Adaptive Levels of Evidence

Evidence, Eminence and Extrapolation
An extrapolation framework to specify requirements for drug development in children

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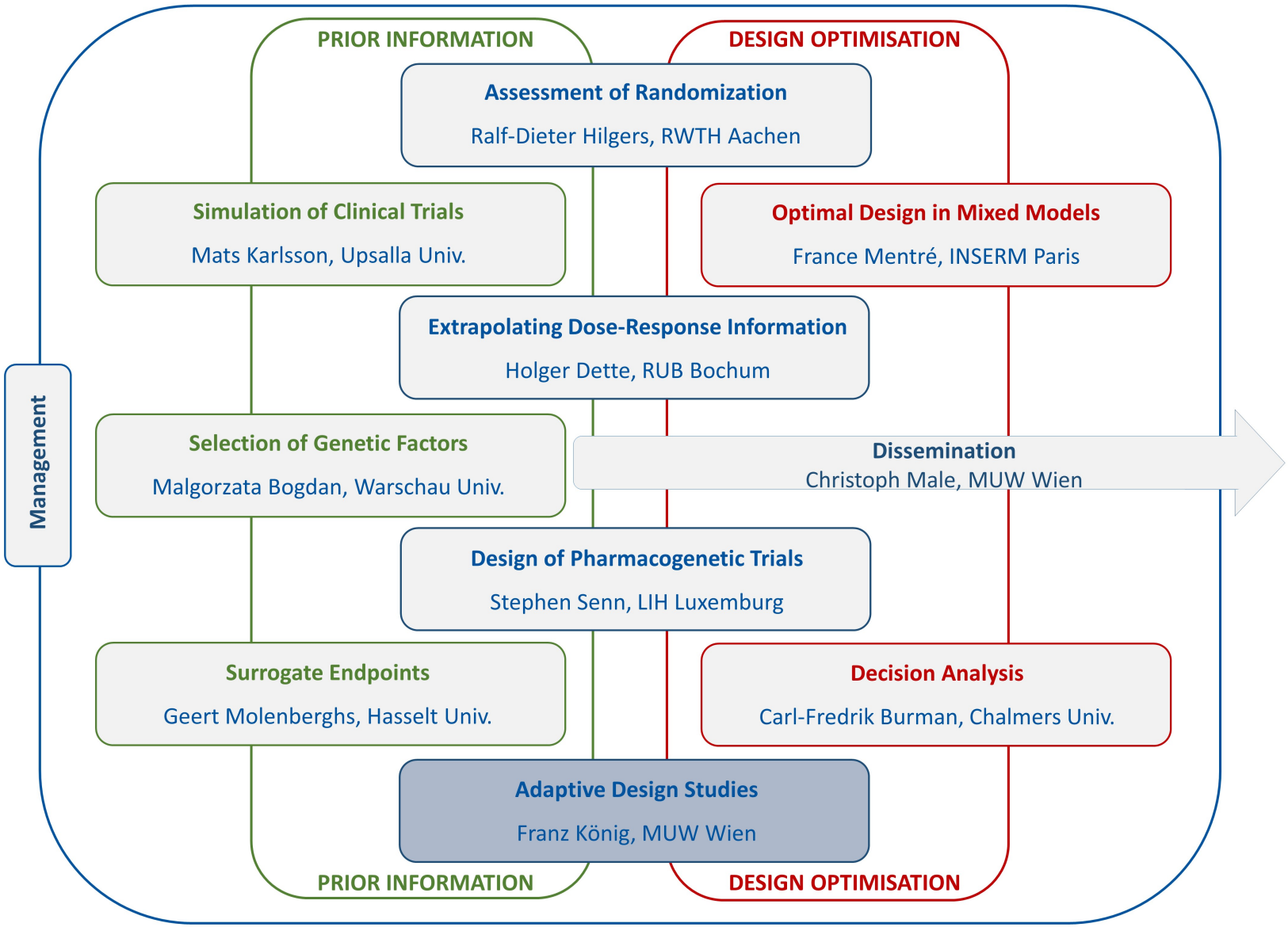
The IDeAI Webinar Series



Research Team Medical University of Vienna

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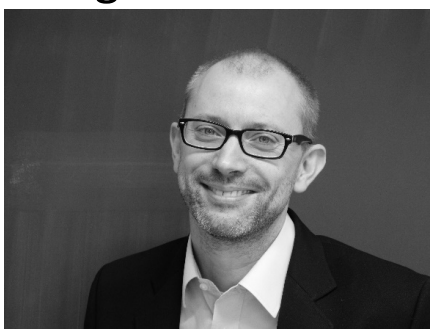
Peter Bauer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Agenda

- Drug Development in children: the European Paediatric Regulation
- EU Draft Reflection Paper on Extrapolation
- A Quantitative Concept for Extrapolation
- Adaptive Paediatric Investigation Plan
- Summary

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)

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

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

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 (open for comments later this year)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 1 April 2016
2 EMA/199678/2016

3 Reflection paper on extrapolation of efficacy and safety in
4 paediatric medicine development
5 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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Can one Quantify the Prior Information on Similarities?

"Quantitative approaches that summarise the prior information whilst integrating expert judgement could be considered as part of the extrapolation exercise, although methods to do this are still in the early stages of development."

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

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).
- 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?

  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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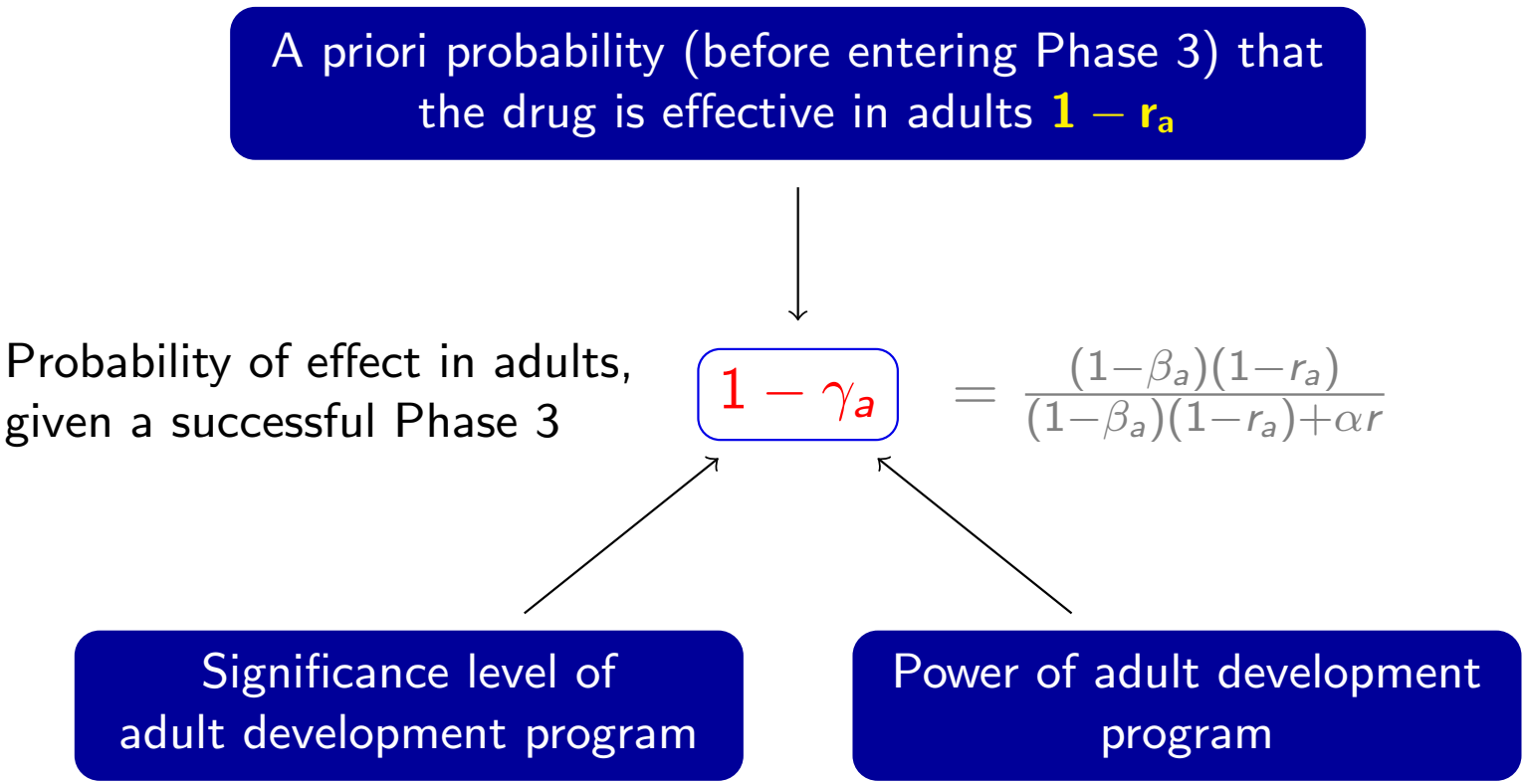

How to determine the prior probability for efficacy $1 - r_a$?

- 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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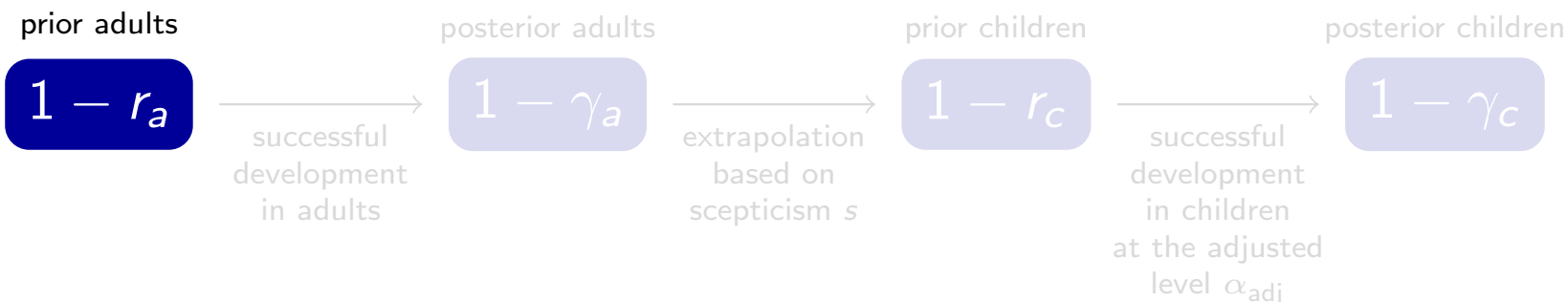

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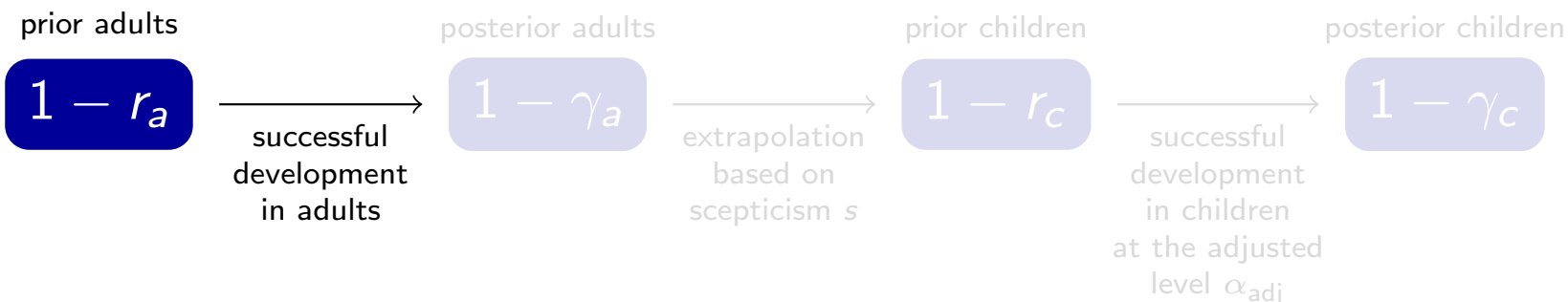

