Generalised evidence synthesis for clinical trials in small patient populations

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InSPiRe
Innovative methodology for small populations research

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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 even 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 recruitment is challenging.

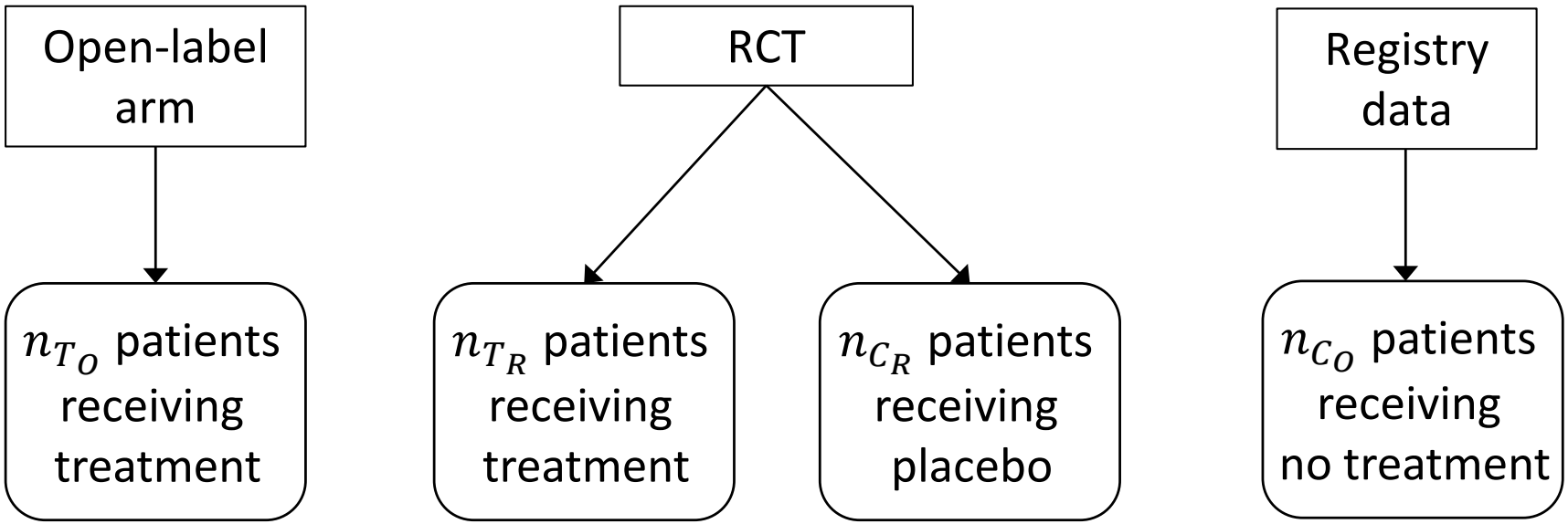
Alport syndrome

- 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).

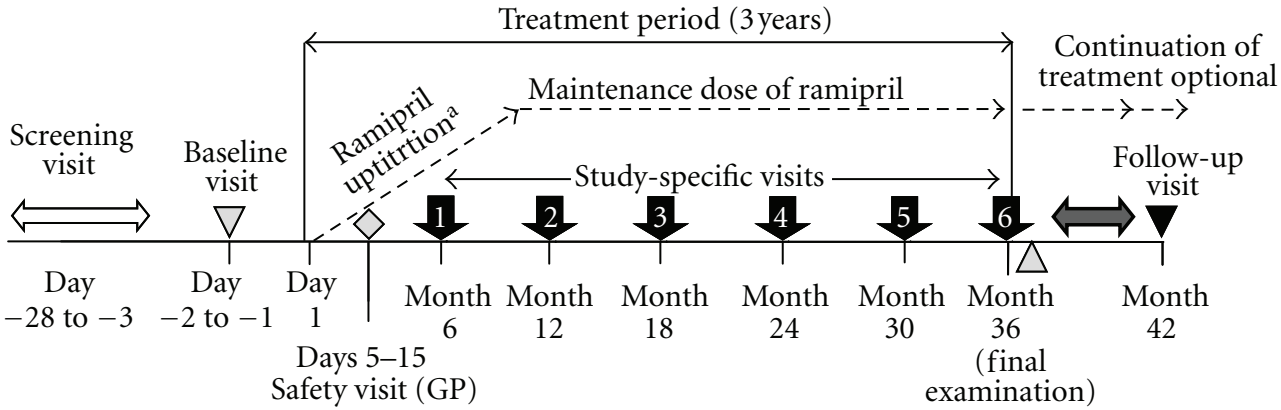
The EARLY PRO-TECT trial and observational data

