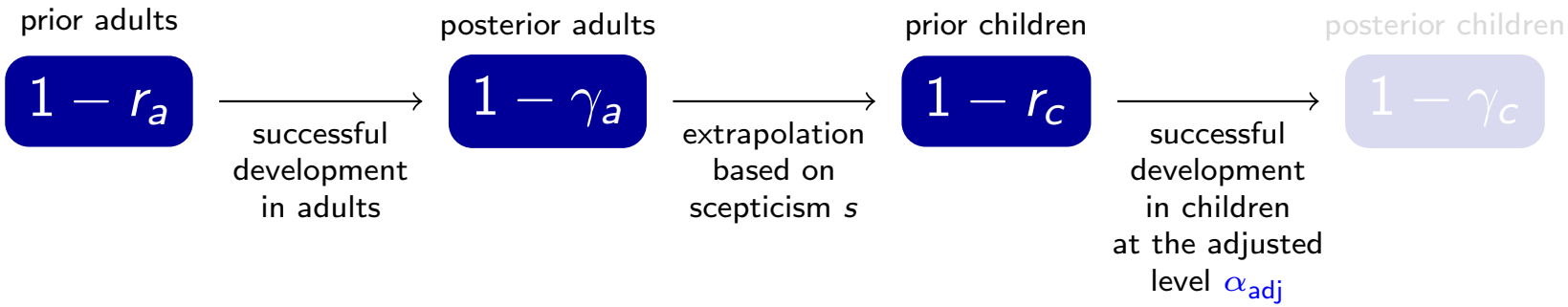

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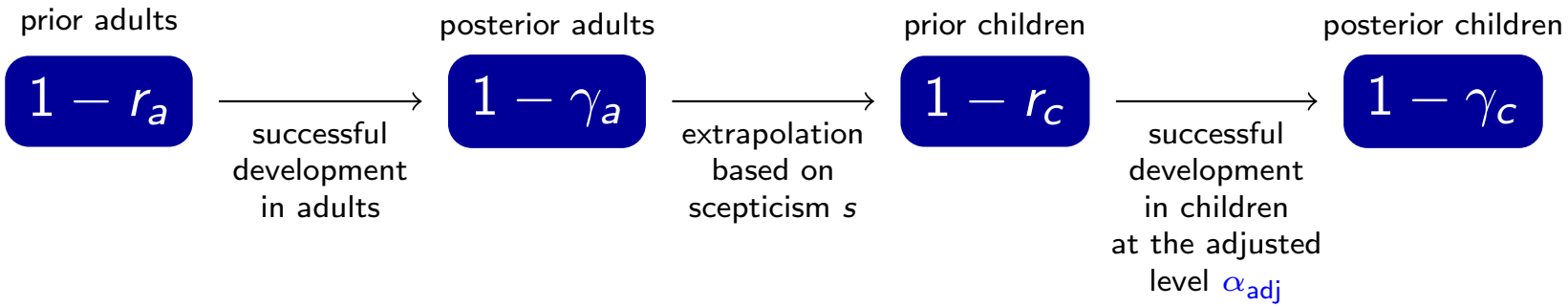

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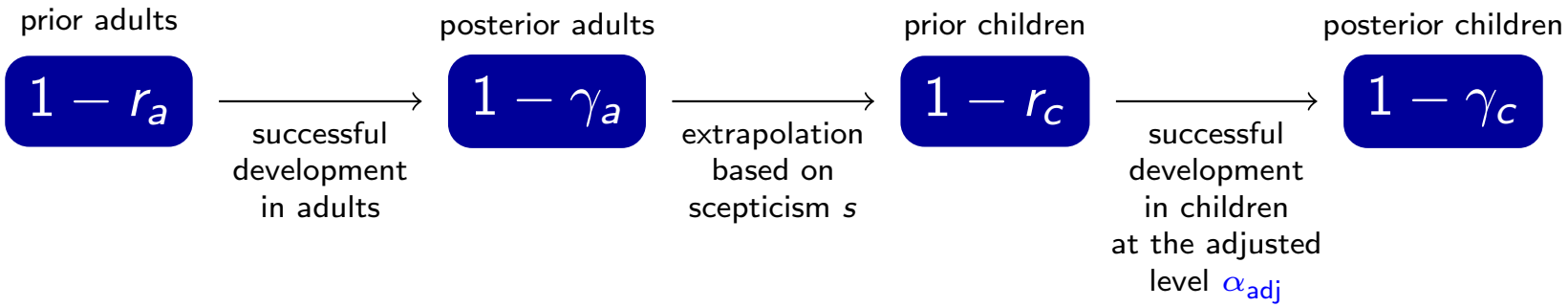

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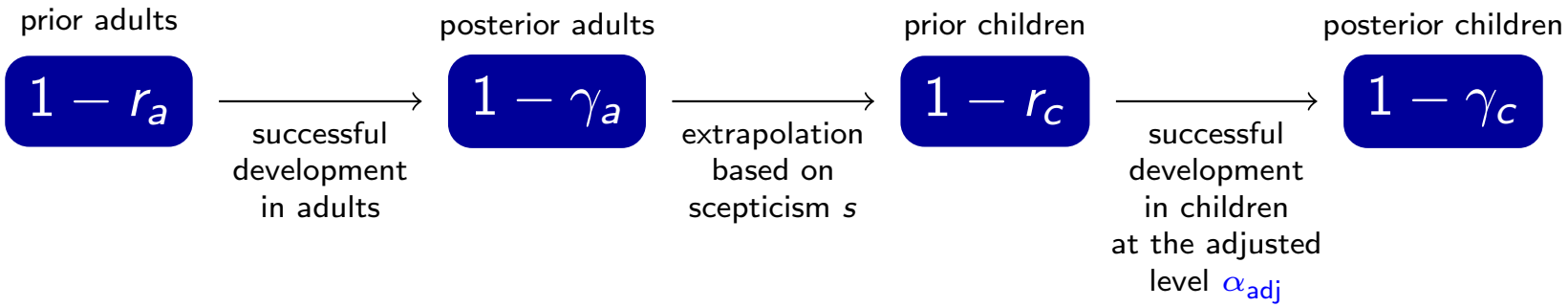