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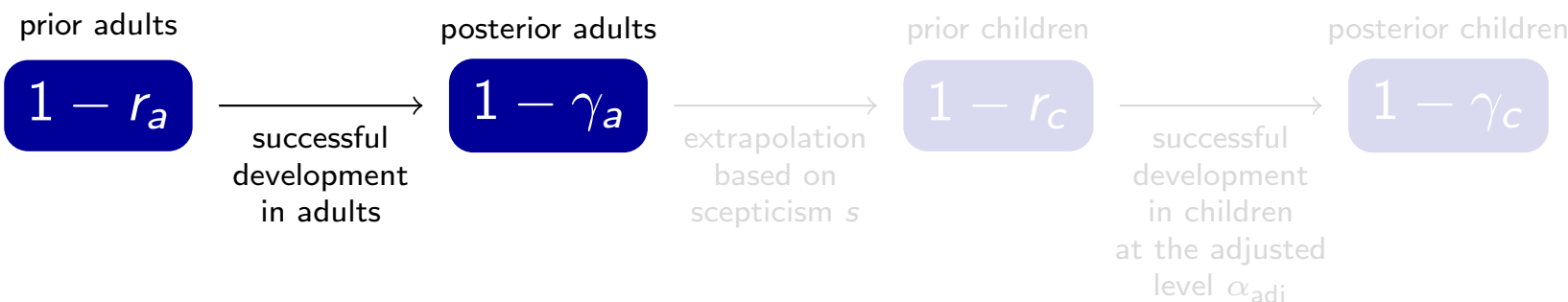


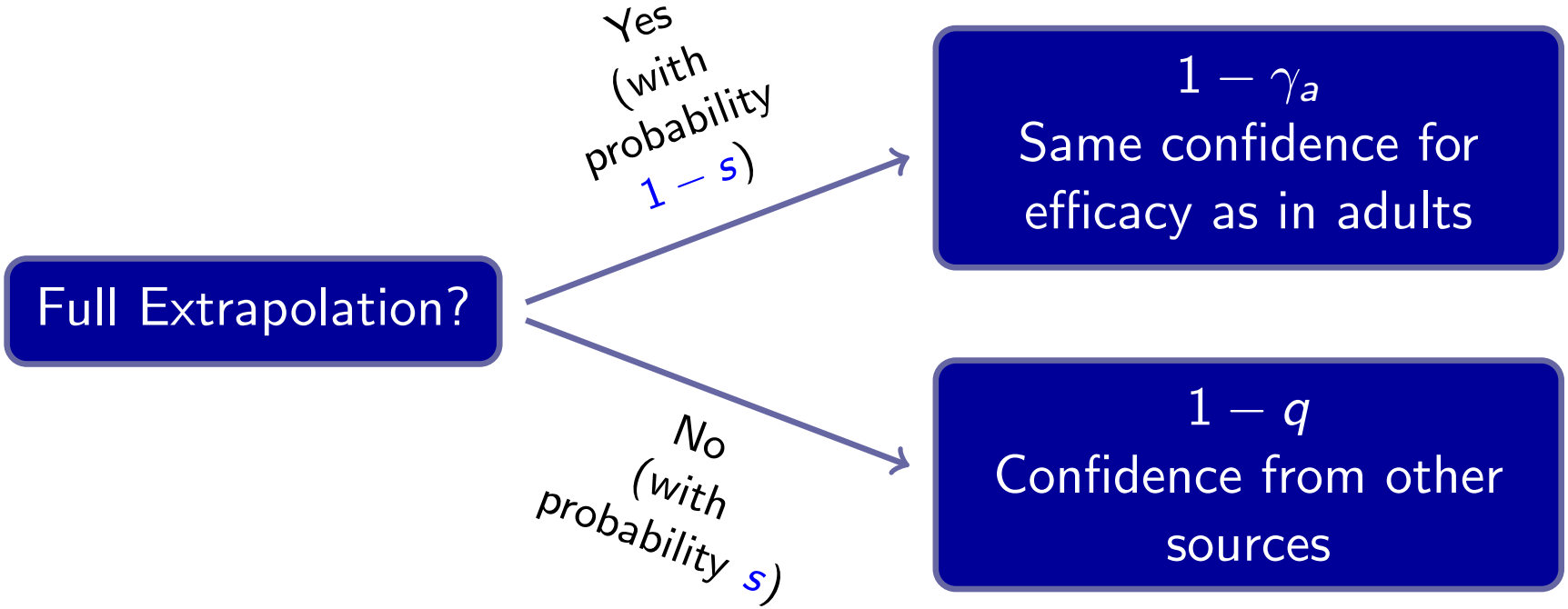
Extrapolation from Adults to Children

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

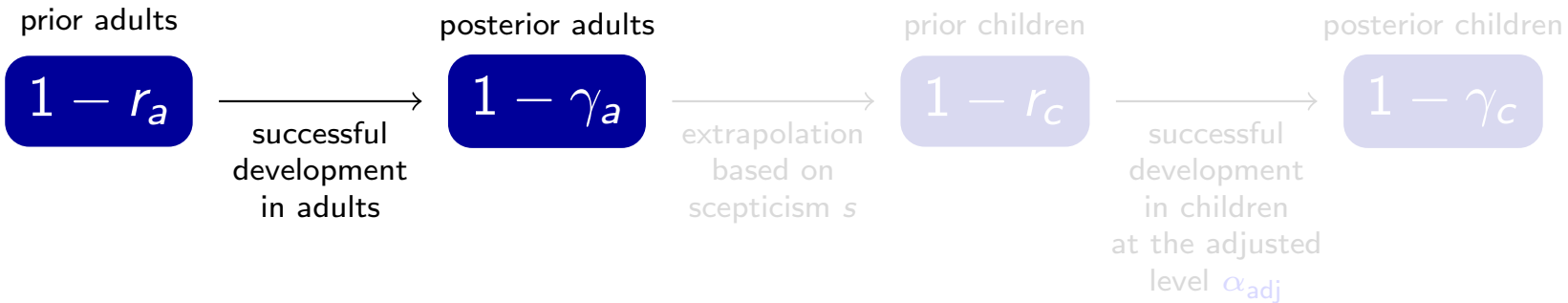


The overall early confidence for efficacy in children conditional on a future successful drug development in adults is

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

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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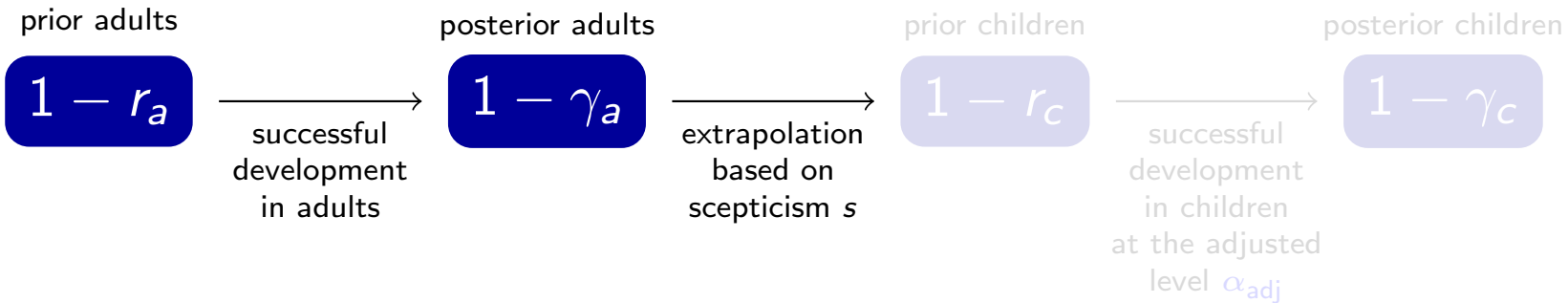

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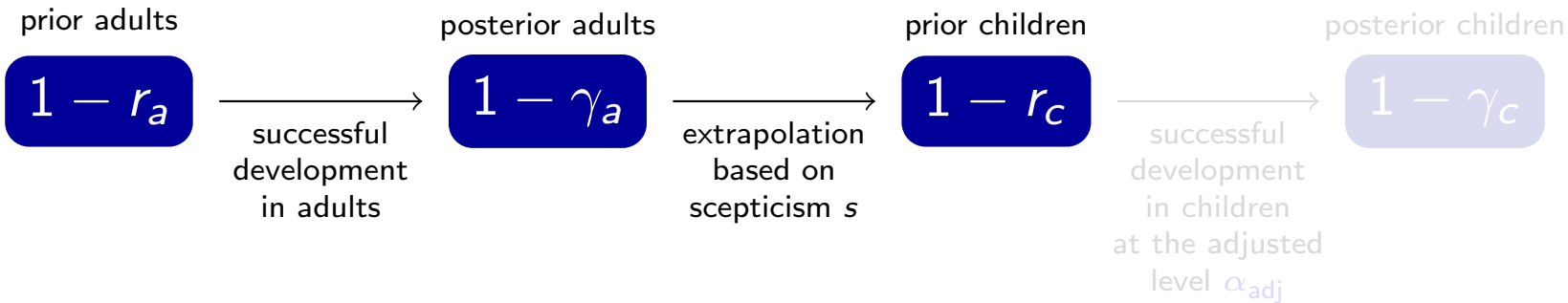

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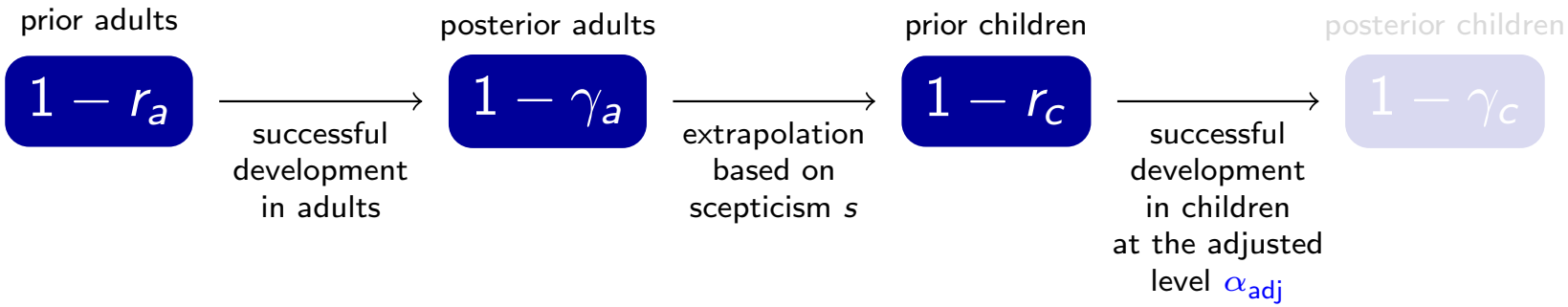

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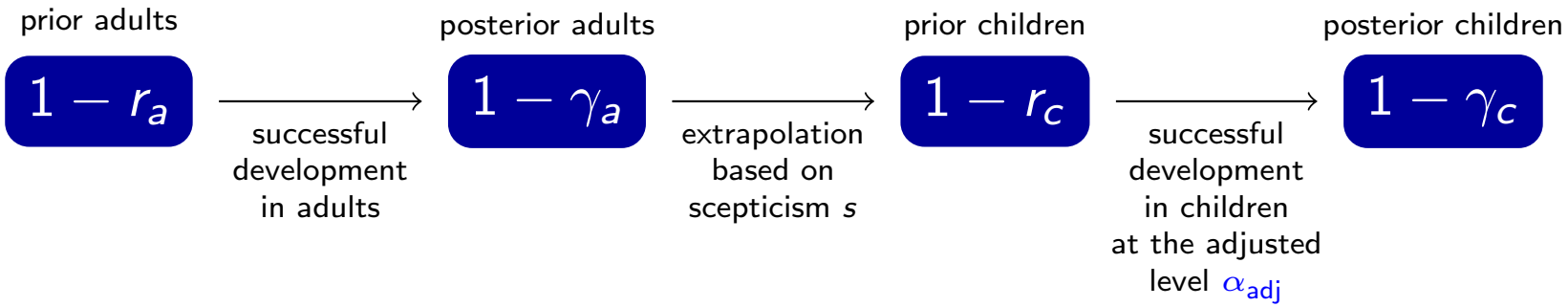

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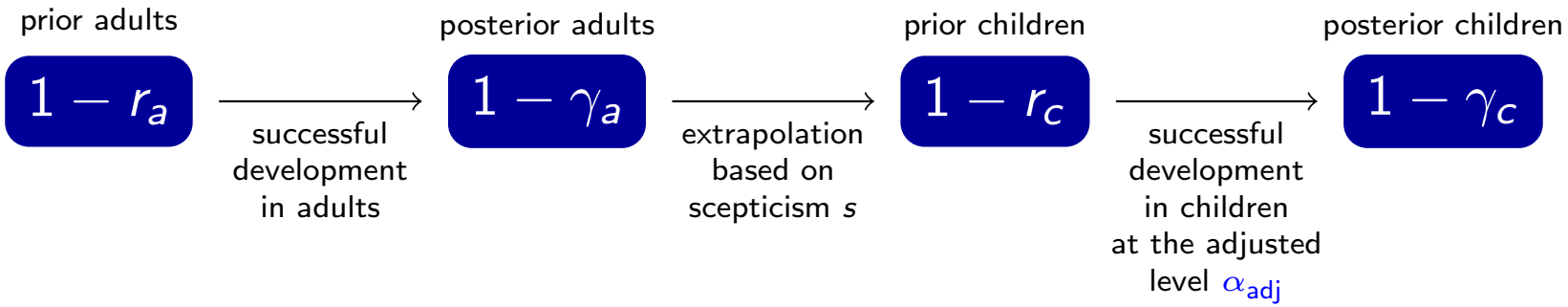