- The course of the disease and its hereditary nature 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



Study visits for the individual patient (Gross et al. 2012a)



Screening assessments on day −28 to day −3 days prior to first dosing occasion (day 1)

Baseline assessments: history, physical exam, vital signs, safety labs, renal function, adverse events, concomitant medications, and so on

Safety assessment at patient's GP to assess drug tolerability during uptitration of study drug

Study-specific safety and efficacy assessments

Follow-up period of 6 months after last study-specific dosing occasion or premature study termination

Repeat assessment of renal function at patient's GP within 1 week of final examination (month 36)

Follow-up visit at 6 months after last study-specific dosing occasion or premature study termination

[a]Uptitration from day 1 for patients randomised to receive ramipril. Placebo patients with disease progression will be uptitrated upon progression. Patients who have been pretreated with an ACEi will start at a higher dose of ramipril.

Endpoints

- The primary efficacy endpoint in the EARLY PRO-TECT Alport trial is "time-to-progression to the next disease level".
- This time-to-event endpoint will be assessed in 6-monthly intervals over the treatment period of 3 years.
- The second efficacy endpoint "albuminuria after 3 years corrected for baseline albuminuria for patients randomized to receive ramipril compared to placebo" is continuous.
- One might also think of binary endpoints such as "progression to the next disease level within 3 years (yes/no)".

