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

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Presentation overview

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Overview - our focus

- **Focus:** 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 (even when patients are recruited for several years)

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Overview - the problem and solution

- **Problem:** Sample size needed to meet a conventional Frequentist power requirement is infeasible
- **Solution:** 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
  - Systematic elicitation from clinicians of their beliefs concerning treatment efficacy is used to establish priors, including the use of results from related trials

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Basics of a Bayesian approach

- Papers prior to 2014 by Lilford et al. and Billingham et al. suggest the Bayesian approach as a suitable alternative for communicating the results of small trials
  - Posterior distribution can be used to assess treatment options
  - Informative prior information for the unknown treatment effect can be determined from:
    - expert knowledge
    - related existing data like historical randomized controlled trials
- May be necessary in clinical research involving children - can use down-weighted priors from meta-analyses of adult data

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Limitations of Bayesian analysis

- Bayesian analysis of a smaller sample can lead to some improvement in the understanding of a treatment, but not to inferences/conclusions of comparable confidence
- Methods discussed here should not be considered when a conventional high-powered trial with a satisfactory sample size can be achieved

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Example/motivation

- **MYPAN trial** – multicenter randomized controlled trial comparing two treatments of polyarteritis nodosa (PAN)
  - rare and serious inflammatory blood vessel disease in children for which there has never been a clinical trial
- Treatments to compare:
  - **Cyclophosphamide (CYC):** has been standard for 35+ years but is toxic with adverse side effects
  - **Mycophenolate mofetil (MMF):** new orally-administered immunosuppressant expected to have a better toxicity profile than CYC and is likely to be almost as effective.
- This is a non-inferiority trial with margin of 0.1 on probability difference scale ($\eta = 0.1$)
- MMF will be chosen if we have sufficient evidence that the probability of remission is no worse than 0.1 less than that of CYC.

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Motivation to use Bayesian methods

- **Primary endpoint:** disease remission within 6 months of randomization
- **Sample:** consortium of 20-30 centers from 14 European countries recruits about 14 suitable patients per year; target sample size of 40 patients
- Group sequential monitoring can achieve reductions in expected sample size of up to 40%
  - Benefits would have little impact on the feasibility of the trial – sample size required by Frequentist fixed sample size test is 383-513 patients per treatment arm

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MYPAN TRIAL NOTATION

- Patients who will receive MMF: n_M
- Patients who will receive CYC: n_C
- Total patients to be recruited: $n = n_M + n_C$
- Successes (# of remissions) on MMF treatment: S_M
- Successes (# of remissions) on CYC treatment: S_C
- Failures on MMF treatment: F_M
- Failures on CYC treatment: F_C
- Total treatment successes: $S = S_M + S_C$
- Total treatment failures: $F = F_M + F_C$
- Probability of success (remission) on MMF: p_M
- Probability of success (remission) on CYC: p_C

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Prior distributions

- Probability of remission on CYC: $p_C \sim Beta(a, b)$
- Measure treatment effects using the log odds ratio where:

$$\theta = log\left(\frac{p_M(1-p_C)}{p_C(1-p_M)}\right) \sim N(\mu, \sigma^2)$$

  which is independent of prior for p_C - opinions about these two parameters are likely to be unrelated
- **Note:** Opinions about p_C and p_M are not independent. Prior opinion about θ and p_M are also not independent.

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Joint prior distributions

Joint prior distribution of p_C and θ is $f_0(p_C, \theta) = h_0(p_C)k_0(\theta)$ because $p_C \perp \theta$ where:

$$h_0(p_C) = \frac{1}{B(a,b)} p_C^{a-1}(1-p_C)^{b-1}$$

$$k_0(\theta) = \frac{1}{\sqrt{2\pi\sigma^2}} exp\Big\{ -\frac{1}{2\sigma^2}(\theta - \mu)^2 \Big\}$$

Joint density of p_C and p_M is:

$$g_0(p_C, p_M) \propto \frac{p_C^{a-1}(1-p_C)^{b-1}}{p_M(1-p_M)} exp\Big\{ -\frac{1}{2\sigma^2}\Big(log\Big(\frac{p_M(1-p_C)}{p_C(1-p_M)}\Big) - \mu \Big)^2 \Big\}$$

This implies prior opinion about both probabilities are correlated.

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Form of the posterior

Posterior will take the form:

$$g(p_C, p_M|z) \propto p_C^{S_C+a-1}(1-p_C)^{F_C+b-1} p_M^{S_M-1}(1-p_M)^{F_M-1}$$
$$\times exp\Big\{ -\frac{1}{2\sigma^2}\Big(log\Big(\frac{p_M(1-p_C)}{p_C(1-p_M)}\Big) - \mu\Big)^2\Big\}$$

How are **parameters of the prior distributions** for p_C and θ determined?