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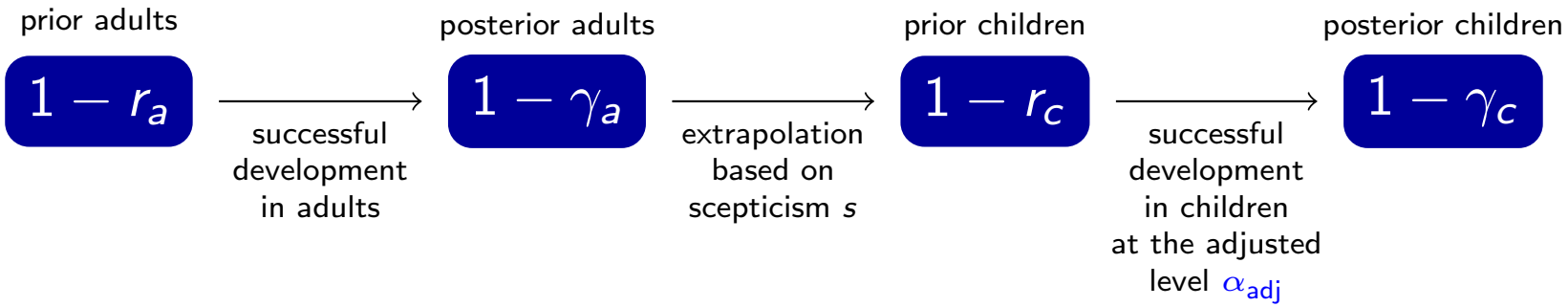

Which significance level α_{adj} do we need to apply in children to achieve the same confidence for efficacy for children as for adults?

$$1 - \gamma_a =$$

confidence efficacy adults

Conditional future confidence for efficacy in children

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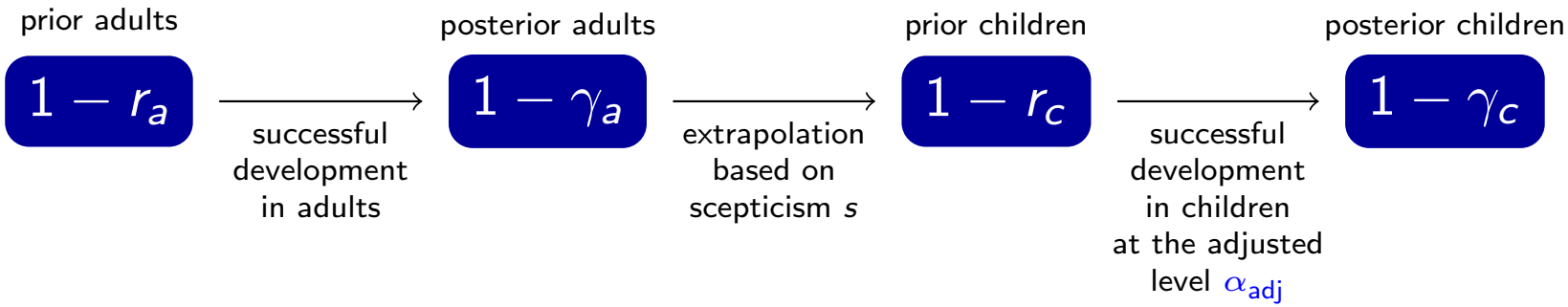
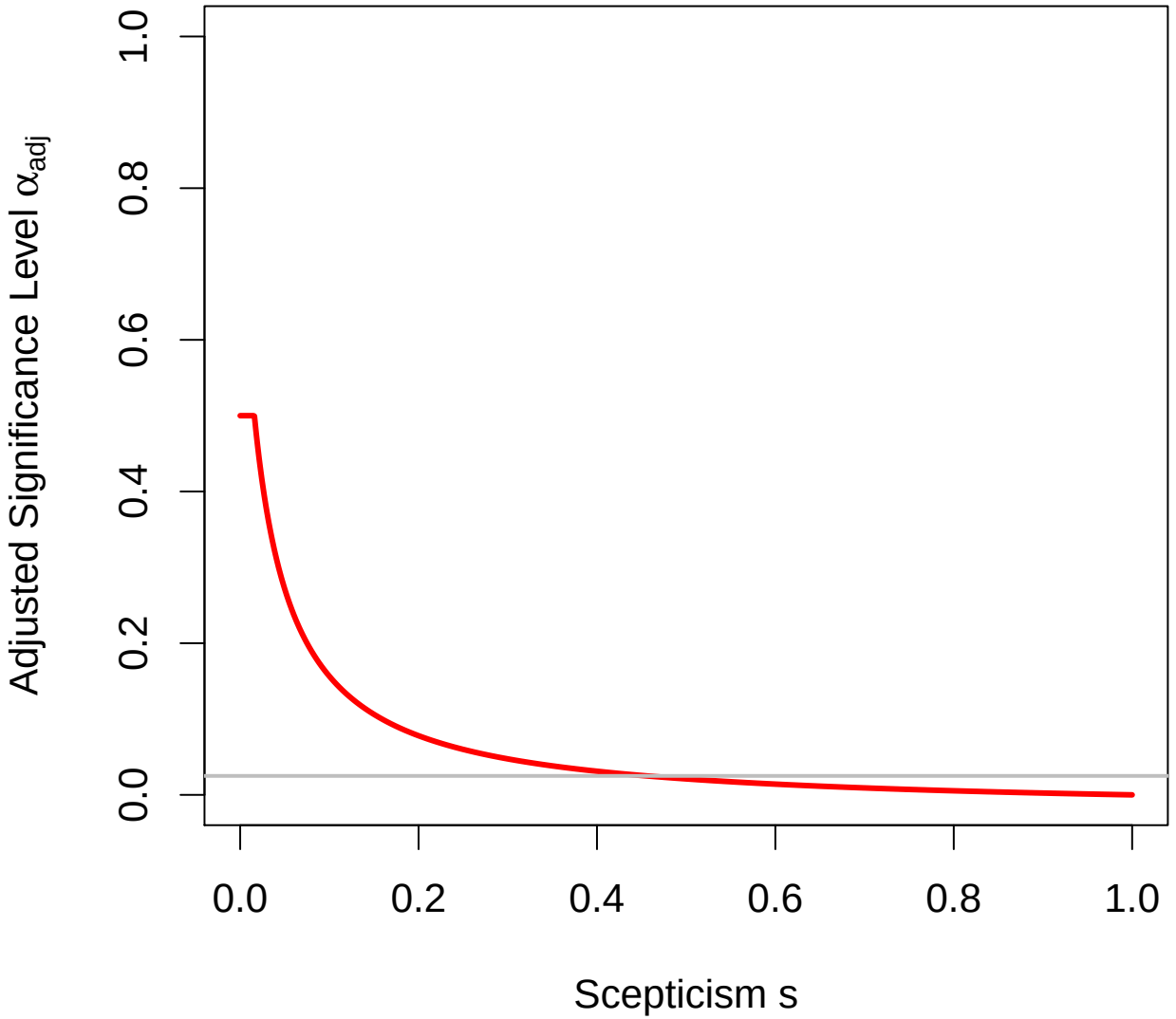


Which significance level α_{adj} do we need to apply in children to achieve the same confidence for efficacy for children as for adults?

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

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



- 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 $1 - \gamma_c = 0.973$
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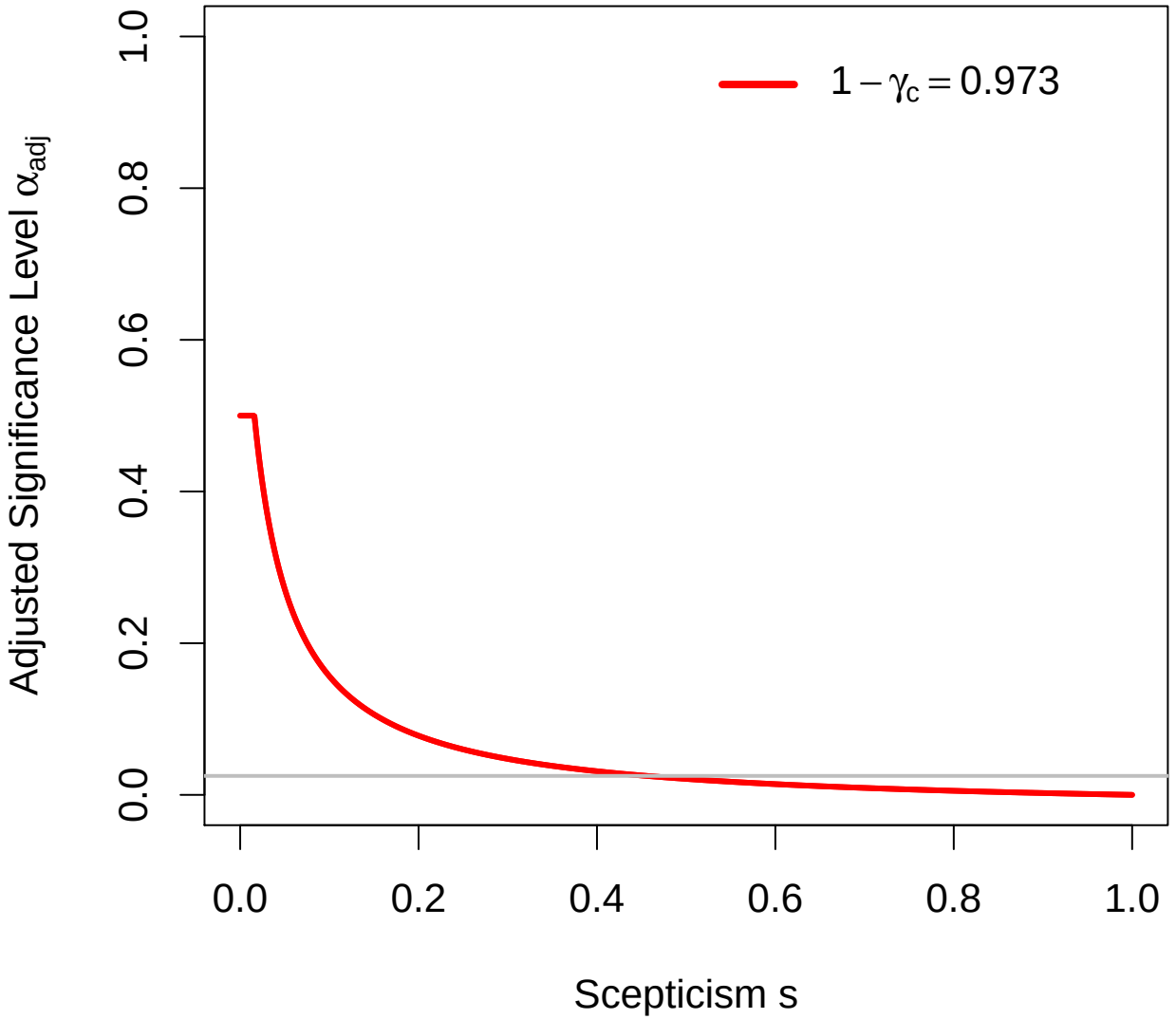