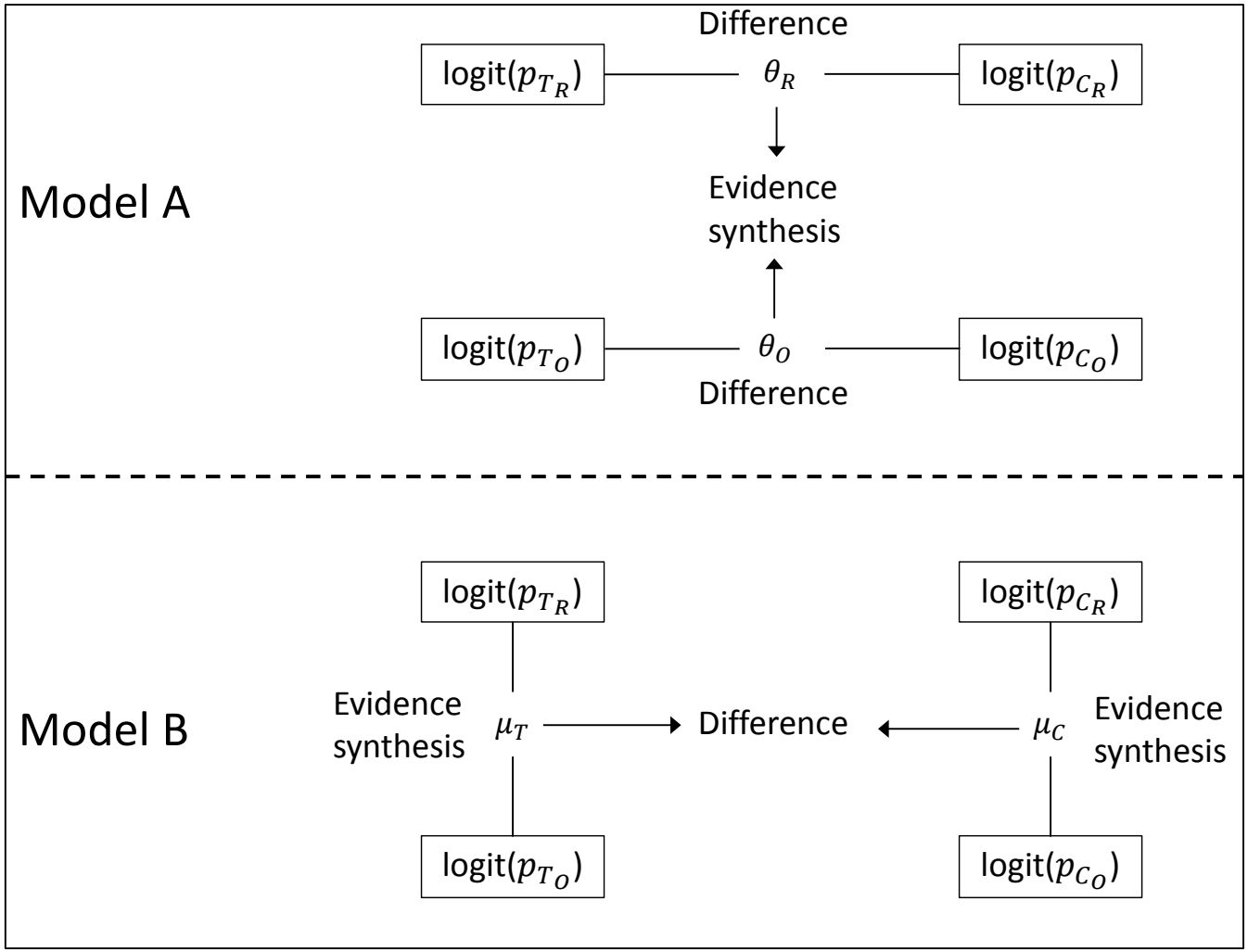
Data and treatment effects

- Randomized arms: let X_{i_R} be the number of events and p_{i_R} denote the probability of an event in group i $(i = T, C)$.
- Non-randomized arms: let X_{i_O} be the number of events and p_{i_O} denote the probability of an event in group i $(i = T, C)$.
- Binomial model:

$$X_{T_R} \sim \mathcal{B}(n_{T_R}, p_{T_R}) \ , \quad X_{C_R} \sim \mathcal{B}(n_{C_R}, p_{C_R}) \ ,$$
$$X_{T_O} \sim \mathcal{B}(n_{T_O}, p_{T_O}) \ , \quad X_{C_O} \sim \mathcal{B}(n_{C_O}, p_{C_O}) \ .$$

- Let $\theta_R = \log\left(\frac{p_{T_R}(1-p_{C_R})}{p_{C_R}(1-p_{T_R})}\right)$ and $\theta_O = \log\left(\frac{p_{T_O}(1-p_{C_O})}{p_{C_O}(1-p_{T_O})}\right)$ denote the logarithmic odds ratio for the randomized and observational data, respectively.

Models for evidence synthesis



Methods for incorporating external data

1. The power prior approach assigns a weight to the external data somewhere in between the cases of irrelevance and full equality.

2. Bias allowance models assume that the external data are potentially biased.

3. Meta-analytic approaches or hierarchical models for evidence from different study designs are an extension of standard random-effects meta-analysis that explicitly model between-study-type variability.

Hierarchical model

- The random-effects meta-analysis model may be stated as

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

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

- There are two unknown parameters, namely the mean effect μ and the between-study-type variability or heterogeneity τ.

- Alternatively, the model may be formulated 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 the θ_j differ from study to study and are distributed around a common mean μ with standard deviation τ.

Generating data

RCT	Treatment	Control
No event	31	9
Event	9	11
$\sum$	$n_{T_R} = 40$	$n_{C_R} = 20$

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

Observational data	Treatment	Control
No event	29	29
Event	11	31
$\sum$	$n_{T_O} = 40$	$n_{C_O} = 60$

