Incorporating expert opinion in a clinical trial: The MYPAN experience

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Bayesian methods for the design and interpretation of clinical trials in very rare diseases

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This paper considers the design and interpretation of clinical trials comparing treatments for conditions so rare that worldwide recruitment efforts are likely to yield total sample sizes of 50 or fewer, even when patients are recruited over several years. For such studies, the sample size needed to meet a conventional frequentist power requirement is clearly infeasible. Rather, the expectation of any such trial has to be limited to the generation of an improved understanding of treatment options. We propose a Bayesian approach for the conduct of rare-disease trials comparing an experimental treatment with a control where patient responses are classified as a success or failure. A systematic elicitation from clinicians of their beliefs concerning treatment efficacy is used to establish Bayesian priors for unknown model parameters. The process of determining the prior is described, including the possibility of formally considering results from related trials. As sample sizes are small, it is possible to compute all possible posterior distributions of the two success rates. A number of allocation ratios between the two treatment groups can be considered with a view to maximising the prior probability that the trial concludes recommending the new treatment when in fact it is non-inferior to control. Consideration of the extent to which opinion can be changed, even by data from the best feasible design, can help to determine whether such a trial is worthwhile.

Keywords: allocation ratio; Bayesian model; expert opinion; prior elicitation; prior power; rare diseases

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RESEARCH ARTICLE

Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa

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MYPAN study motivation

MYPAN study - Mycophenolate mofetil for childhood polyarteritis nodosa (PAN)

- Cyclophosphamide (CYC) - standard treatment for 35 years;
- Mycophenolate mofetil (MMF) thought to have a lower toxicity risk.

MYPAN non-inferiority trial to compare MMF versus CYC for the treatment of childhood PAN.

- Primary endpoint: Remission within 6-months;
- p_E: Probability of remission on MMF;
- p_C: Probability of remission on CYC;
- MMF preferred to CYC if $p_E - p_C \geq -0.1$

Bayesian justification

Recruitment for a definitive frequentist trial would not have been feasible.

A frequentist non-inferiority trial with

- 90% power,
- 2.5% one-sided significance level,
- remission rates on both treatments assumed to be 70%

would have required 513 patients on each treatment arm.

Previous studies of PAN suggested recruitment would have taken over 30 years.

Bayesian trial design chosen to improve understanding about treatments for PAN.

Bayesian approach

Prior uncertainty of remission rates on MMF and CYC quantified by elicited expert opinion, ultimately will be updated with new data to form posterior opinion to inform treatment decisions.

Advantage of MMF over CYC measured using log-odds ratio:

$$\theta = \log \left\{ \frac{p_E(1 - p_C)}{p_C(1 - p_E)} \right\}$$

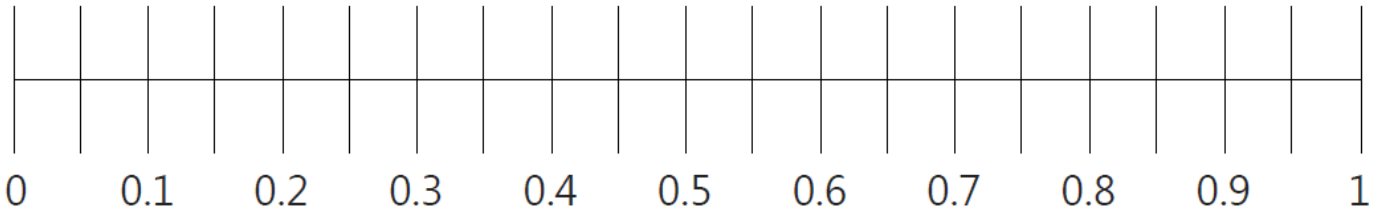
Parameters p_C and θ assumed to be independent

Expert opinion

15 paediatric consultants specialising in rheumatology, nephrology or immunology (with experience of treating children with PAN) attended a 2-day meeting to elicit priors.

Expert opinion on p_C and θ was elicited by asking six questions about different probabilities and proportions.

- Answers were marked on a visual analogue scale ranging from 0 to 1,
- Answers rounded to the nearest 0.05 probability.



Prior for p_C

Prior for p_C modelled as a beta distribution - $p_C \sim \text{Beta}(a, b)$

- Experts were asked questions to establish the mode and lower quartile to infer the distribution.

Question 1: What do you think the 6-month remission rate for children with PAN on CYC is?

- Prior mode = $\frac{a-1}{a+b-2}$.

Question 2: Provide a proportion such that you are 75% sure the true remission rate on CYC exceeds this value.

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

Prior for θ

Prior for θ modelled as a normal distribution - $\theta \sim \mathrm{N}(\mu, \sigma^2)$

- Experts were asked questions to establish the prior probability that $p_E > p_C$ and $p_E - p_C < -0.1$;
- Answers to these questions were used to infer values for the mean and variance.

Question 3: What is chance that the remission rate on MMF is higher than that on CYC?

- $\Pr\{p_E > p_C\} = \Phi(\mu/\sigma)$.

Question 4: What is chance that the remission rate on CYC exceeds that on MMF by more than 10%?

- $\Pr\{p_E - p_C < -0.1\}$.

Redundant questions regarding p_E were also asked in order to assess goodness of fit of the model and the consistency of expert opinion.