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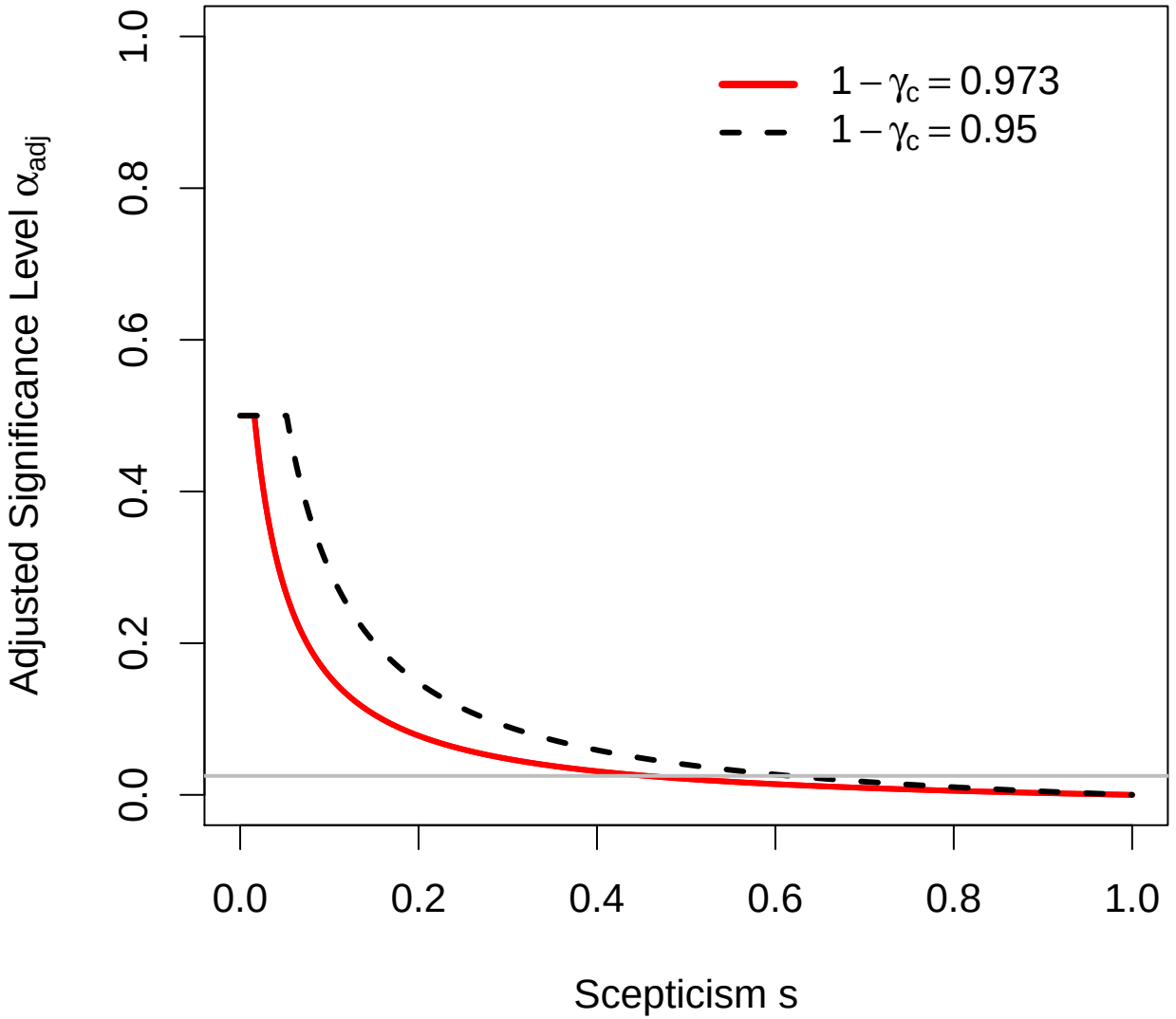

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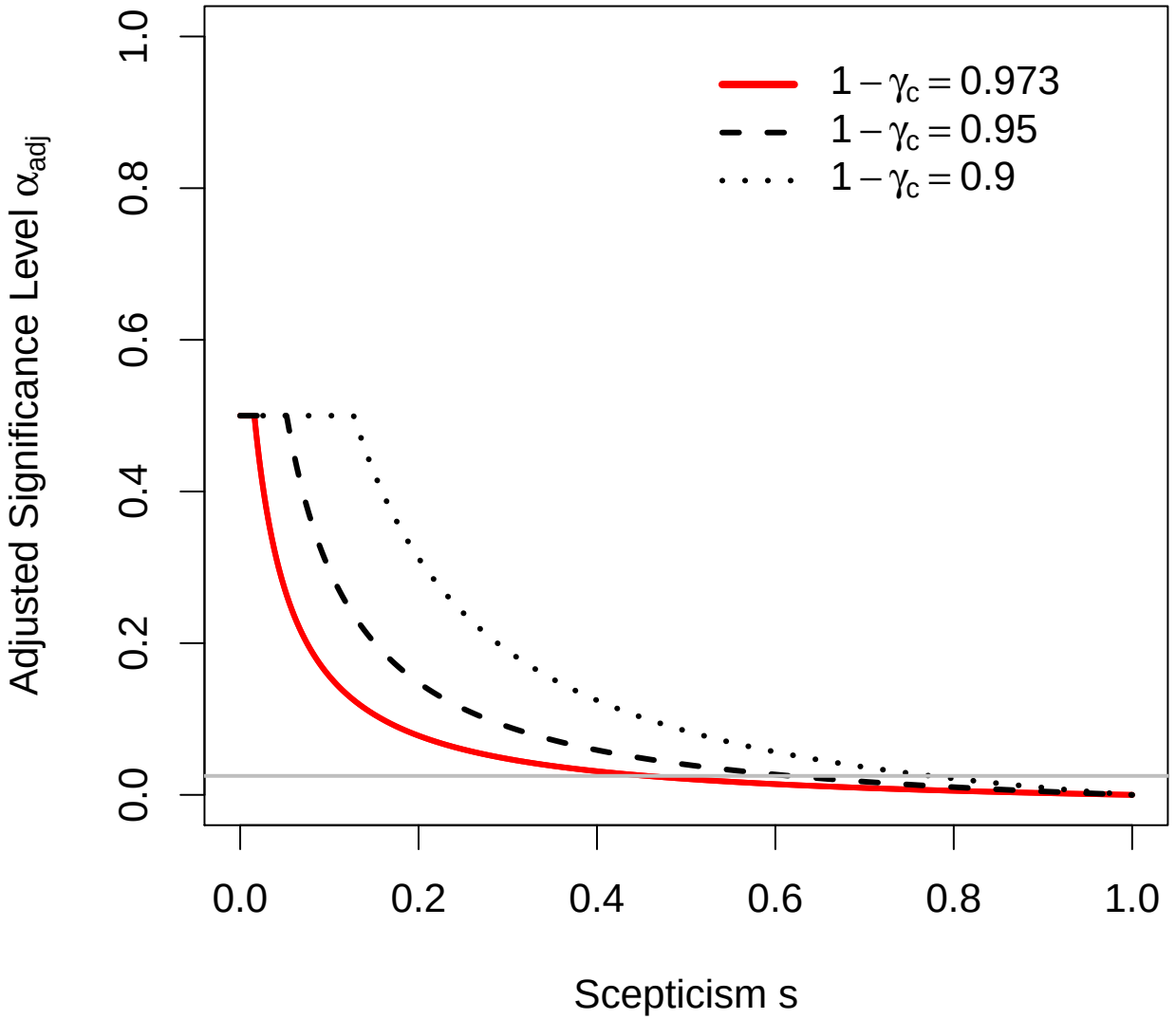

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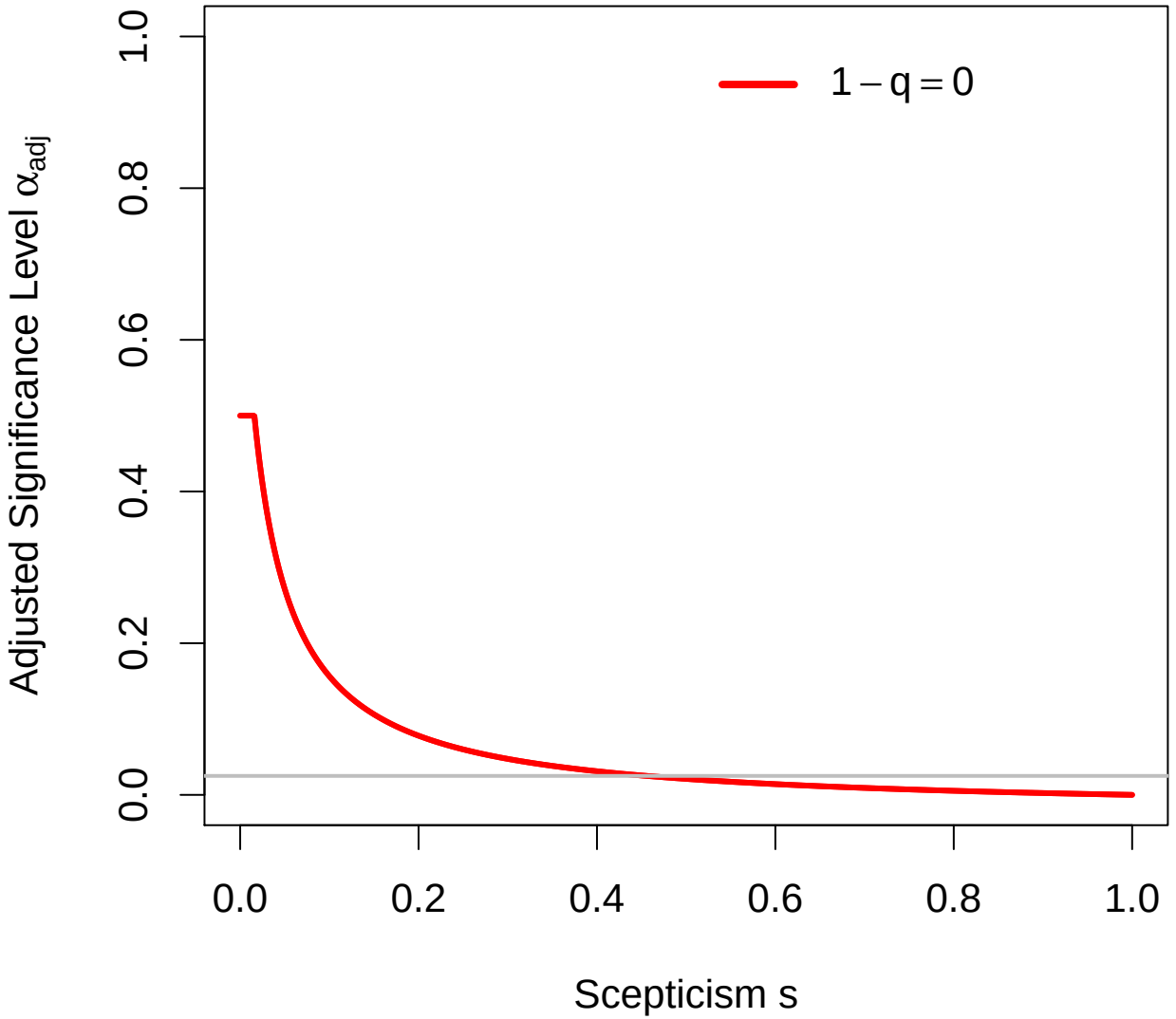

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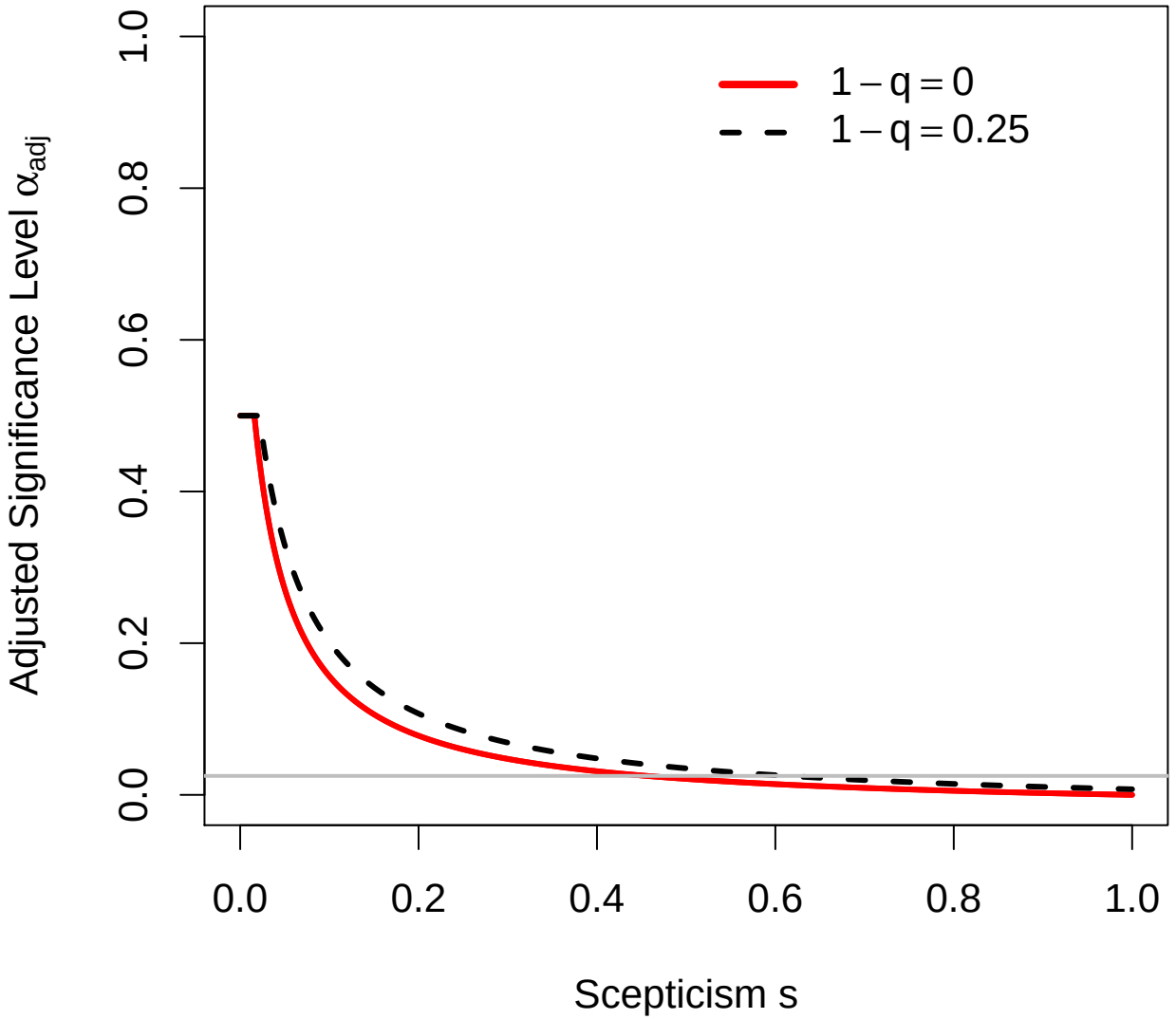