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

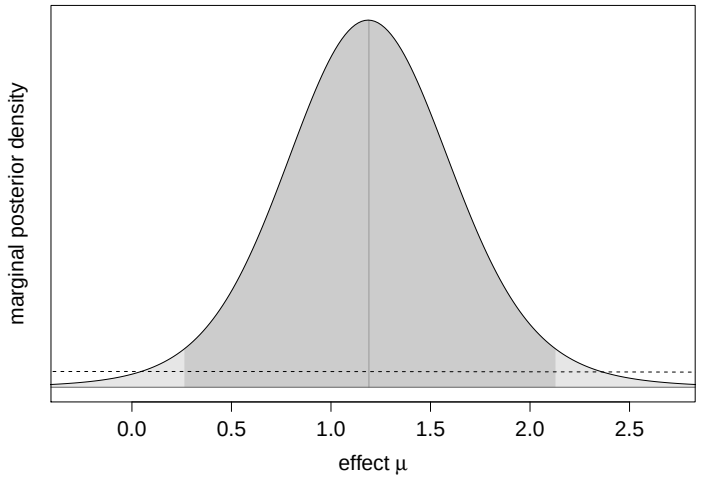
Fitting model A

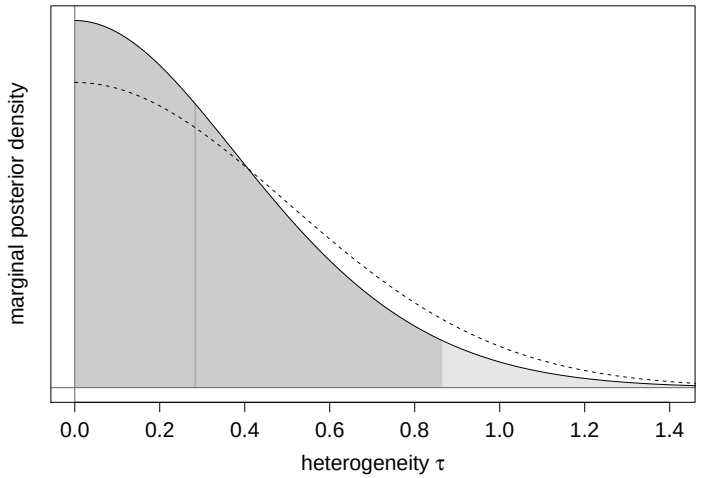
- We use a Bayesian approach for fitting the hierarchical model.
- Inference for μ and τ is captured by the joint posterior distribution, from which the marginal distribution of μ is used to derive point estimates and probability intervals for μ.
- Our approach requires prior distributions for μ and 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_{i_j}) ($i = T, C; j = R, O$) 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).
  ```

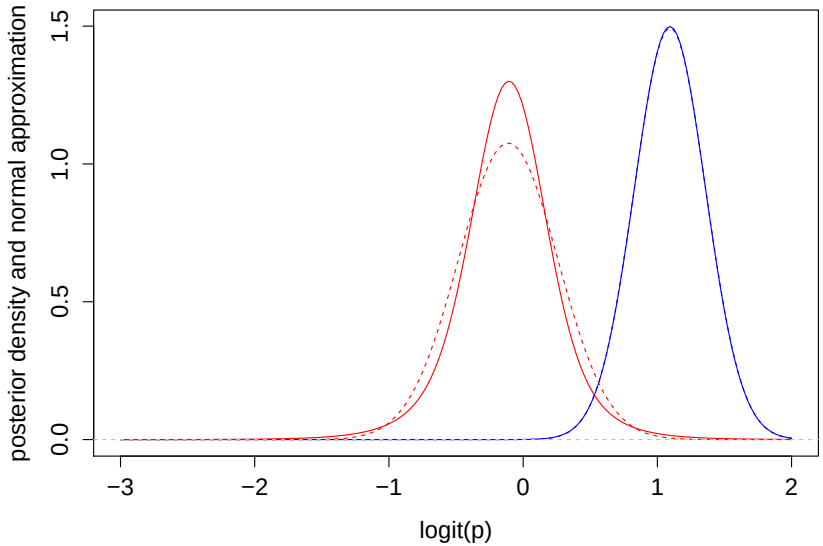
Fitting model B (2)

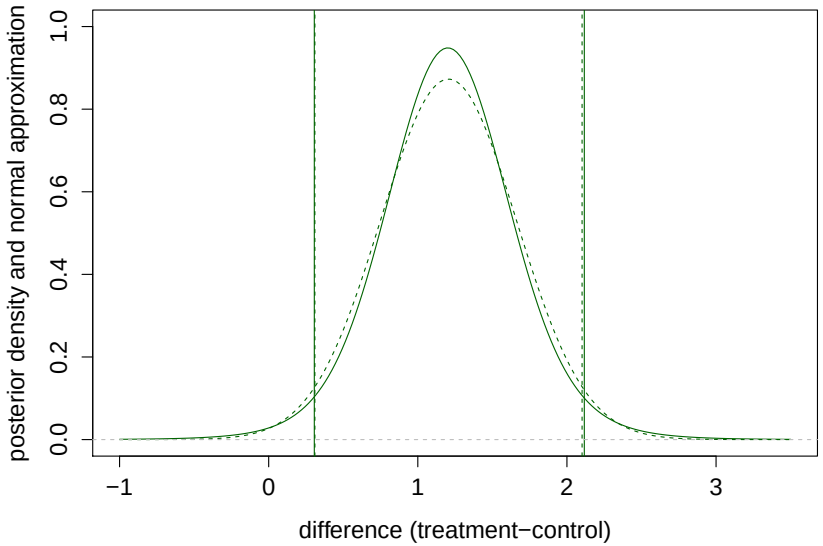
- Difference

mean	standard error
1.2056	0.4571

Model A

mean	sd
1.1931	0.4699





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	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 τ.
- What is the best method to deal with confounding?
- In the future, we will also consider continuous and time-to-event endpoints.

References


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Evidence in rare conditions

RESEARCH | OPEN ACCESS

Systematic reviews in paediatric multiple sclerosis and Creutzfeldt-Jakob disease exemplify shortcomings in methods used to evaluate therapies in rare conditions

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The European Medicines Agency's perspective

European Medicines Agency

London, 27 July 2006
Doc. Ref. CHMP/EWP/83561/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

"Studies with few patients are often perceived as presenting a rather simple situation: there is not much information (data) and so simple (often descriptive) analyses are all that are warranted. It seems quite counterintuitive, therefore, that for 'simple' situations more complex approaches should be applied but this is exactly what is necessary."