

Evidence synthesis for a single randomized controlled trial and observational data in small populations

Steffen Unkel, Christian Röver and Tim Friede

Department of Medical Statistics
University Medical Center Göttingen, Germany



Motivation

- **Randomized controlled trials (RCTs)** are widely accepted as the gold standard design of clinical research to assess therapeutic interventions.
- Usually two independent RCTs are required to demonstrate efficacy and safety for marketing authorization.
- In **small populations** the conduct of a single RCT with a sufficient sample size might be extremely difficult or not feasible.
- This is particularly the case
 - 1 in paediatric studies,
 - 2 if the intervention is to treat a rare disease, or
 - 3 if randomization is challenging.

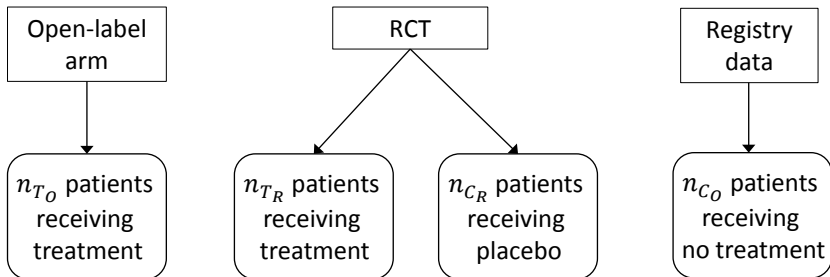
Alport syndrome

- **Alport syndrome** (AS) is a rare genetic disorder that inevitably leads to end-stage kidney disease.
- There is no known cure for AS. About 50% of patients develop end-stage kidney disease by the age of 20 years.
- Observational data suggest that the angiotensin-converting enzyme inhibitor **ramipril** delays renal failure and improves life-expectancy in Alport patients with proteinuria.
- The ongoing **EARLY PRO-TECT Alport study** is the first double-blind RCT that assesses the safety and efficacy of early therapy onset with ramipril in paediatric Alport patients ([ClinicalTrials.gov identifier: NCT01485978](https://clinicaltrials.gov/ct2/show/study/NCT01485978)).

The EARLY PRO-TECT trial and observational data

- The **course of the disease**, its **hereditary nature** and **persuasive observational data** affect the willingness of patients to consent to randomization.
- One could randomize patients in a 2:1 ratio to ramipril or placebo and combine the treatment effect estimate in the control arm with **Alport registry data**.
- Alport registries:
 - ① **Alport Syndrome Treatments and Outcomes Registry (ASTOR)**, located at the University of Minnesota.
 - ② **European Alport Therapy Registry** - European Initiative Towards Delaying Renal Failure in Alport Syndrome.
- In addition, evidence from an **open-label arm** of patients receiving ramipril will be available.

Trial design



Data

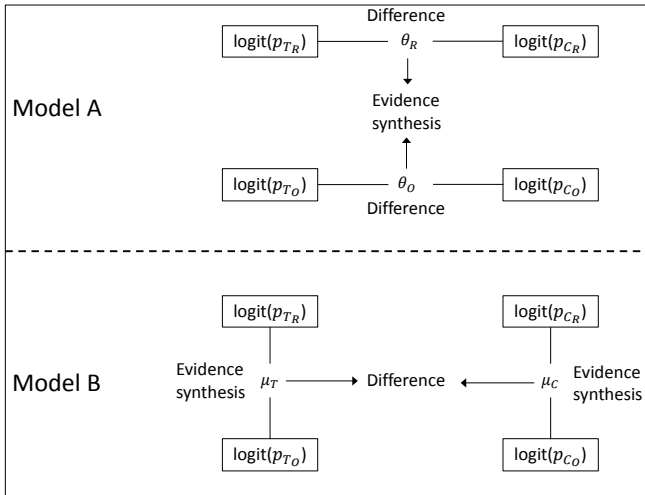
- We consider a **binary** endpoint.
- **Randomized arms**: let X_{iR} be the number of events and p_{iR} denote the probability of an event in group i ($i = T, C$).
- **Non-randomized arms**: let X_{iO} be the number of events and p_{iO} denote the probability of an event in group i ($i = T, C$).

- **Binomial model**:

$$X_{ij} \sim \mathcal{B}(n_{ij}, p_{ij}) \quad , \quad i = T, C; j = R, O \quad .$$

- Let $\theta_R = \log \left(\frac{p_{TR}(1-p_{CR})}{p_{CR}(1-p_{TR})} \right)$ and $\theta_O = \log \left(\frac{p_{TO}(1-p_{CO})}{p_{CO}(1-p_{TO})} \right)$ denote the **log odds ratio** for the randomized and observational data, respectively.

Model frameworks



Evidence synthesis

- The **hierarchical structure of model A** may be stated as

$$y_j | \theta_j, s_j \sim \mathcal{N}(\theta_j, s_j^2) ,$$
$$\theta_j | \mu, \tau \sim \mathcal{N}(\mu, \tau^2) , \quad j = R, O ,$$

where y_j is an estimate of θ_j and s_j is its standard error.

The θ_j differ from study to study and are distributed around a **common mean** μ with **between-study-type variability** or **heterogeneity** τ .

- The framework for **model B** consists of **two hierarchical structures** with parameters (μ_T, τ_T) and (μ_C, τ_C) .

The overall treatment effect is computed as a contrast: $\mu_T - \mu_C$.

