Bayesian prior elicitation: an application to the MYPAN trial in childhood polyarteritis nodosa

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Acknowledgements

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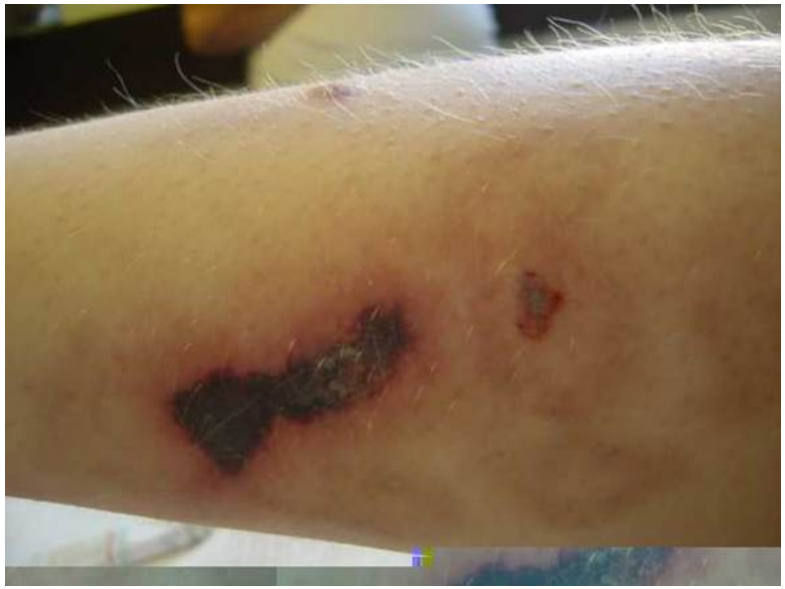
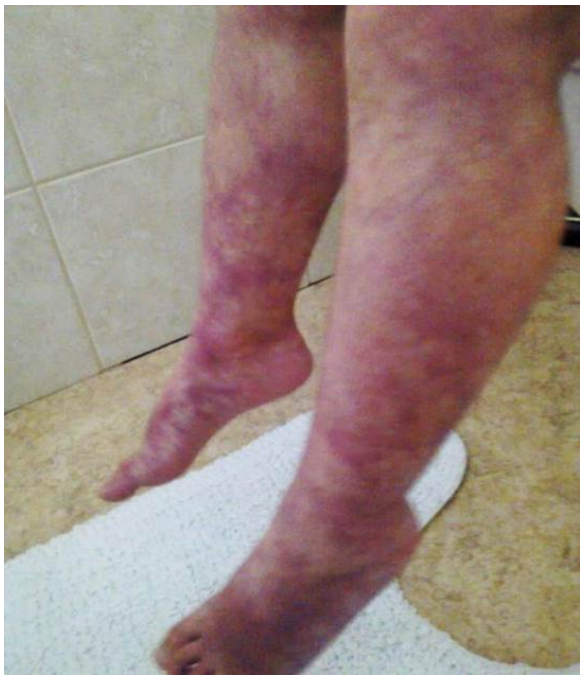
The MYPAN trial

Childhood polyarteritis nodosa (PAN) is a serious inflammatory blood vessel disease affecting around 1 per million children.





The MYPAN trial

- Cyclophosphamide (CYC) has been standard treatment for past 35 years.
- Mycophenolate mofetil (MMF) is an immunosuppresant thought to have a lower risk of toxicity.
- MYPAN trial will compare MMF versus CYC for the treatment of childhood PAN.
- The primary endpoint is remission within 6-months. Probabilities of remission on MMF and CYC are p_E and p_C. MMF will be preferred to CYC if $p_E - p_C \geq -0.1$.
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PROBLEM: 20-30 European centres could recruit 40 patients over 4 years.

SOLUTION: Aim for a more modest objective – to improve our understanding of treatment options for PAN.

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No high quality data to base priors upon. Instead we elicit prior opinion on p_C and θ, modelling it as:

- $p_C \sim \text{Beta}(a, b)$
- $\theta \sim N(\mu, \sigma^2)$.