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Background of experts consulted

- 15 experts across the EU elicited their prior beliefs about 6 month remission rates on CYC and relative efficacy of the trial treatments
- All experts were pediatric consultants experienced in treating at least one case of PAN every 2 years
- Experts drew on experiences treating PAN and current evidence of treatments including results of adult RCTs and low-level evidence such as case reports and retrospective case studies

Goal: Establish prior distributions by eliciting likely parameters a and b for the Beta distribution and μ and σ^2 for the Normal distribution.

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Questionnaire to inform prior parameters

To achieve this, we must ask questions of the experts:

To determine $Beta(a, b)$ for p_C:

- **1.** What do you think the 6-month remission rate for children with PAN treated with CYC is? (Taken as prior mode for p_C, $\frac{a-1}{a+b-2}$)
- **2.** Provide a proportion such that you are 75% sure that the true 6-month remission on CYC exceeds this value. (Taken as 25th percentile of beta distribution)

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Questionnaire cont.

To determine $N(\mu, \sigma^2)$ for θ:

- **3.** What is the chance that the 6-month remission rate on MMF is higher than that on CYC? (Taken as the prior probability that $p_M > p_C$, which is $\Phi(\frac{\mu}{\sigma})$)
- **4.** What is the chance that the 6-month remission rate on CYC exceeds that on MMF by more than 10%? (Taken as the prior probability that $p_C - p_M > 0.1$; MMF is inferior to CYC by at least the non-inferiority margin)

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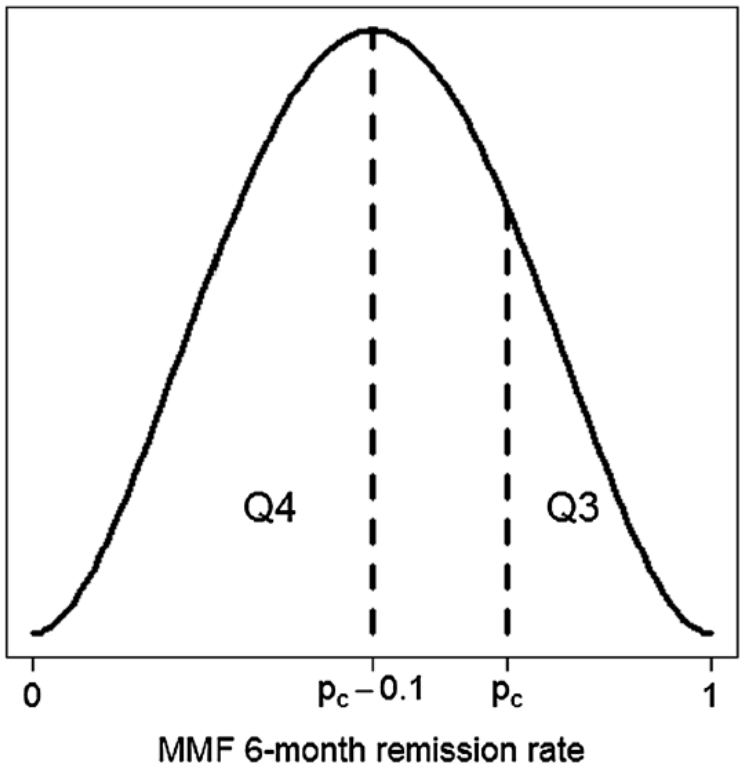
Visualization of questions 3 and 4

Recall:

Q3: $P(p_M > p_C) = \Phi(\frac{\mu}{\sigma})$

Q4: $P(p_C - p_M > 0.1) = P(p_M < p_C - 0.1)$



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Additional questions

Useful to ask more questions than there are hyperparameters to allow assessment of goodness of fit and detect inconsistencies of opinion:

- **5.** What do you think the 6-month remission rate on MMF is?
- **6.** Provide a proportion such that you are 75% sure that the true 6-month rate on MMF exceeds this value.

Note: Notice that these are analogues to questions 1 and 2.

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Review and revision phase

Once each expert completes the questionnaire, they have a one-on-one meeting with the statistician:

- Shows them plots of the prior distributions and information on their choices
- Emphasis placed on parameters that are challenging to interpret - log odds ratio
  - PDF of θ is interpreted in terms of a prior distribution for p_M holding their choice for p_C constant at the mode generated by their answer to question 1
- Experts are then allowed to revise answers to questions 1-4 until they are satisfied with their fitted prior PDFs

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Experts develop a consensus

A consensus of expert opinion can then be developed via:

- **Mathematical aggregation:** pooling of prior parameters, or
- **Behavioral aggregation:** experts interact to reach a mutually agreeable consensus through constructive discussion

Behavioral aggregation was used in this example.

Experts are then asked whether these prior distributions for p_C, p_E, and θ have face validity as a set of consensus priors, and they deliberate.