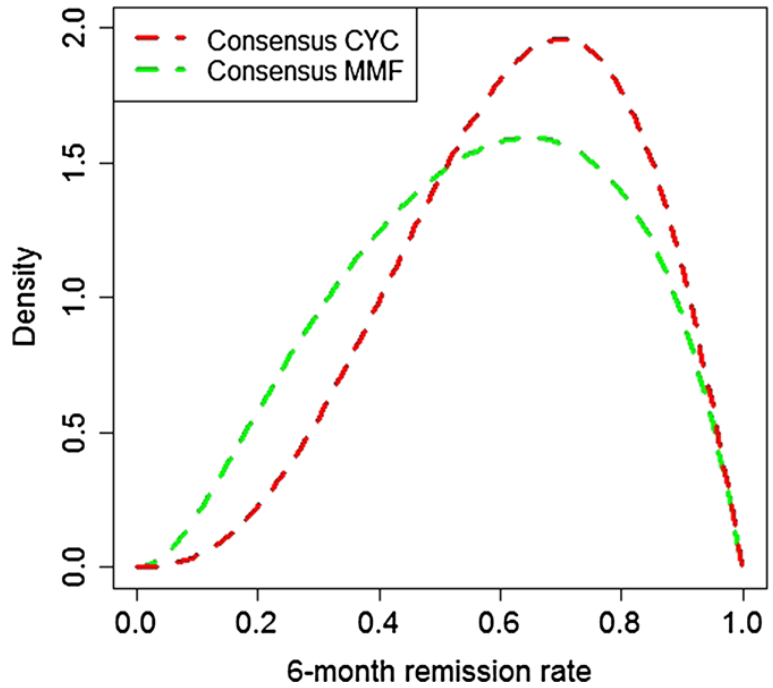
Forming consensus opinion

Plots of the probability density functions for p_C and p_E were presented to each expert.

Experts were allowed to make changes to previously answered questions until they felt the plots represented their prior belief.

All experts were then brought together to discuss their individual opinions, displaying and discussing answers in a structured way.

- Means and medians of the expert's final answers used as starting point for consensus answers;
- Set of consensus prior distributions were determined that all experts agreed upon.



Incorporating existing relevant data

Expert opinion elicited regarding the relevance of MYCYC trial of MMF and CYC treating a different (but related) condition to PAN.

- MYCYC trial data unknown to experts,
  - Similar primary endpoint (remission within 6 months);
  - 132 adults and 8 children.

Before revealing MYCYC results, opinion elicited on the relevance of MYCYC trial.

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Link between probabilities of remission in the MYCYC (p_{CR} and p_{ER}) and MYPAN (p_C and p_E) trials modelled by log-odds ratios:

$$\lambda_k = \log\left\{\frac{p_{kR}(1-p_k)}{p_k(1-p_{kR})}\right\}, \qquad \text{for } k = C, E.$$

Prior opinion on the λ_C and λ_E parameters modelled as:

$$\lambda_k \sim \mathrm{N}(\alpha_k, \gamma_k^2), \qquad \text{for } k = C, E.$$

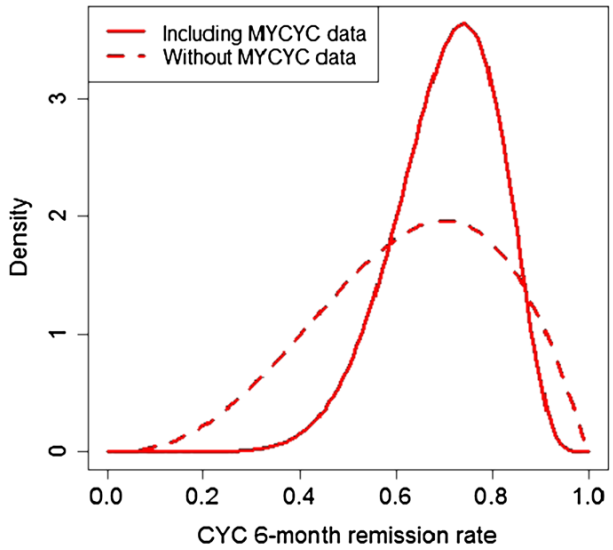
Opinion regarding these log-odds ratios elicited similarly to previous log-odds prior

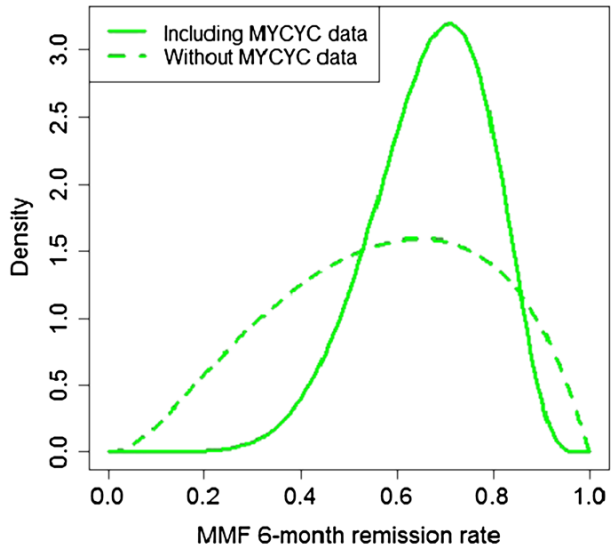
Incorporating existing relevant data

To reach a consensus prior:

- Experts gave individual opinions;
- Came together to agree on a single set of answers to the elicitation questions.

Existing data from the relevant trial were then revealed, updating the priors for p_C, p_E and θ to be shared with the experts.





Experts agreed on these updated prior distributions (incorporating MYCYC data) as the consensus prior for the Bayesian trial.

Summary

The MYPAN experience highlights:

- the complexity of expert opinion that can be elicited;
- the worth of eliciting opinion to inform decision making in rare diseases or small populations;
- that Bayesian approaches can be accepted by funders.

From the Bayesian prior elicitation, most likely rates of disease remission within 6 months on CYC and MMF are 74% and 71%.

- These results to be updated with MYPAN trial data;
- Until then, provide quantification of knowledge and uncertainty;
- Posterior results still likely to be unable to provide definitive results;
- However, can still inform clinical practice.

References

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