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$$1 - \gamma_a =$$

confidence efficacy adults

Conditional future confidence for efficacy in children

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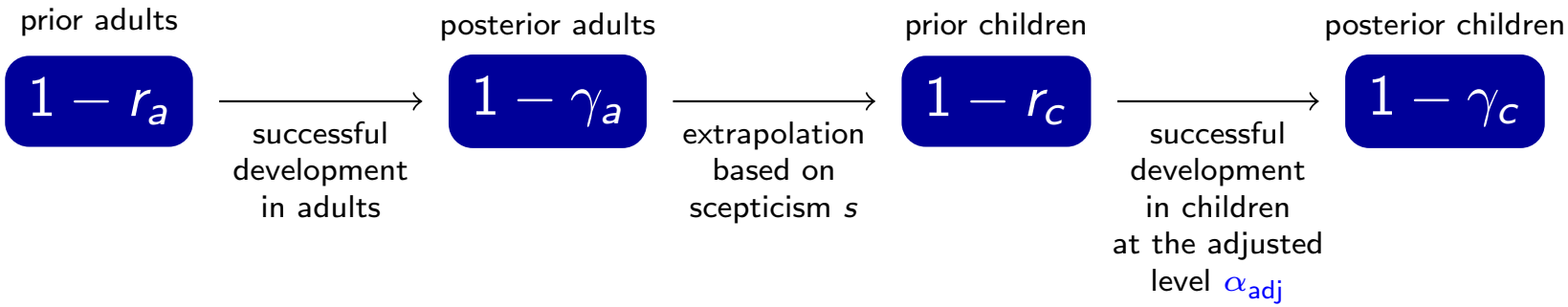
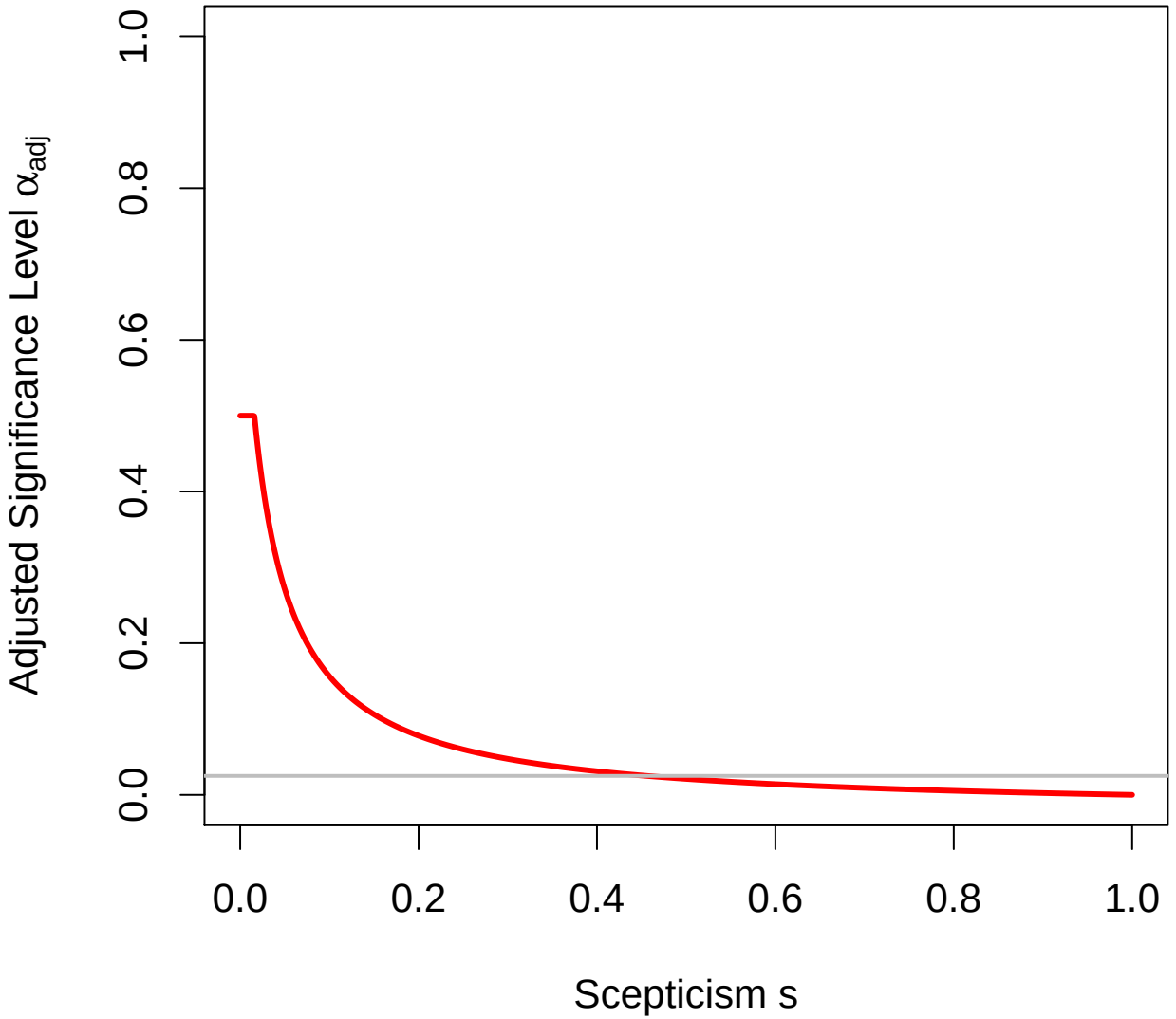


Which significance level α_{adj} do we need to apply in children to achieve the same confidence for efficacy for children as for adults?