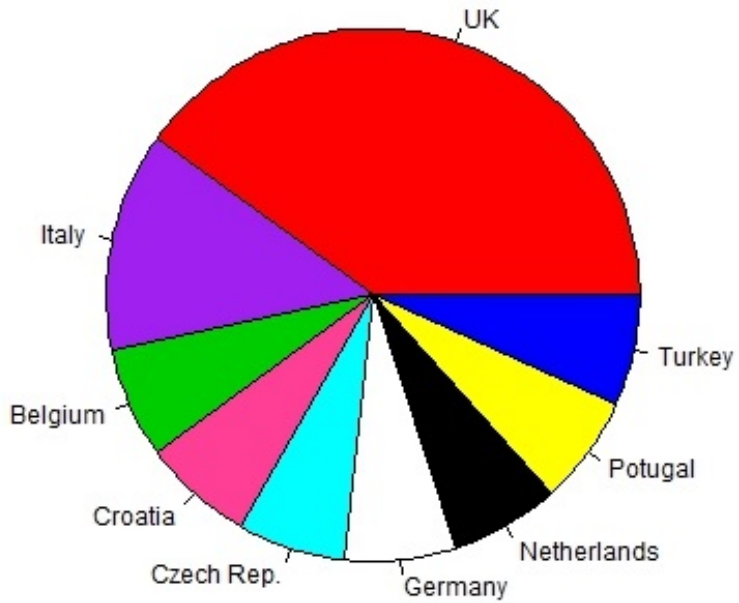
} independent

Identifying experts in childhood PAN

We defined an expert as a paediatric consultant

- Specialising in rheumatology, nephrology or immunology;
- With experience of treating children with PAN (on average 1 case every 2 years).

15 experts from across the EU and Turkey attended 2-day prior elicitation meeting.



Structure of the elicitation meeting

Day 1 objectives:

- Provide experts with relevant training;
- Elicit expert opinion about p_C and θ.
- Elicit individuals' opinions first . . .

Day 1: Eliciting individual opinion on p_C

Q1: What do you think the 6-month remission rate for children with PAN on CYC is?

- A1: Prior mode $= (a-1)/(a+b-2)$.

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Q2: Provide a proportion which you are 75% sure the true remission rate p_C exceeds.

- A2: $\pi_{0.25}$ satisfying $\Pr\{p_C < \pi_{0.25}; a, b\} = 0.25$.

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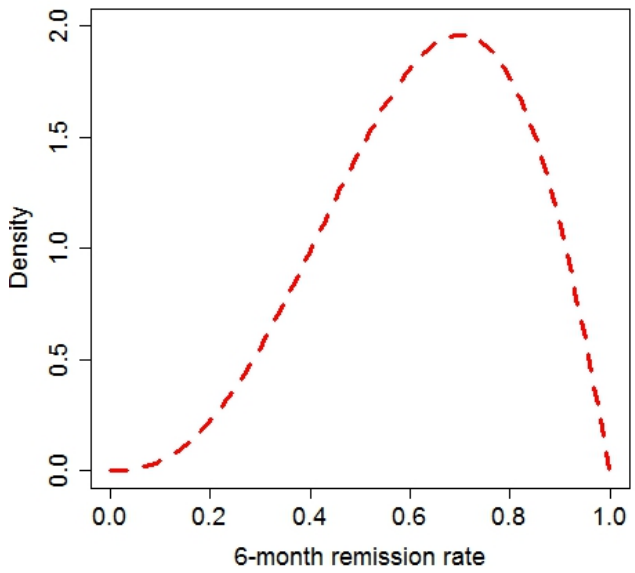

Consensus: A1 = 0.7, A2 = 0.5 $\rightarrow p_C \sim$ Beta(3.6, 2.11)

Day 1: Eliciting individual opinion on θ

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Q4: What is chance that p_C exceeds p_E by more than 10%?

- A4: $\Pr\{p_E - p_C < -0.1\} = \int_0^1 \int_0^{\max\{p_C - 0.1, 0\}} g_0(p_C, p_E; a, b, \mu/\sigma, \sigma)\, \mathrm{d}p_E\, \mathrm{d}p_C$

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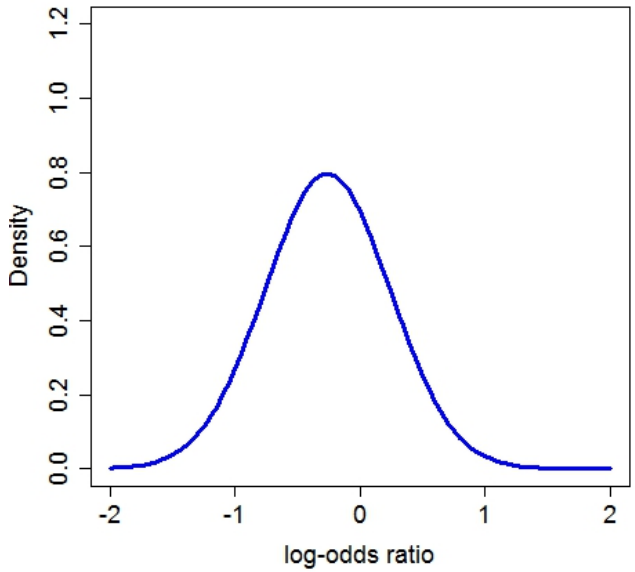