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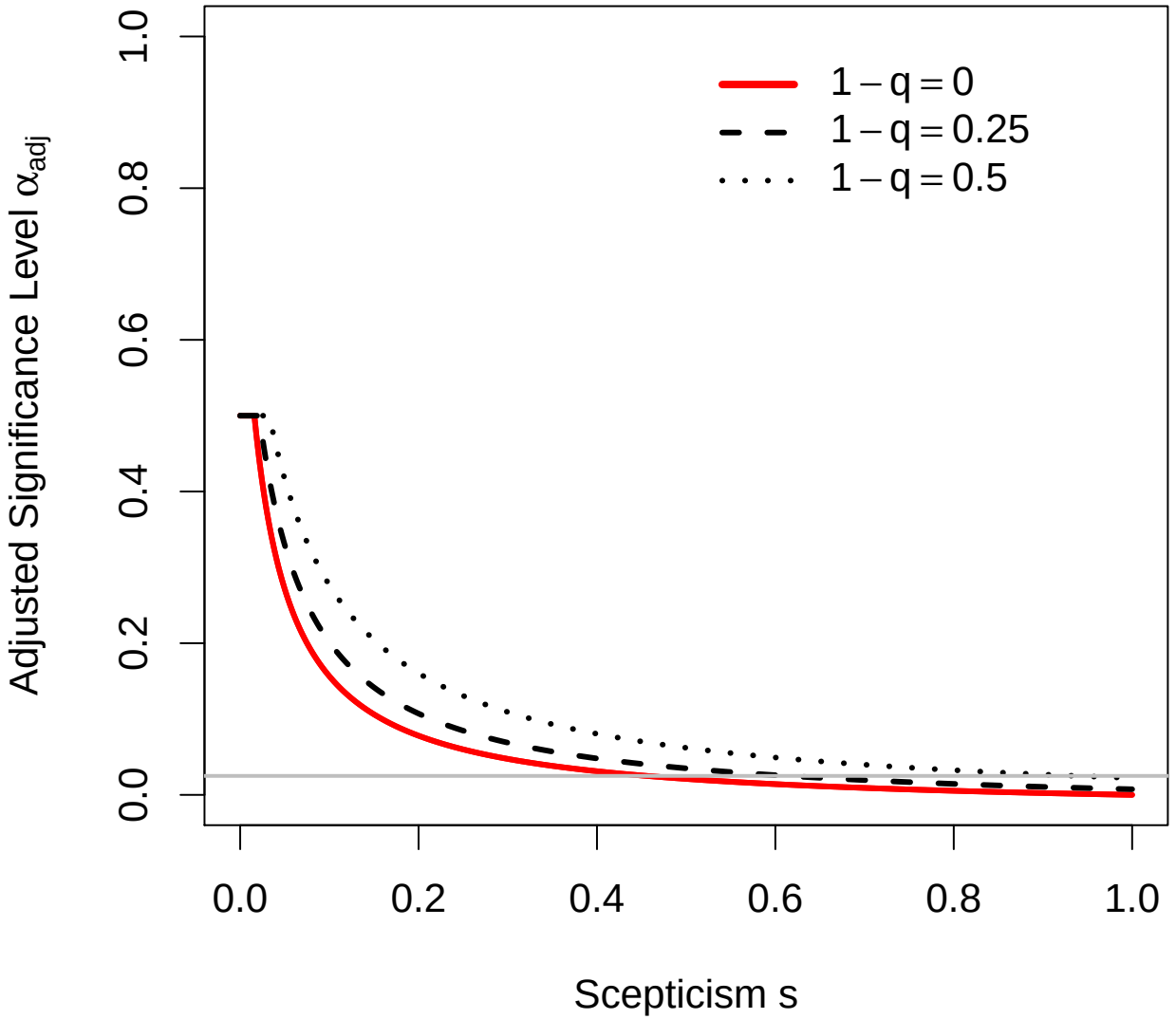

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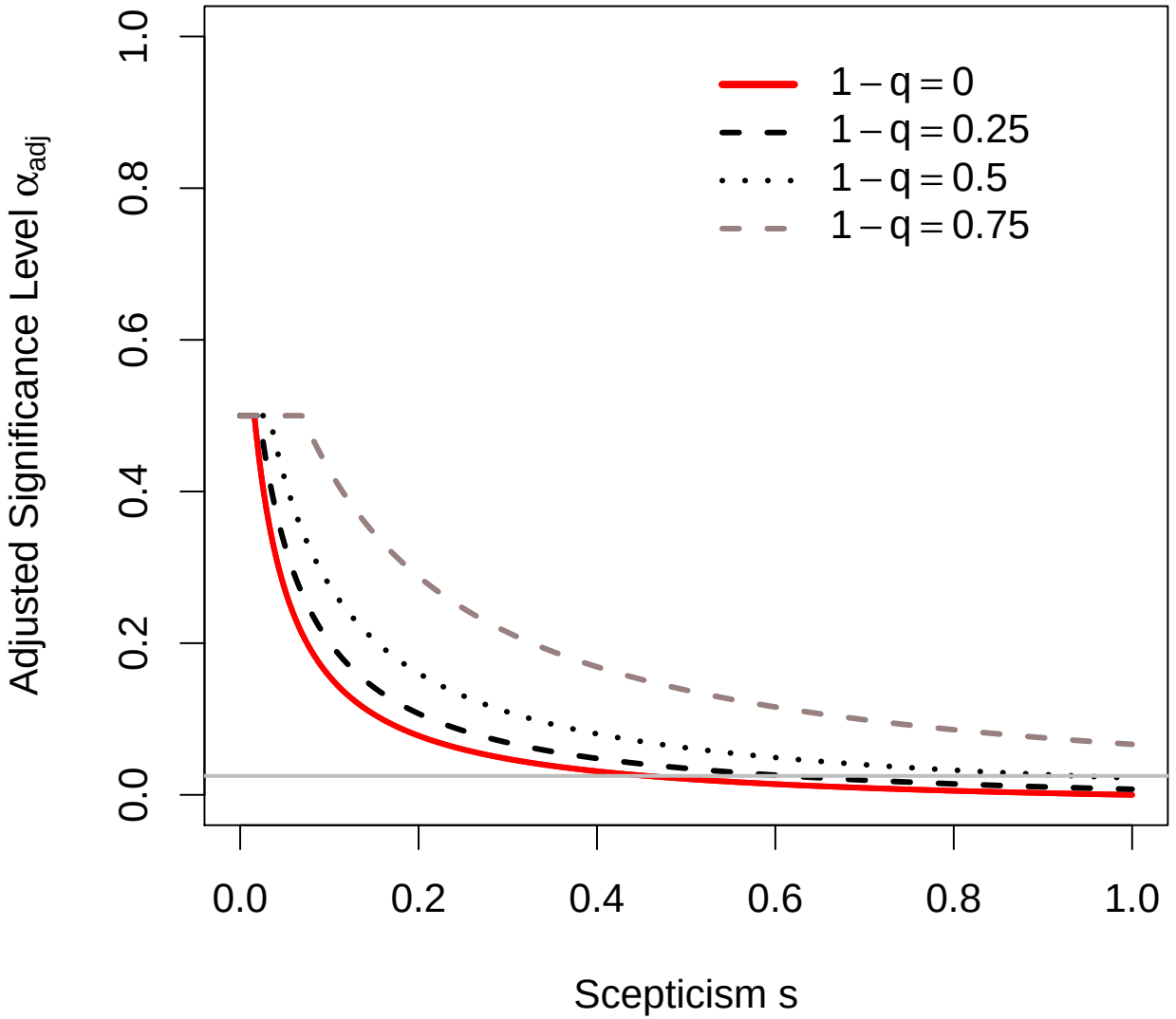

- Power for the paediatric study $1 - \beta_c = 0.8$
- Confidence in efficacy in adults $1 - \gamma_a = 0.973$
- Targeted confidence in efficacy in children $1 - \gamma_c = 0.973$
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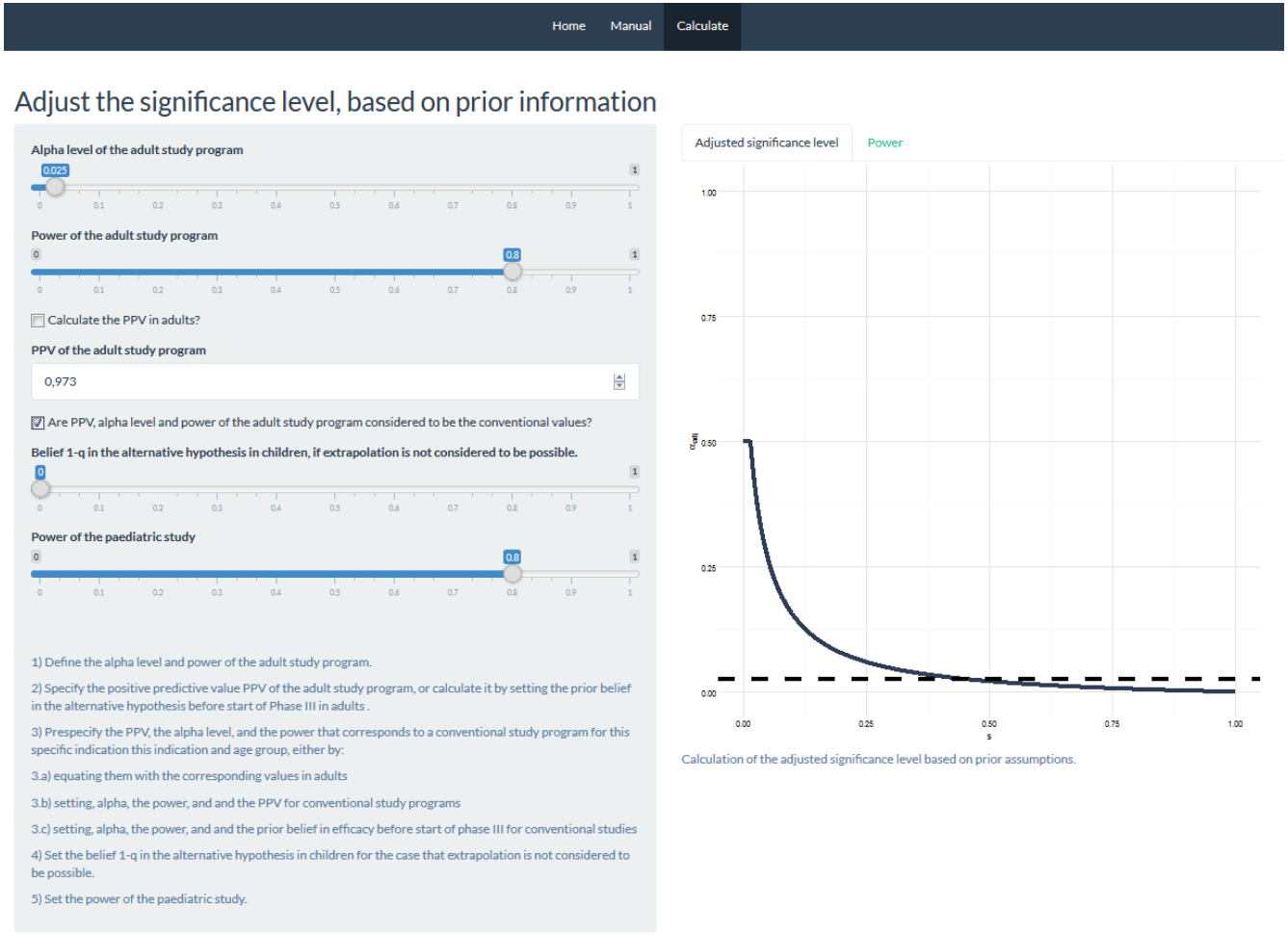
Online R-Shiny Extrapolation Application