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

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



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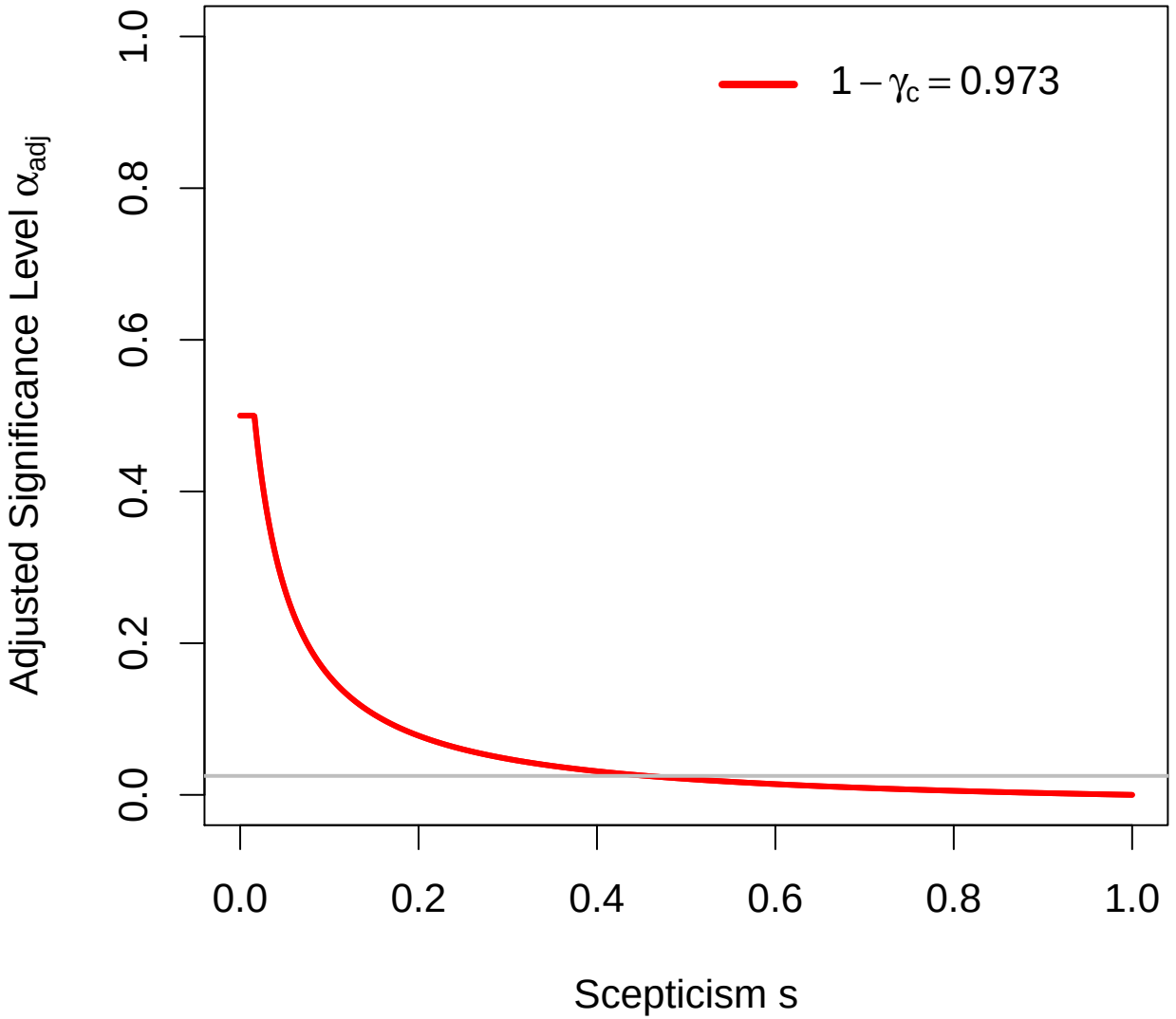