Consensus: A3 = 0.3, A4 = 0.3 $\rightarrow \theta \sim N(-0.26, 0.25)$

Day 1: Quantifying the strength of prior opinion

Morita et al. (2008), Neuenschwander.et al (2010)

A prior **Effective Sample Size** (ESS) characterises the strength of prior opinion:

- ESS is the number of observations needed to obtain the same amount of statistical information for a parameter as is represented by its prior distribution.

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Calculate the ESS of $\omega = \log\{p_C/(1-p_C)\}$ as the sample size $n_C^\star$ satisfying

$$n_C^\star \int_{-\infty}^{\infty} \frac{1}{\mathrm{B}(a,b)} \frac{\exp\{(a+1)\omega\}}{\{1+\exp(\omega)\}^{a+b+2}} d\omega = \frac{1}{\mathrm{Var}_0(\omega)}$$

Interpretation: size of a single arm study evaluating CYC for which the expected Fisher's information for $\log\{p_C/(1-p_C)\}$ equals precision of elicited prior.

Day 1: Quantifying the strength of prior opinion

Calculate the ESS of θ as the sample size $n_\theta^\star$ satisfying

$$\int_0^1 \int_0^1 \frac{n_\theta^\star \bar{p}(1-\bar{p})}{4} g_0(p_E, p_C) dp_E dp_C = \sigma^{-2},$$

where $\bar{p} = (p_E + p_C)/2$.

Interpretation: sample size needed for an RCT allocating equal numbers to MMF and CYC to have expected Fisher's information for θ equal to precision of elicited prior.

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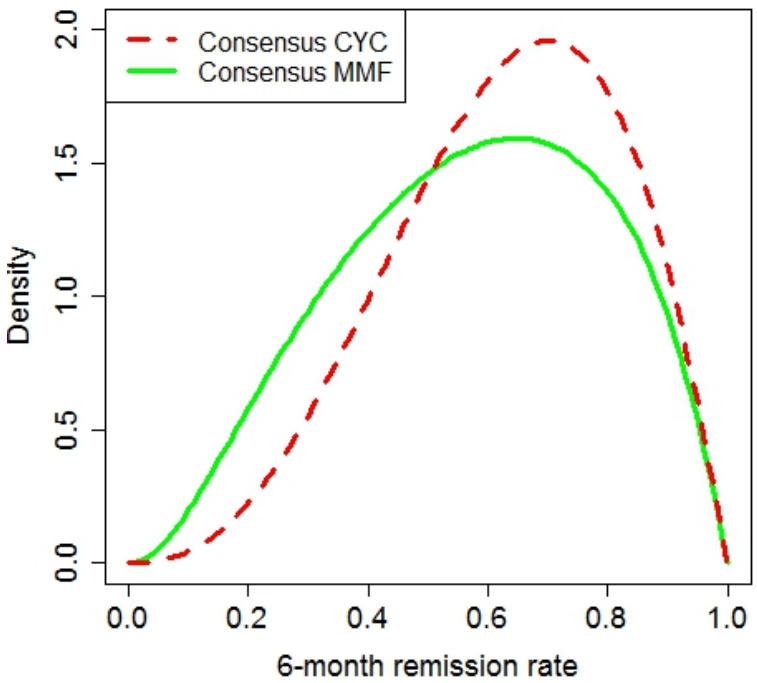
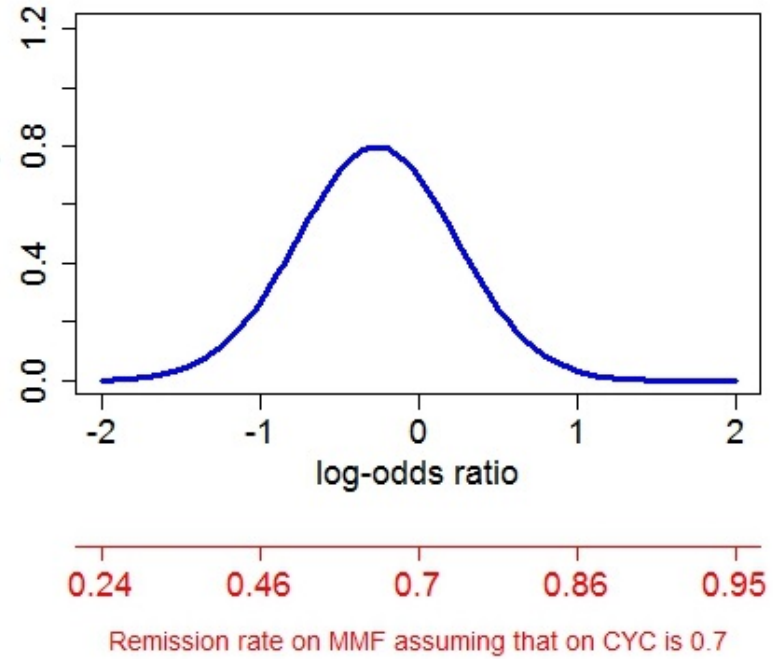
Reaching a consensus:

- A1-4 were displayed and discussed in a structured way.
- Mean and median answers were used as 'initial values' for consensus answers.
- Consensus answers determined by voting when choice was not unanimous.
- ESSs were influential in the group's final consensus decisions.

Day 1: Consensus prior distributions





- p_C: mode = 0.7, ESS = 5 patients on CYC
- θ : mode = -0.26, ESS = 39 patients per treatment
- p_E: mode = 0.65

Day 2: Extrapolating from adult data & across conditions

Expert opinion was combined with data from the MYCYC trial:

- MYCYC data were genuinely unknown to the experts on Day 1.
- MYCYC trial involved 132 adults and 8 children with a condition related to PAN.
- MYCYC compared MMF vs CYC.
- MYCYC primary endpoint was similar to MYPAN primary endpoint.

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Sought opinion on the relevance of MYCYC data **before** revealing the primary results.

Remission probabilities in the MYCYC and MYPAN trials linked via log-odds ratios

$$\lambda_C = \log\left\{\frac{p_{CR}(1-p_C)}{p_C(1-p_{CR})}\right\} \qquad \lambda_E = \log\left\{\frac{p_{ER}(1-p_E)}{p_E(1-p_{ER})}\right\}.$$

Day 2: Extrapolating from existing data

Prior opinion on the relevance of the MYCYC data was modelled as

$$\lambda_C \sim N(\alpha_C, \gamma_C^2) \quad \text{and} \quad \lambda_E \sim N(\alpha_E, \gamma_E^2).$$

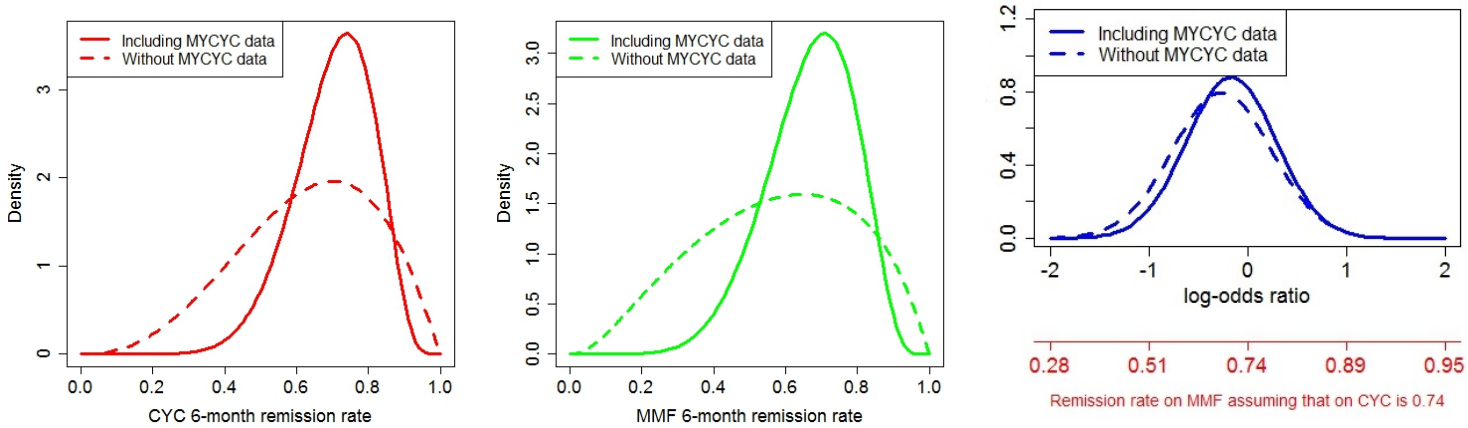
Experts were asked:

1. Q(a): What is the chance that the CYC remission rate in the MYCYC patient group exceeds that in the MYPAN patient group?
2. Q(b): What is the chance that the CYC remission rate in the MYPAN patient group exceeds that in the MYCYC patient group by more than 10%?
3. Q(c) - (d): Questions worded in terms of MMF.