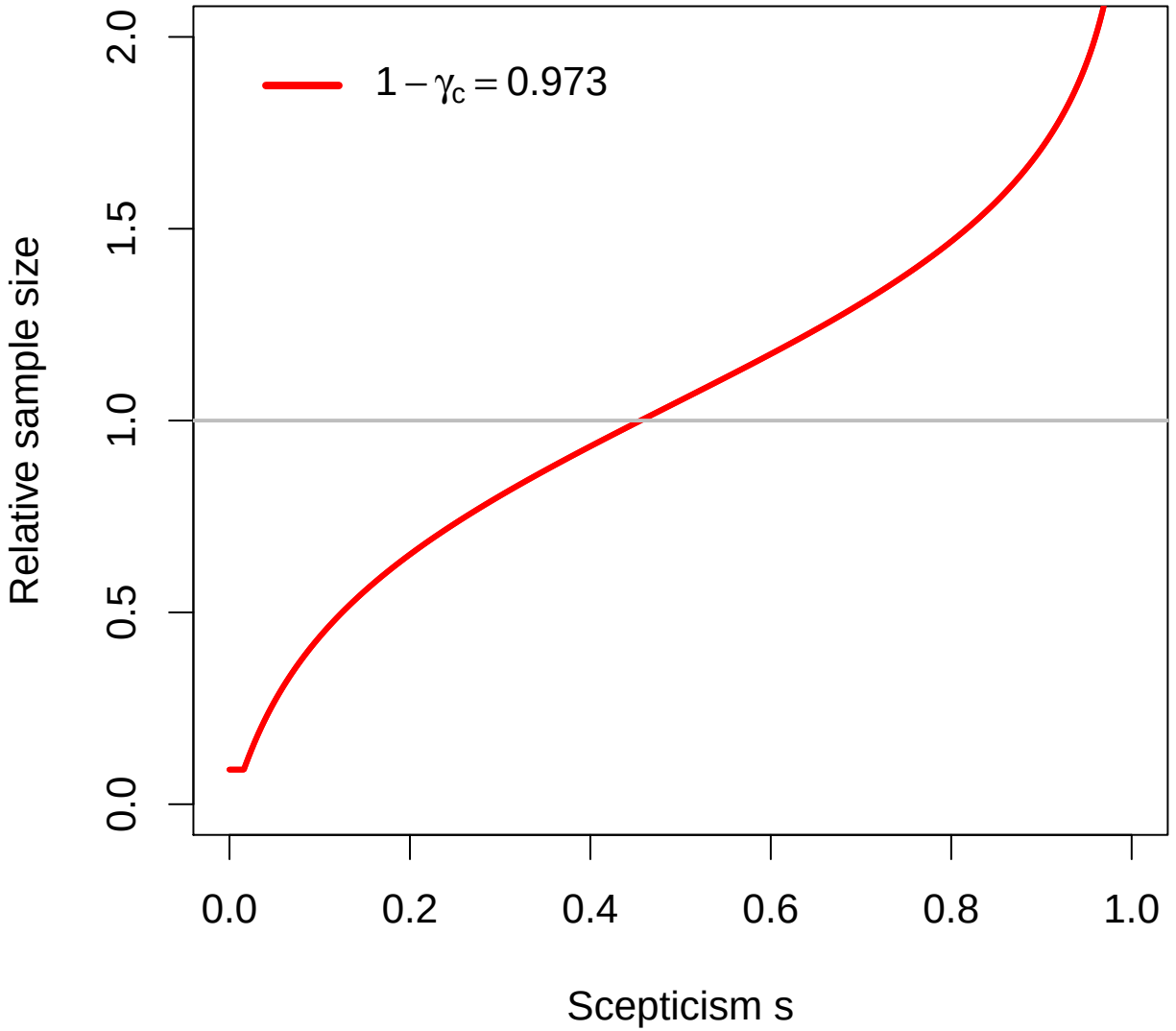
- R-Shiny Extrapolation App by Gerald Hlavin (beta-version)
- http://www.ideal-apps.rwth-aachen.de:3838/Extrapolation/

Impact on sample sizes needed

For example

- RCT with two treatment arms (experimental vs control)
- Compare
  - Extrapolation Approach using adjusted level (depending on s)
  - Standard RCT at one-sided level $\alpha = 0.025$
- both powered at 80%

Impact on sample sizes needed for RCT with 2 arms



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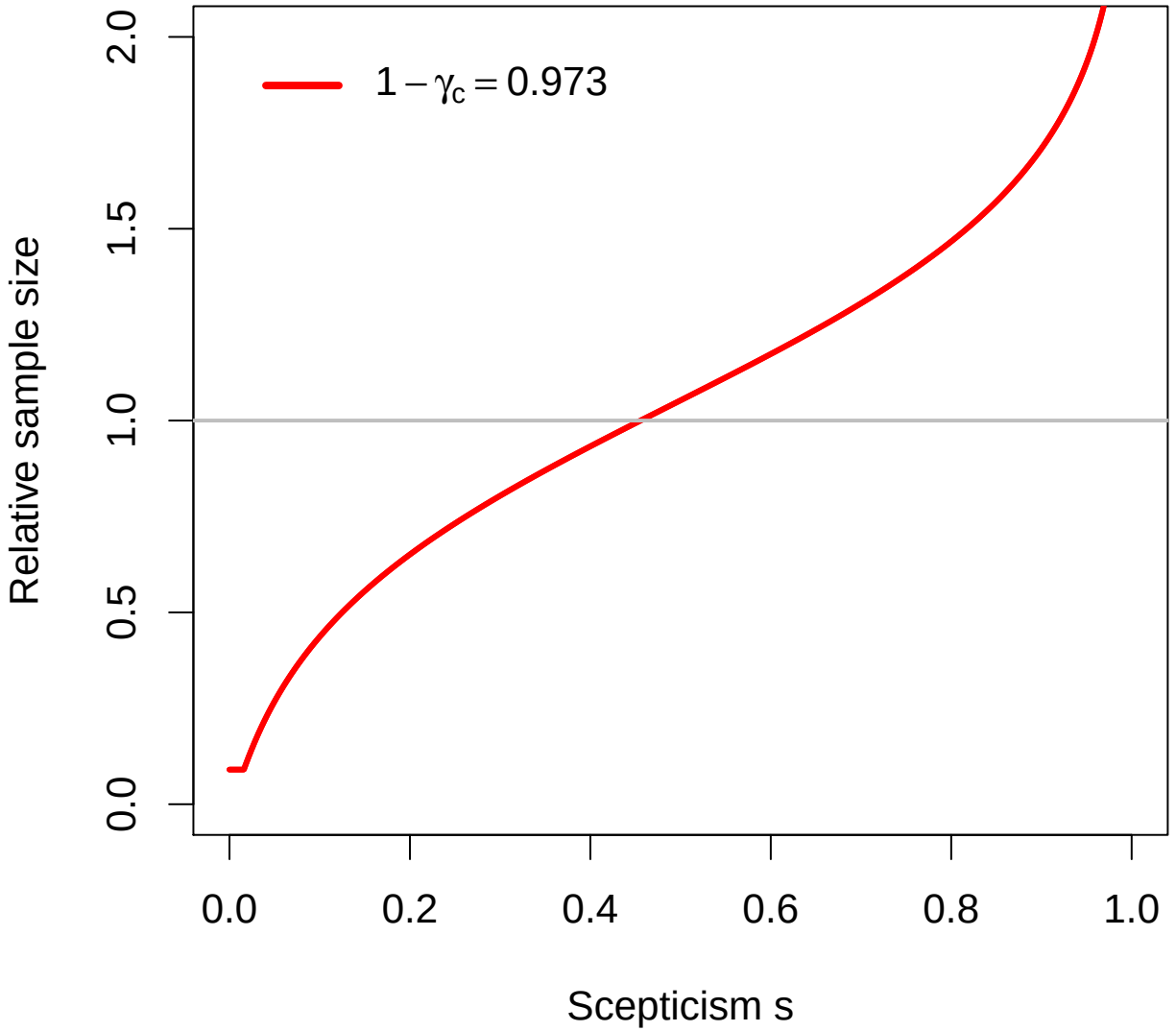

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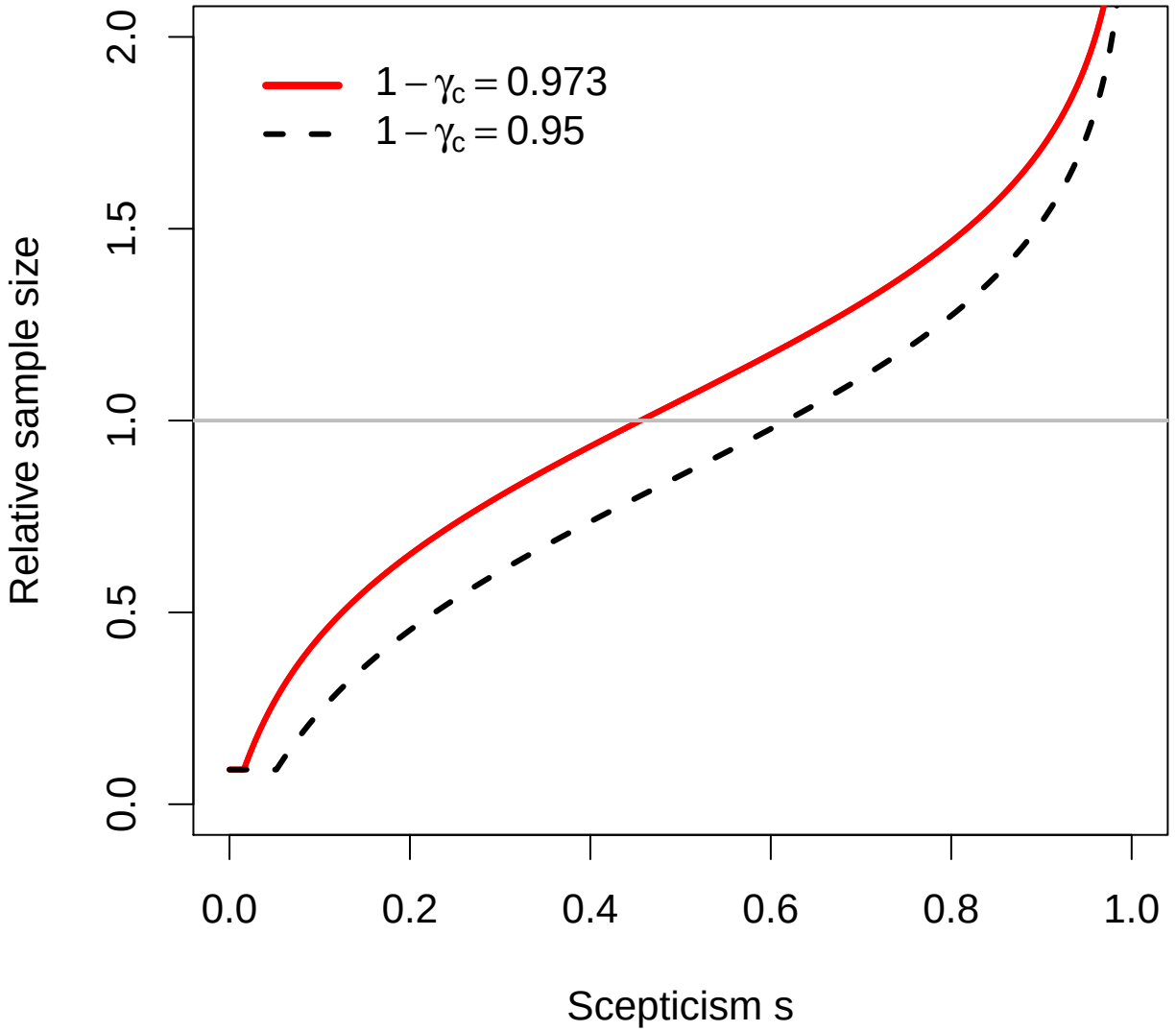