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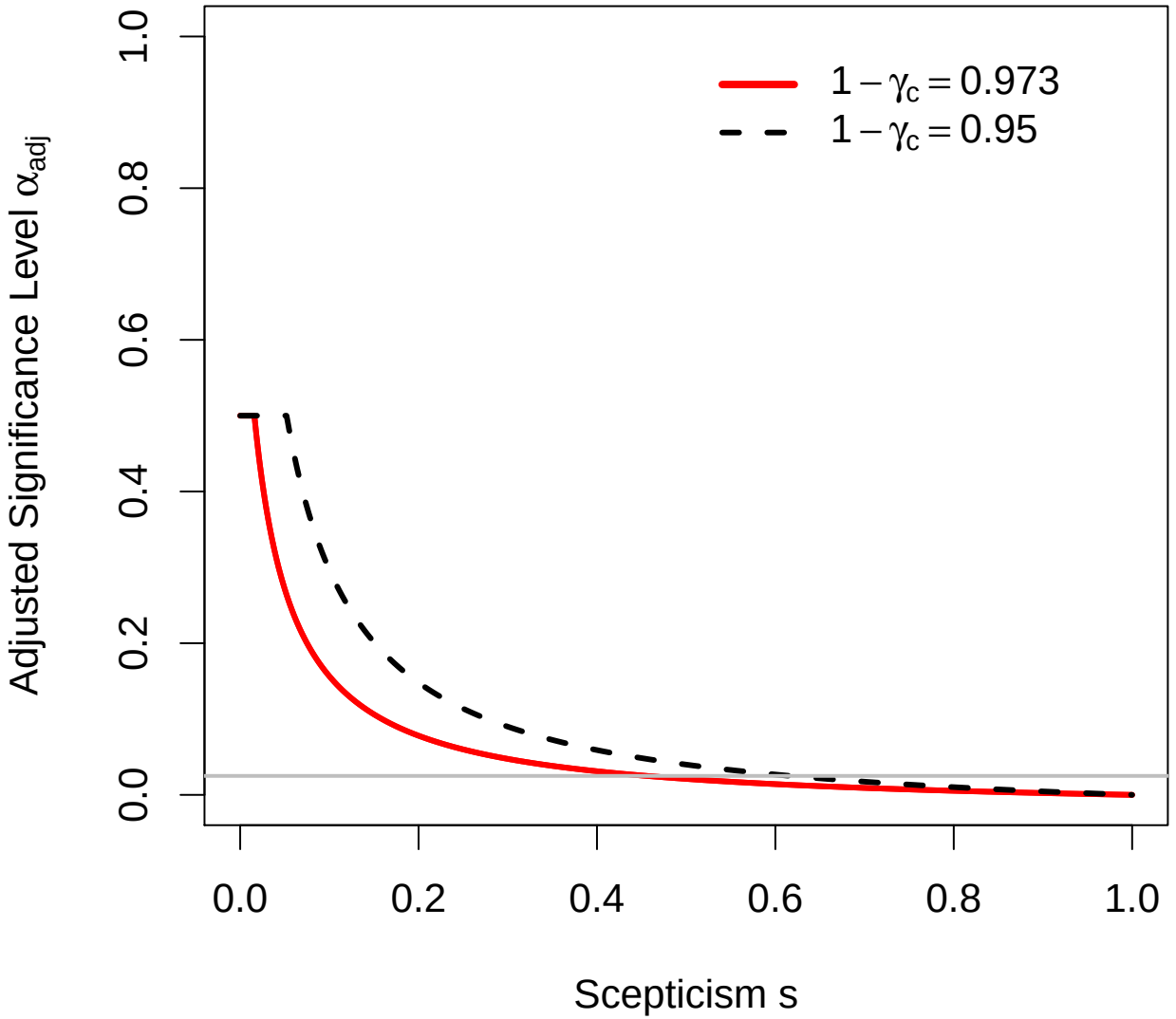

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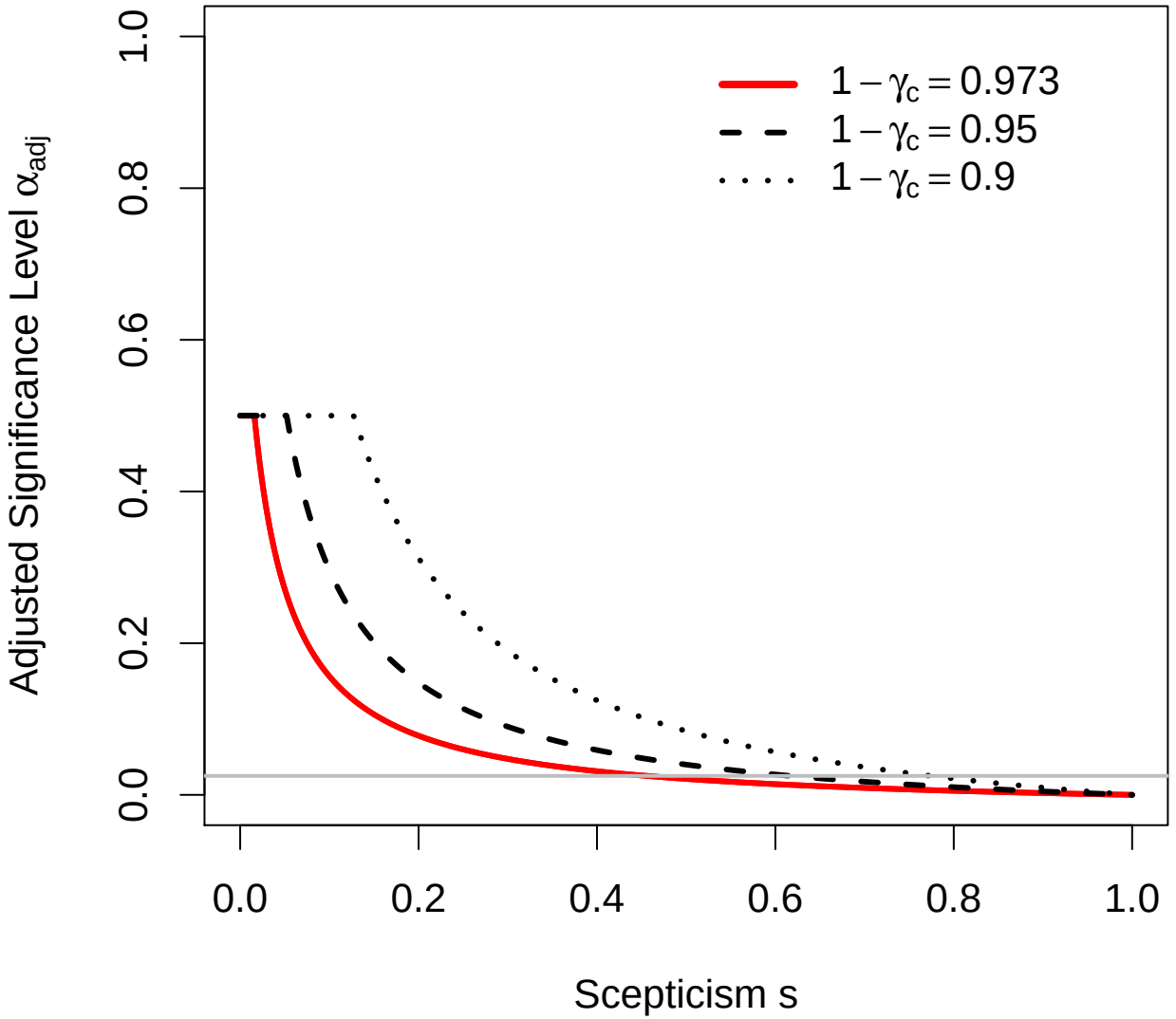