We did not attempt to quantify the effective sample size of these priors.

Day 2: Extrapolating from existing data

MYCYC results: 74% successes on CYC; 73% successes on MMF.



Optimistic prior distribution with $\Pr\{p_E > p_C - 0.1\} = 0.77$.

Effective sample sizes were updated: 70 MYCYC patients per treatment increased the

- Effective Sample Size for p_C by 12;
- Effective Sample Size for θ by 9 per arm.

Summary
Schmidli et al. (2014)

MYPAN trial illustrates how a Bayesian approach can use existing information (expert opinion; adult data) to support paediatric drug development.

Bayesian methods could be used at different stages of the extrapolation process:

- Extrapolation concept: Quantify evidence supporting relevance of source data;
- Extrapolation plan: Determine expected value of new trial in target population;
- Extrapolation plan: Identify knowledge gaps – tailor studies to focus on parameters about which least is known or which have greatest impact on improving decision making (e.g., inform randomisation ratios, PK sampling times)
- Validation: Robust priors downweight source data when prior-data conflict.

Summary

Acceptability: The proposed approach would be used only if (after all reasonable efforts) a conventional trial in target population is deemed infeasible:

- Bayesian approach switches focus from hypothesis testing to estimation.
- A small Bayesian randomised trial may be ethically acceptable (if the data can shift the prior) because a more informative interpretation of the data is possible.

Challenges: Several potential contentious issues remain:

- Selection of experts.
- How to handle prior-data conflicts.

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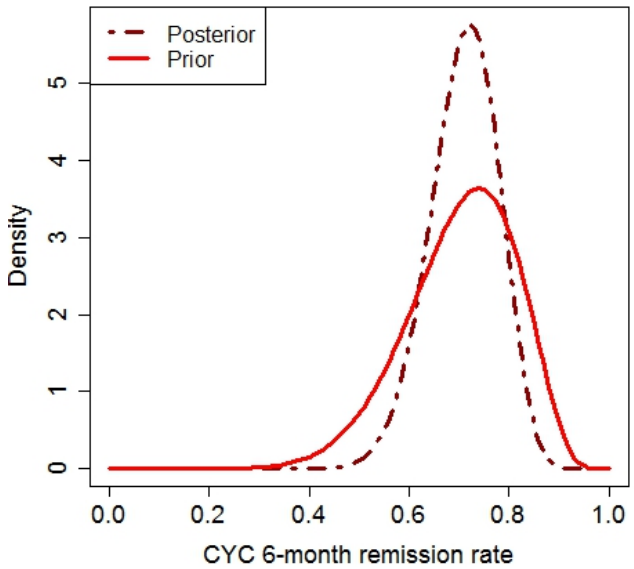
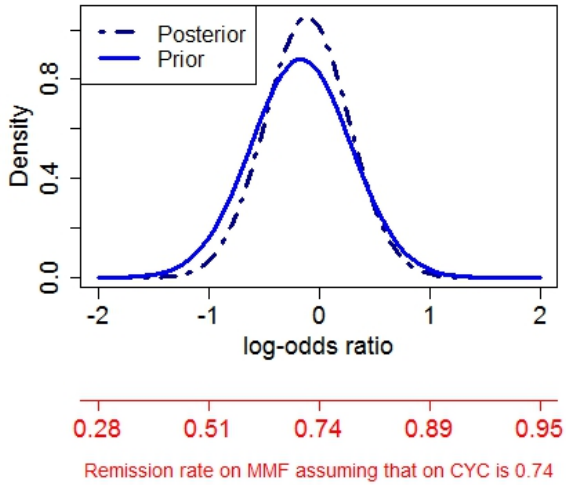
Verifing consensus prior distributions

Idea: Present experts with hypothetical MYPAN datasets and ask whether they agree with 'their' posteriors derived using Bayes Theorem.

Example: Suppose we observed $n_E = 20$, $S_E = 14$, $n_C = 20$, $S_C = 14$.





- Posterior for p_C: mode = 0.72; Posterior for p_E: mode = 0.70
- $\Pr\{p_E > p_C - 0.1 \mid \text{data}\} = 0.84$.
- $\Pr\{p_E > p_C \mid \text{data}\} = 0.38$.