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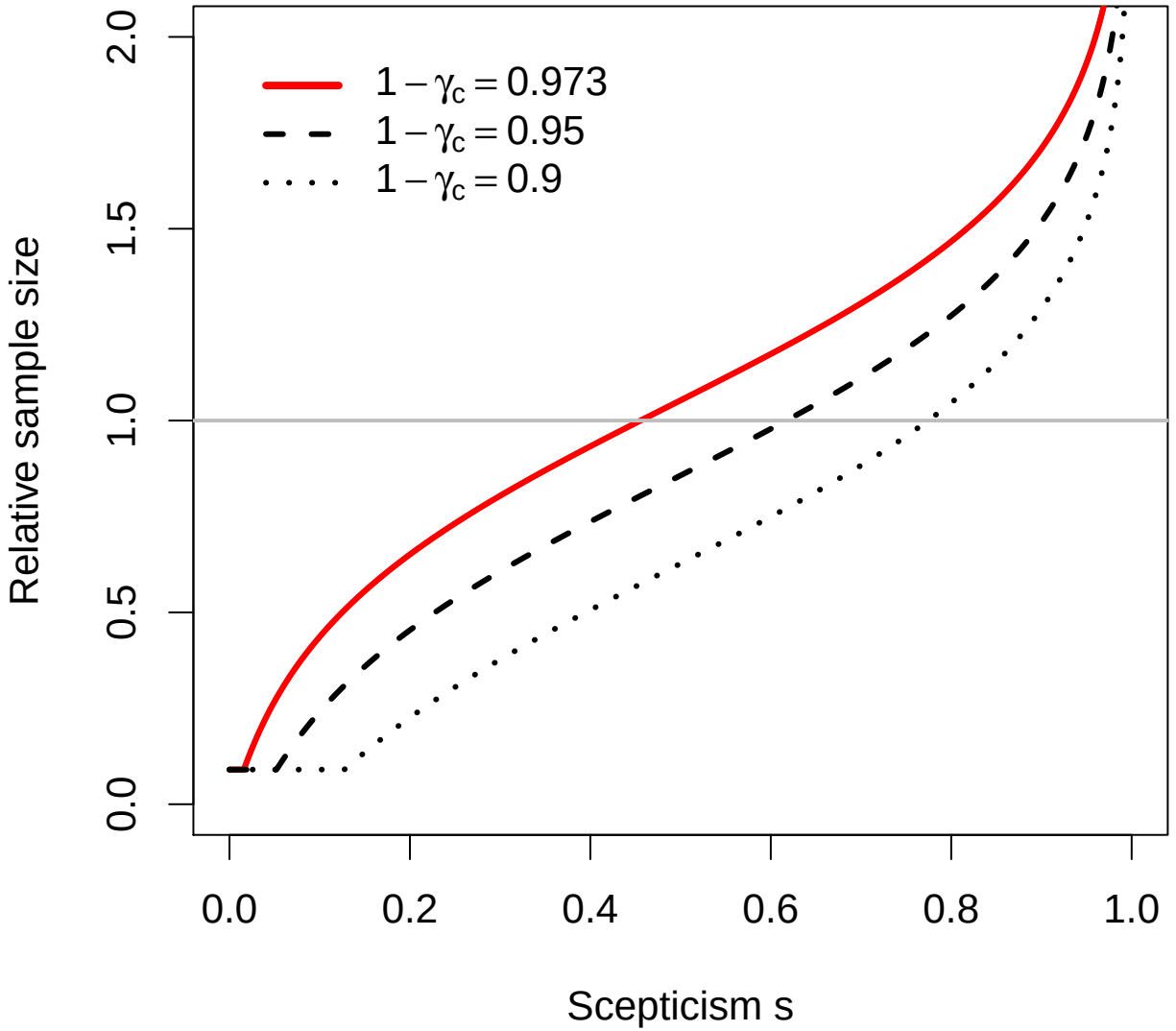

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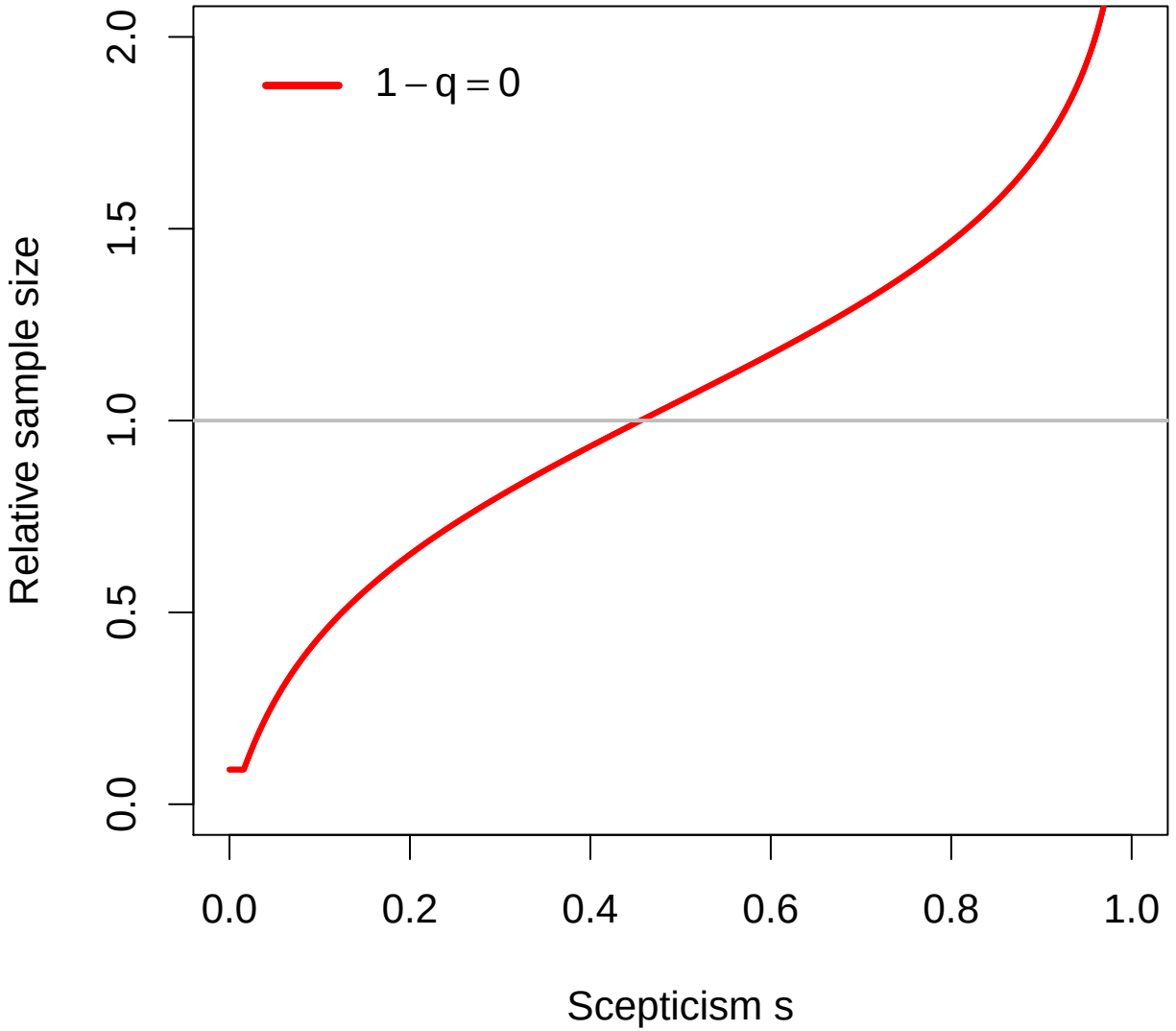

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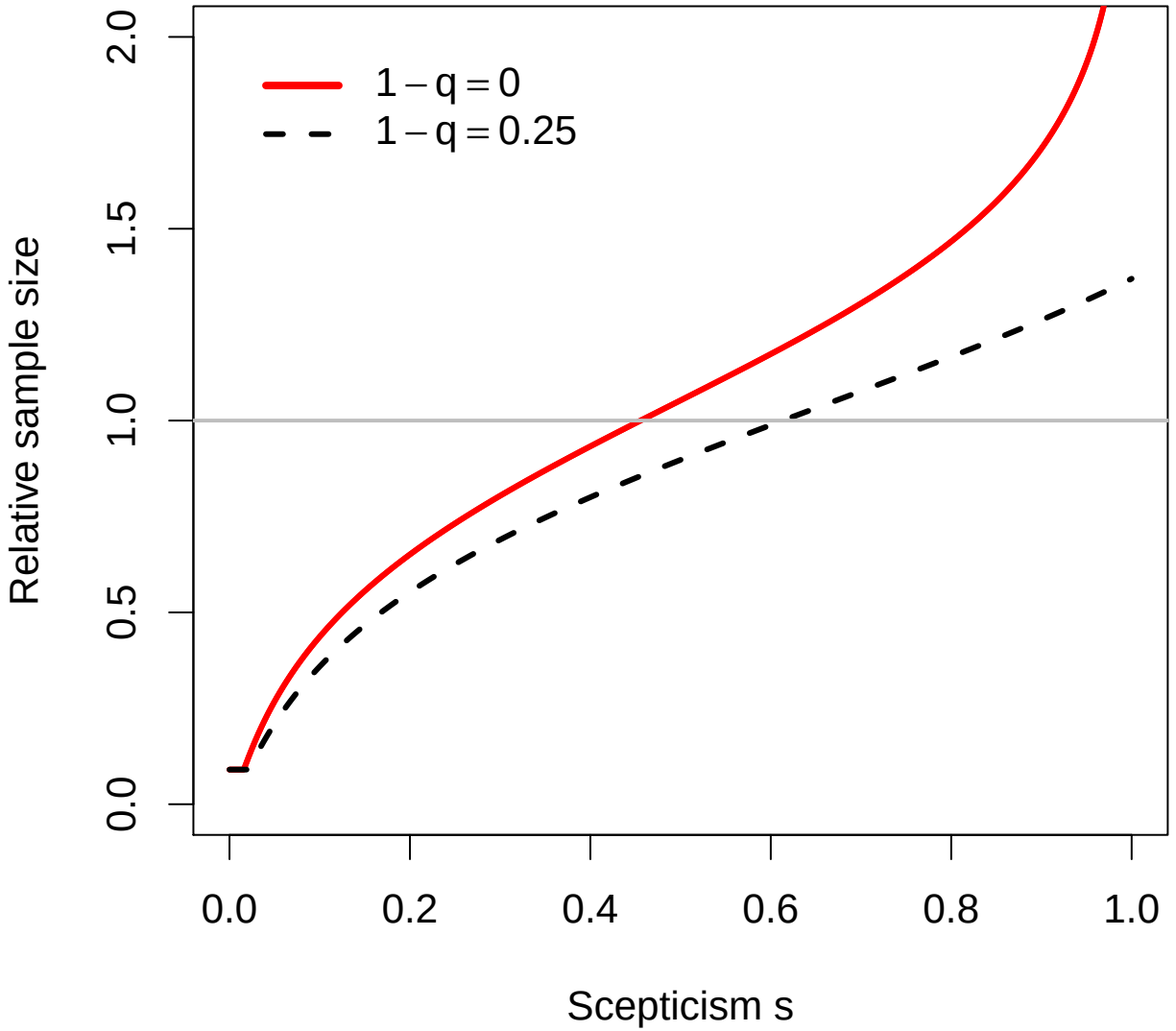