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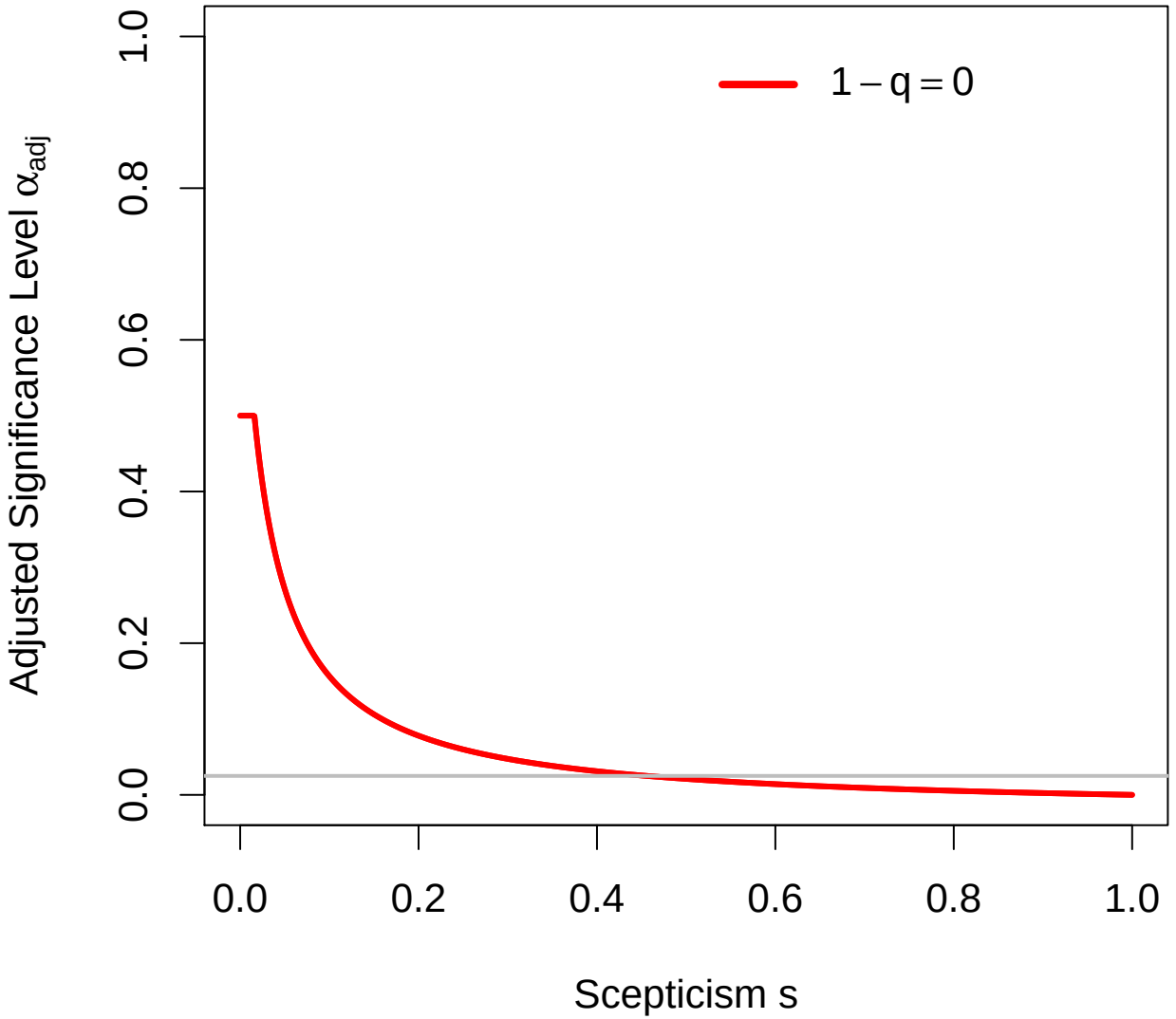