Generating data

RCT	Treatment	Control
No event	31	9
Event	9	11
Σ	$n_{TR} = 40$	$n_{CR} = 20$

Observational data	Treatment	Control
No event	29	29
Event	11	31
Σ	$n_{TO} = 40$	$n_{CO} = 60$

Log odds ratio $y_R = 1.4374$
Standard error $s_R = 0.5877$

Log odds ratio $y_O = 1.0361$
Standard error: $s_O = 0.4383$

Fitting model A

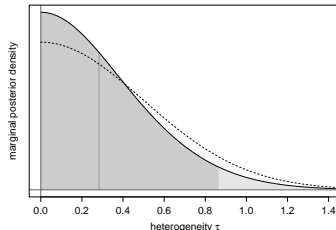
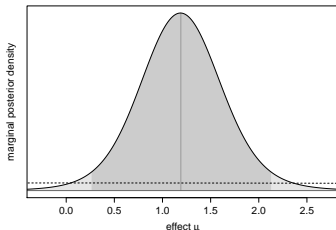
- We use a **Bayesian approach** for fitting the hierarchical models.
- Inference for μ and τ is captured by the joint **posterior distribution**, from which the marginal distribution of μ is used to derive point estimates and probability intervals for μ .
- Our approach requires **prior distributions** for μ and τ :
 - For μ one may use a noninformative (improper) uniform prior or a normal prior with mean zero and large variance.
 - For τ we use half-normal (HN) prior distributions.
- The R package `bayesmeta` provides a collection of functions to facilitate Bayesian inference in the random-effects meta-analysis model.

Fitting model A (2)

- `bma <- bayesmeta(y, s, mu.prior.mean=0, mu.prior.sd=10, tau.prior=function(t){dhalfnormal(t,scale=0.5)})`

- Marginal posterior summary:

	tau	mu
mode	0.0000	1.1870
median	0.2833	1.1960
mean	0.3428	1.1931
sd	0.2680	0.4699
95% lower	0.0000	0.2637
95% upper	0.8651	2.1278



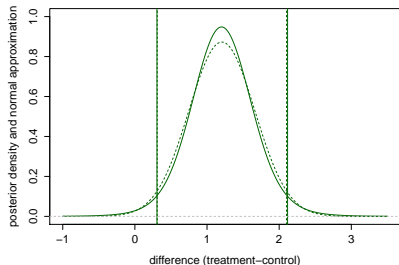
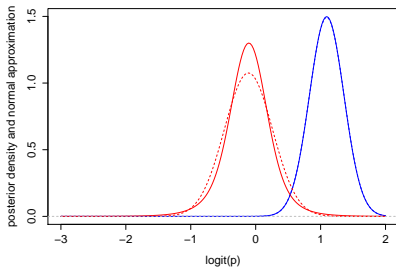
Fitting model B

- Compute estimates for the logits(p_{ij}) ($i = T, C; j = R, O$) and associated standard errors.
- ```
bma.t <- bayesmeta(y=yt, s=st, labels=names(yt),
 mu.prior.mean=0, mu.prior.sd=10,
 tau.prior=function(t){dhalfnormal(t, scale=0.1)})

bma.c <- bayesmeta(y=yc, s=sc, labels=names(yc),
 mu.prior.mean=0, mu.prior.sd=10,
 tau.prior=function(t){dhalfnormal(t, scale=0.5)})
```
- Compute the **convolution**, that is, the distribution of the difference (treatment - control).

# Fitting model B (2)

|   |            |                |         |        |
|---|------------|----------------|---------|--------|
| • | Difference |                | Model A |        |
|   | mean       | standard error | mean    | sd     |
|   | 1.2056     | 0.4571         | 1.1931  | 0.4699 |



|   |               |        |        |
|---|---------------|--------|--------|
| • |               | 2.5%   | 97.5%  |
|   | Normal approx | 0.3097 | 2.1015 |
|   | Convolution   | 0.3059 | 2.1165 |
|   | Model A       | 0.2637 | 2.1278 |

## Summary and future work

- We have synthesized evidence from a single RCT and observational data in small populations.
- External data that can be used on the
  - ① experimental arm could come from an additional non-randomized arm receiving the treatment;
  - ② on the control arm could come from a registry.
- Recent computational advances in evidence synthesis facilitate the application of hierarchical models.
- A meta-analysis of only two studies is a challenging problem, in particular the choice of a prior distribution for  $\tau$ .
- Current work involves the inclusion of covariates and the comparison of the performance of model frameworks A and B.
- In the future, we will also consider continuous and time-to-event endpoints.

## References



Welton, N. J., Sutton, A. J., Cooper, N. J. et al. (2012):  
*Evidence Synthesis for Decision Making*, Wiley.



Röver, C. et al. (2015):  
bayesmeta: Bayesian Random-Effects Meta-Analysis, R package version 1.1,  
<https://cran.r-project.org/package=bayesmeta>.



Gross, O. et al. (2012a):  
Safety and efficacy of the ACE-inhibitor ramipril in Alport syndrome: The double-blind, randomized, placebo-controlled, multicenter phase III EARLY PRO-TECT Alport trial in pediatric patients, *ISRN Pediatrics*, Volume 2012, Article ID 436046, 6 pages.



Gross, O. et al. (2012b):  
Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy, *Kidney International*, Vol. 81, pp. 494-501.



Unkel, S., Röver, C., Gross, O. and Friede, T. (2016):  
A Bayesian hierarchical framework for evidence synthesis for a single randomized controlled trial and observational data in small populations, in preparation.