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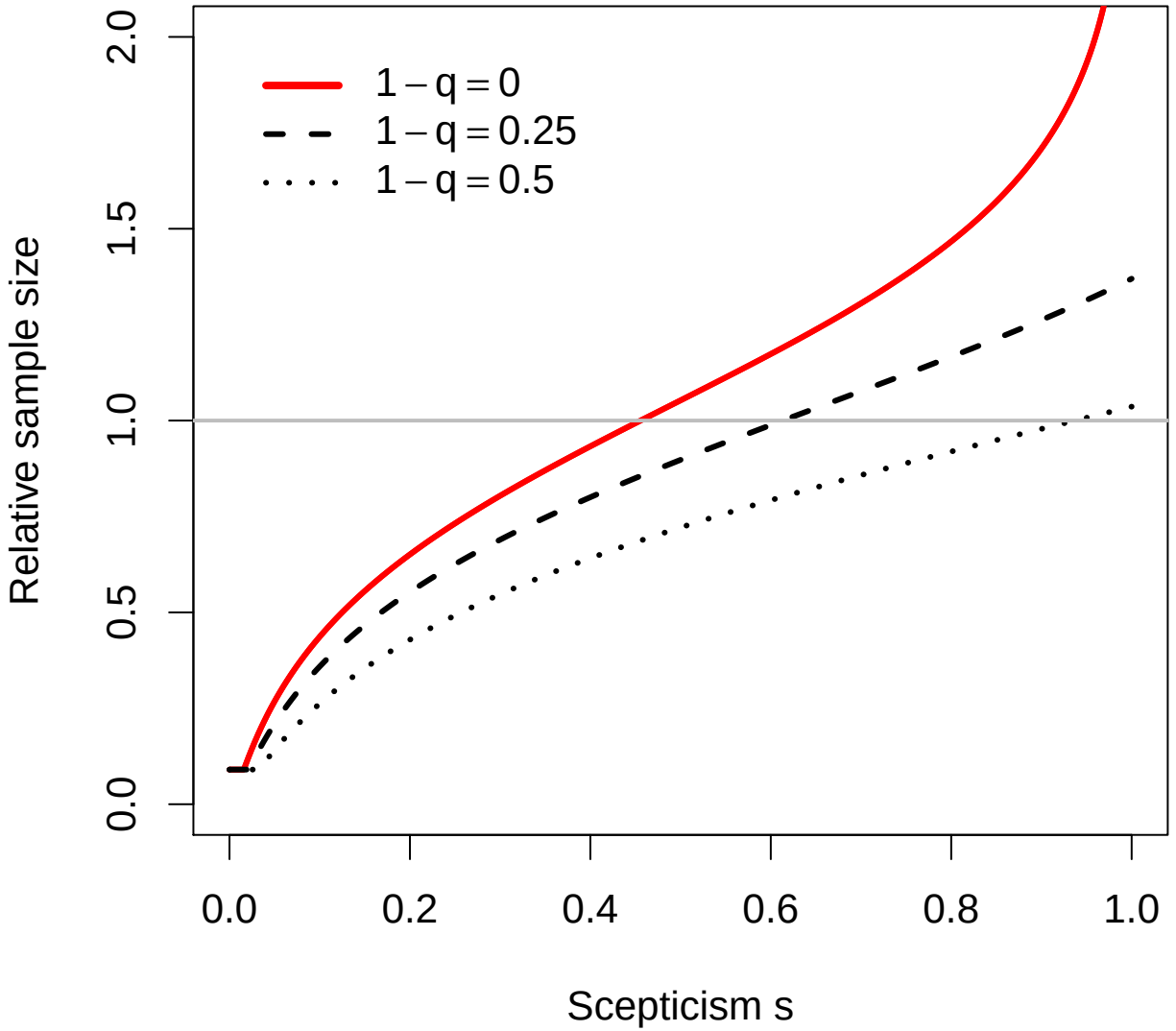

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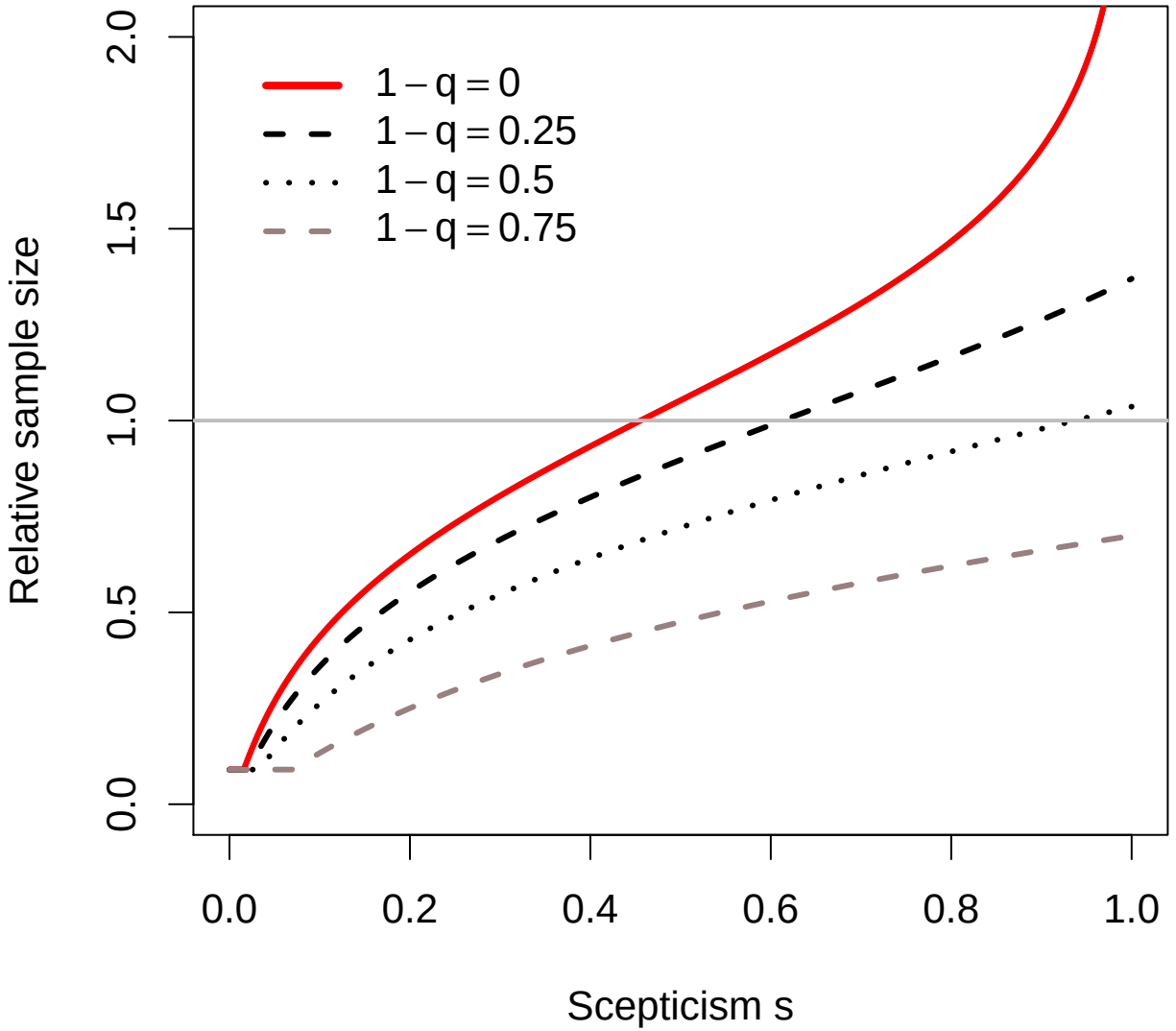

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RCTs or single arm trial?

STATE OF THE ART

"Threshold-crossing": A Useful Way to Establish the Counterfactual in Clinical Trials?

H-G Eichler[1], B Bloechl-Daum[2], P Bauer[3], F Bretz[4], J Brown[5], LV Hampson[6], P Honig[7], M Krams[8], H Leufkens[9], R Lim[10], MM Lumpkin[11], MJ Murphy[12], F Pignatti[1], M Posch[3], S Schneeweiss[13], M Trusheim[14] and F Koenig[3]

A central question in the assessment of benefit/harm of new treatments is: how does the average outcome on the new treatment (the factual) compare to the average outcome had patients received no treatment or a different treatment known to be effective (the counterfactual)? Randomized controlled trials (RCTs) are the standard for comparing the factual with the counterfactual. Recent developments necessitate and enable a new way of determining the counterfactual for some new medicines. For select situations, we propose a new framework for evidence generation, which we call "threshold-crossing." This framework leverages the wealth of information that is becoming available from completed RCTs and from real world data sources. Relying on formalized procedures, information gleaned from these data is used to estimate the counterfactual, enabling efficacy assessment of new drugs. We propose future (research) activities to enable "threshold-crossing" for carefully selected products and indications in which RCTs are not feasible.

What is the counterfactual?

The human condition is an uncontrolled experiment. Socrates once advised a young man who asked whether he should get married: "Do as you wish, you will likely regret, no matter what you choose." Why would the sage expect his friend to have postdecision blues? Whatever road the young man takes, he would certainly experience the consequences of his action (the factual) but there is no way he could learn the—possibly superior—consequences of the road not taken (the counterfactual). One might argue that the young man could still explore the counterfactual by marrying later in life or getting a divorce. However, this argument is flawed because the comparison between an early-in-life event with a late-in-life event is inadmissible; in modern research terms, the comparison is confounded. Alas, we shall rarely know the counterfactuals in our lives, the road not taken.

The assessment of the causal effects (benefits and harms) of any treatment revolves around the same question: how does the outcome of (test) treatment (the factual) compare to "what would have happened [if patients] had not received the test treatment or if they had received a different treatment known to be effective"[1] (the counterfactual)? The question is asked by clinicians treating individual patients and by population-level decision-makers, including drug developers, regulators, health technology assessment (HTA) bodies, and payers of health care. However, the counterfactual outcomes of individual patients can rarely be observed. Decision-makers must instead focus on comparing average population counterfactual outcomes between different interventions (which are estimable) to deduce causal effects on a population (see **Table 1**[2–11] for review of the concept of the counterfactual and how it underpins the definition of a causal treatment effect).

How does the concept of the counterfactual underpin the definition of a causal treatment effect? Here, we review the current ways of estimating the counterfactual to enable the assessment of causal treatment effects. We reflect on how scientific and societal developments necessitate and enable a new way of determining the counterfactual for some new medicines. We then propose a new framework for evidence generation, which we will refer to as "threshold-crossing." Finally, we propose future research and other activities to enable a move toward threshold-crossing for

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- EMA data transparency initiative
- make use of available data
- protocol to select controls
- define threshold
- single arm trial
- comparison against threshold (and historical controls)
- http://dx.doi.org/10.1002/cpt.515 (open-access)

Case Study

To demonstrate, how to determine

- s
- q
- r
- ...

Unfortunately, there is no real case study yet.

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- s
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- r
- ...

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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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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

How to quantify similarity?

Slide from C Male, GRIP Workshop, Glasgow, June 2013

Challenges in a Potential Regulatory Application

- Estimation of the parameters based on robust evidence synthesis methods taking into account pharmacometric modelling.
- 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.

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)

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?

Summary

Our framework formally incorporates prior information and expert knowledge, while still applying frequentist testing albeit at a modified significance level.

Other selected highlights [and collaborators] in WP4

- How to incorporate safety data in adapting the significance level?

  [Hlavin, Hampson]
- Extensions of MCPMod to allow
  - confirmatory testing (Closed MCPMod)
  - adaptive interim analysis using combination tests

  [Krazsnozhon, Bornkamp, Glimm, Bretz, Wassmer]
- Issues with response adaptive designs in small populations

  [Krazsnozhon, Rosenberger, Heussen, Hilgers]
- Issues in adaptive designs with time-till-event endpoints

  [Magirr, Jaki, Posch, Brueckner]
- Targeted theraphies: subgroup identification and confirmatory testing

  [Posch, Graf, Ondra, Burman, Jobjoernsson, Beckman, Stallard, Sugitani, Bogdan, Frommlet]

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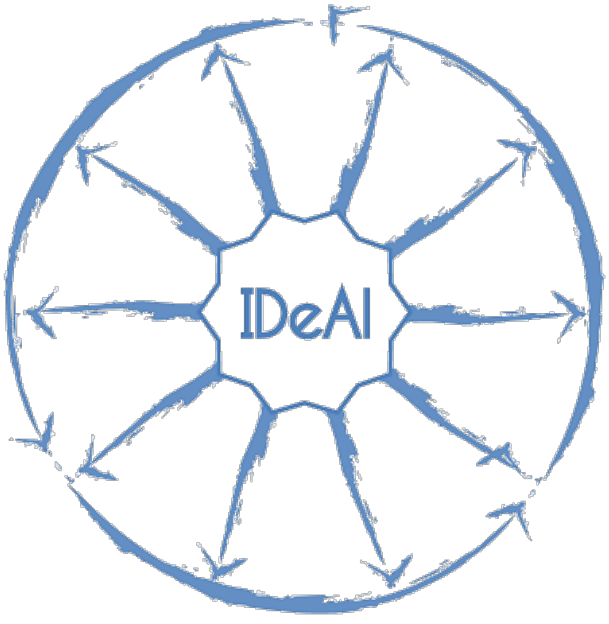
Thank you for your attention!



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