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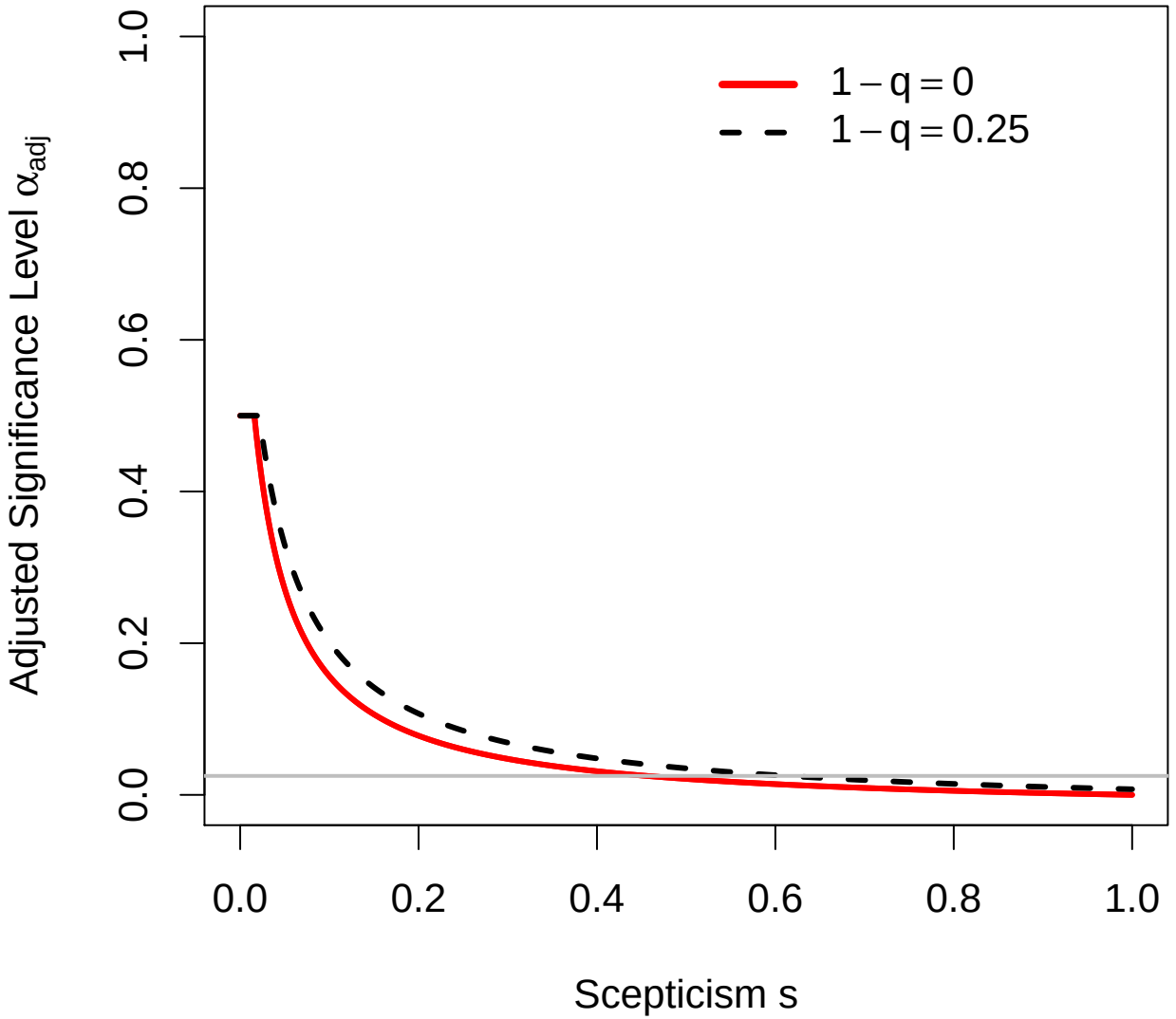

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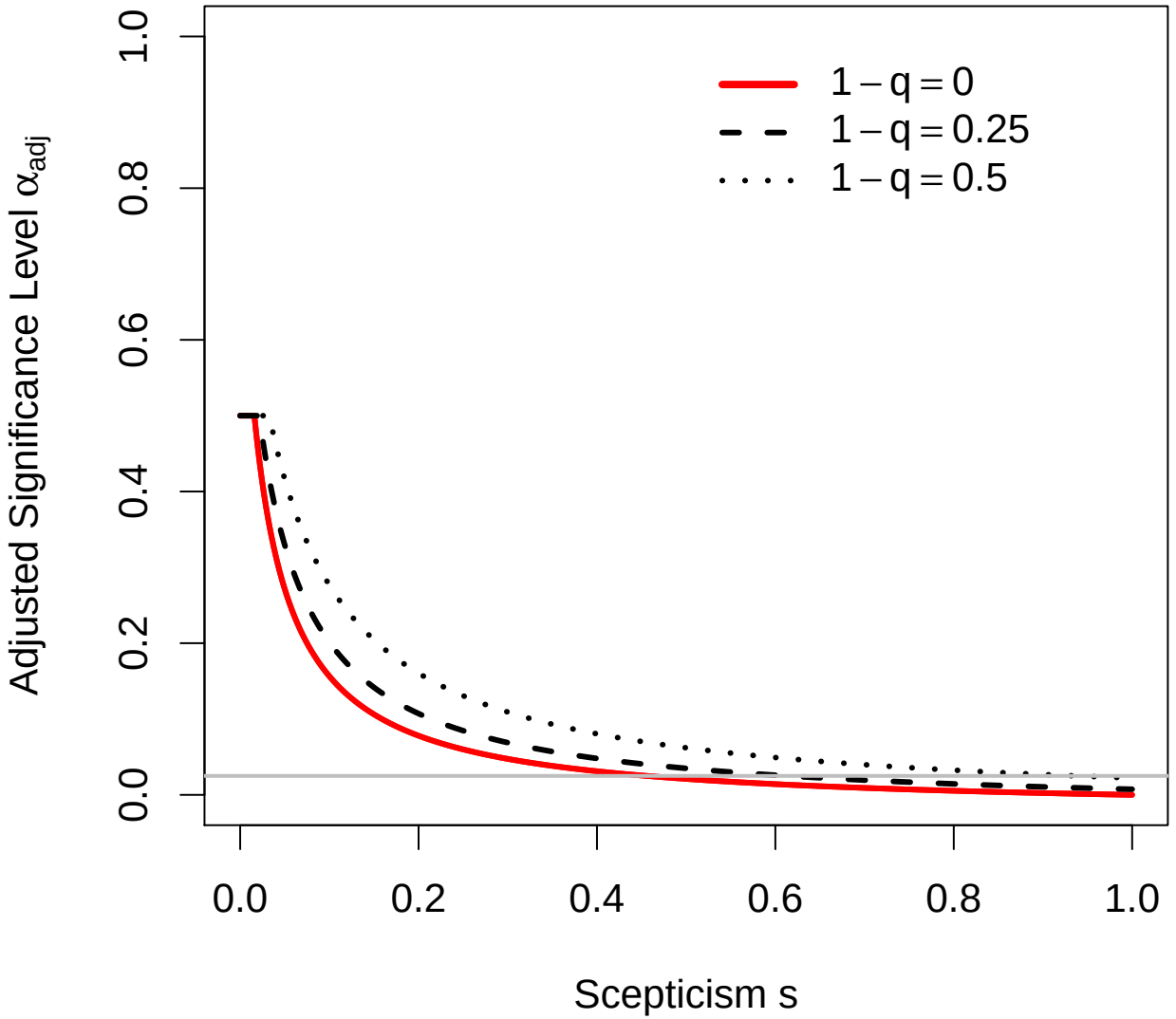

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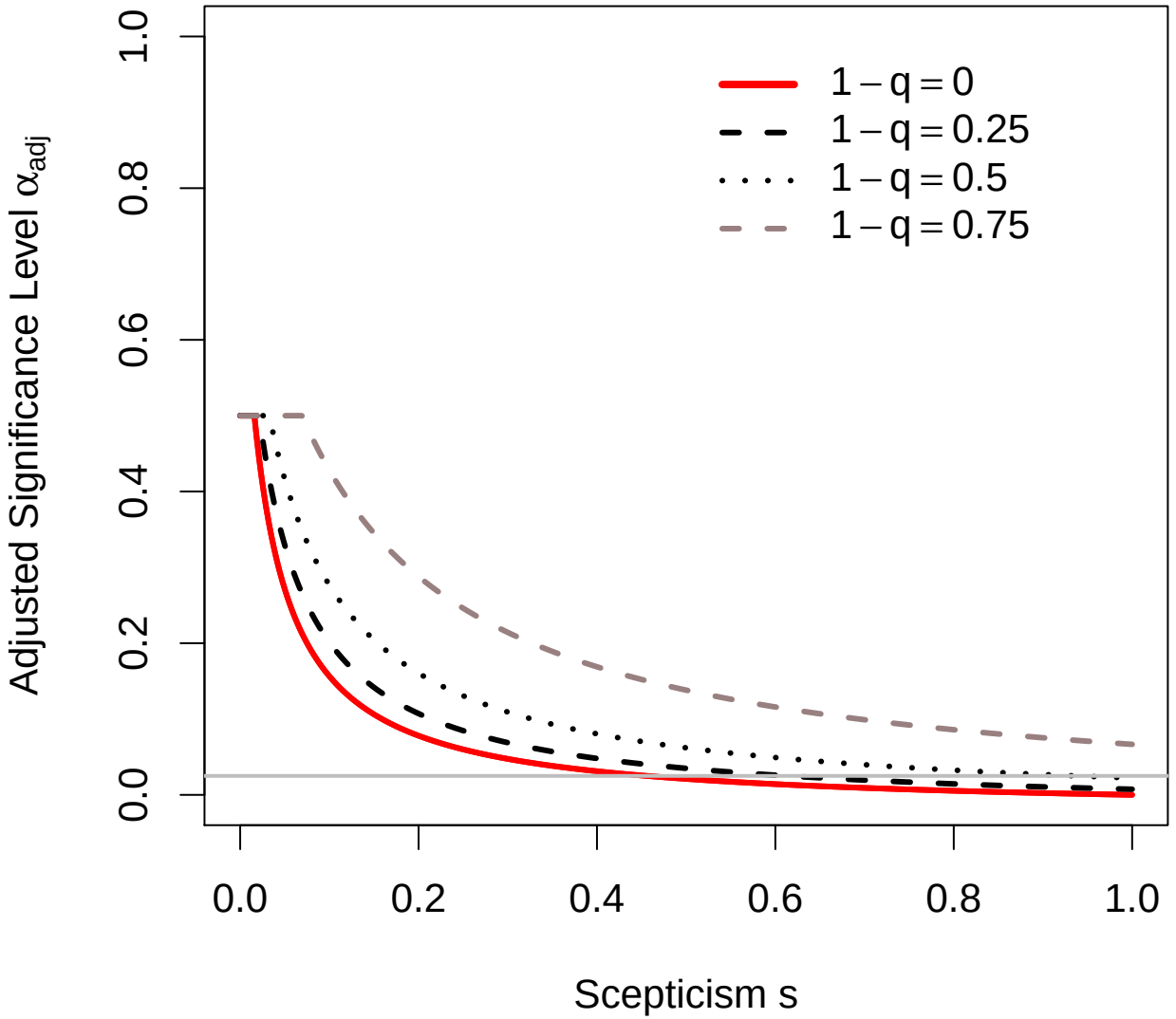

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Hypothetical Case Study: Humira

- 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

Case Study (continued)

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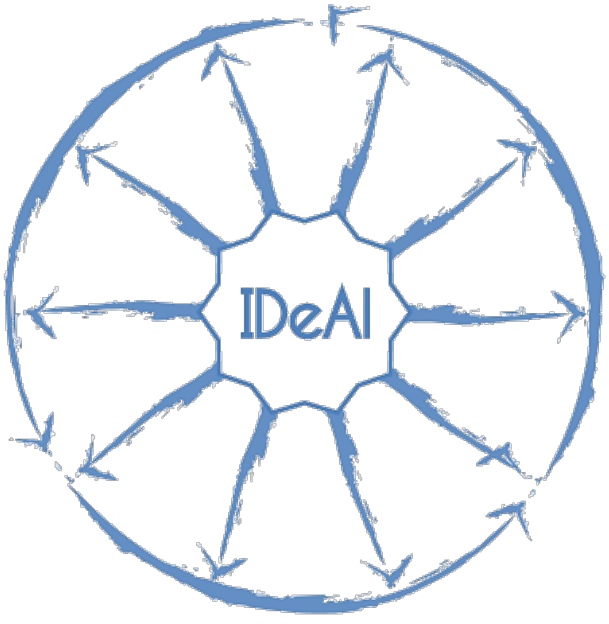
Challenges in a Potential Regulatory Application

- Estimation of the parameters based on robust evidence synthesis methods taking into account pharmacometric modelling.
- 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 (Propose Adaptive PIPs, Bauer and Koenig 2016).
- If data in adults become available, more sophisticated 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.

Thank you for your attention!



This project has received funding from the European Union's 7th Framework Programme for research, technological development and demonstration under Grant Agreement no 602552.

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References

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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

Received 19 December 2014, Accepted 13 December 2015 Published online 11 January 2016 in Wiley Online Library

(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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Adaptive Paediatric Investigation Plans

VIEWPOINT

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1762

Published online 12 July 2016 in Wiley Online Library

Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children?

Peter Bauer* and Franz König

Different arguments have been put forward why drug developers should commit themselves early for what they are planning to do for children. By EU regulation, paediatric investigation plans should be agreed on in early phases of drug development in adults. Here, extrapolation from adults to children is widely applied to reduce the burden and avoids unnecessary clinical trials in children, but early regulatory decisions on how far extrapolation can be used may be highly uncertain. Under special circumstances, the regulatory process should allow for *adaptive paediatric investigation plans* explicitly foreseeing a re-evaluation of the early decision based on the information accumulated later from adults or elsewhere. A small step towards adaptivity and learning from experience may improve the quality of regulatory decisions in particular with regard to how much information can be borrowed from adults. © 2016 The Authors. Pharmaceutical Statistics Published by John Wiley & Sons Ltd.

Keywords: paediatric medicine; adaptive; extrapolation; European regulation; clinical trials; drug development

Drug development in the paediatric population is one of the most sensitive areas in medicine involving various emotional, ethical and methodological challenges. For example, there may be only small numbers of children that can be recruited into studies but increased costs for drug developers which may not be compensated by economic returns especially if the disease is rare in children. Off-label drug use remains an important public health issue for infants, children and adolescents, because an overwhelming number of drugs still have no information in the labelling for use in paediatrics [1]. In 2007, a paediatric regulation (EU 1901/2006) [2] came into force in the EU also motivated by the impression that 'Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorization of, medicinal products for the paediatric population' [2]. A key role in the new regulatory procedures has been taken over by a Paediatric Committee (PDCO) at the European Medicines Agency (EMA) which 'should be primarily responsible for the scientific assessment and agreement of paediatric investigation plans' (PIP). The new obligations are supplemented by a reward of a 6-months patent extension if all the measures included in the agreed PIP are complied with regard to timing with the EU regulation 'aims at ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during product development, …'. [2] An early commitment of the applicant of his plans in children is asked for to avoid any delay of the paediatric development. Another advantage of an early development plan for children is that at this time it could be integrated scientifically in the adult development by planning studies in adults which in turn provide specific data relevant for the paediatric development. However, then, it would be reasonable to define later checkpoints to allow an assessment of the impact of evolving information on the planned paediatric development plan – possibly foreseeing the option of PIP adaptations.

A consequence of the paediatric regulation is that in general development programmes for children are laid down (and agreed on by the PDCO) early often when clinical data on efficacy in adults are still lacking. Here, we rely on our own experiences in the PDCO and EMA, respectively, and therefore focus on EU regulations. The scope of PIPs may reach from the one extreme of 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 to the other extreme of, for example, only a single (pharmacokinetic) case series in children. In the EU regulation, it is stressed that the 'objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials …'. This is referring to the option of fully or partially extrapolating knowledge and data from adults to paediatric populations [3,4] which is an obvious and widely applied approach to reduce the burden of drug development in children [5]: for example, the PDCO may agree that a single study in children with a relaxed level of significance for demonstrating efficacy may be sufficient for market authorization [6], given a successful development in adults. The decision will be based on the nature of the drug and the disease and on

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- explicitly foresees re-evaluation
- modifications can also be requested by regulators
- more strategic, less elaborated on details of studies to be planned
- justification of strategy and timelines
- adaptive interim analysis in paediatric trials
- Change of (interpretation) EU legislation
- HTTP://DX.DOI.ORG/10.1002/PST.1762 (OPEN-ACCESS)

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