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Effective sample size (ESS)

- **Effective sample size (ESS)** - the number of observations that a prior represents - communicates the strength of a prior
- Calculate a prior ESS for 2 priors, $k_0(\theta)$, $\theta = log(\frac{p_E(1-p_C)}{p_C(1-p_E)})$, and for $p_0(\omega)$, $\omega = log(\frac{p_C}{1-p_C})$ - log odds is approximately normal
- Define ESS of $k_0(\theta)$ as the sample size for which a comparative fixed sample trial (frequentist) attains prior expected Fisher's information for θ equal to the precision, $var_0(\theta)^{-1}$ 39 patients/treatment
- Define ESS of $p_0(\omega)$ as the sample size for which the prior expected Fisher's information for ω generated by a single-arm study is equal to the precision, $var_0(\omega)^{-1}$ 5 patients on CYC

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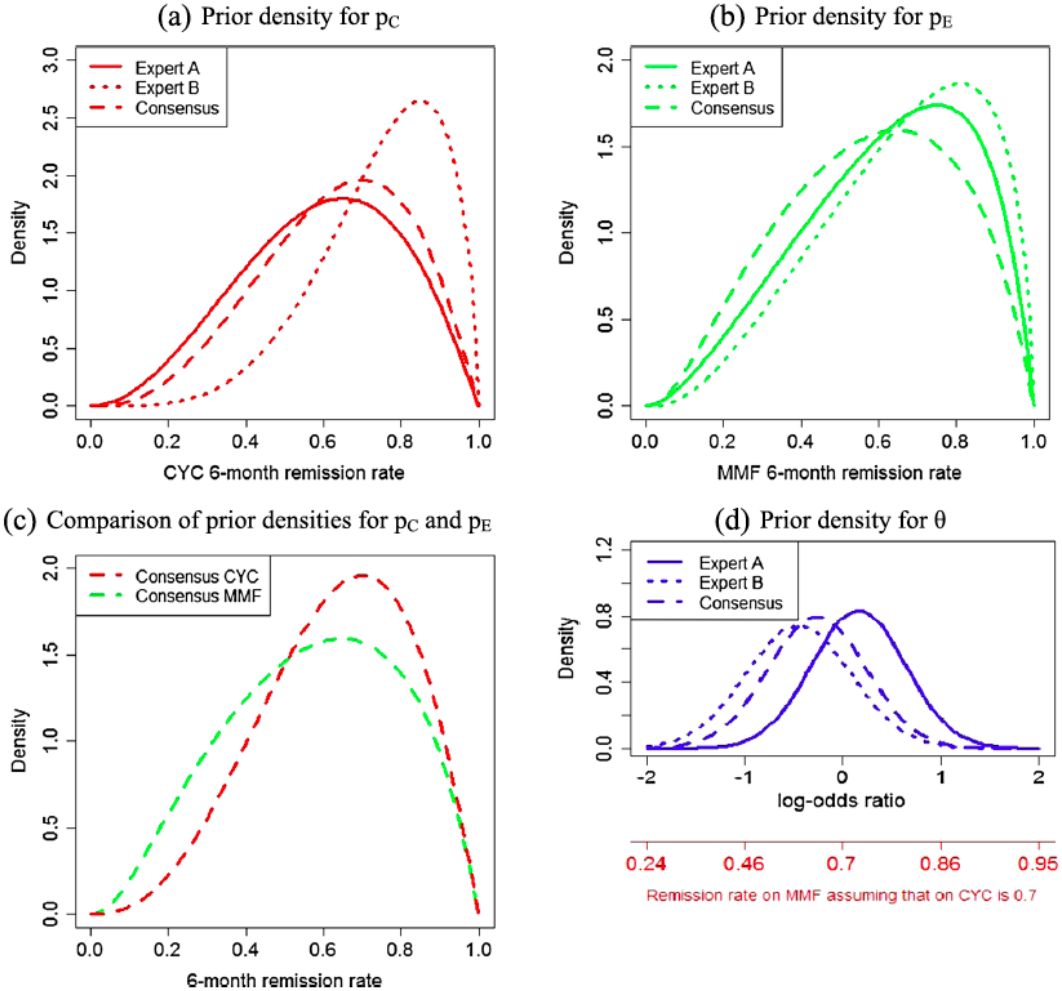
Examples of individual and consensus priors

Final prior distributions for two experts with differing prior opinions - demonstrates the range of responses recorded:



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Consensus priors results

- **1.** What do you think the 6-month remission rate for children with PAN treated with CYC is? (Taken as prior mode for p_C, $\frac{a-1}{a+b-2}$) 0.7
- **2.** Provide a proportion such that you are 75% sure that the true 6-month remission on CYC exceeds this value. (Taken as 25th percentile of beta distribution) 0.5
- **3.** What is the chance that the 6-month remission rate on MMF is higher than that on CYC? (Taken as the prior probability that $p_M > p_C$, which is $\Phi(\frac{\mu}{\sigma})$) 0.3 (converse is 0.7)
- **4.** What is the chance that the 6-month remission rate on CYC exceeds that on MMF by more than 10%? (Taken as the prior probability that $p_C - p_M > 0.1$; MMF is inferior to CYC by at least the non-inferiority margin) 0.3

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Consensus priors results cont.

- Prior for p_C: mode 0.7, mean 0.63, SD 0.19, and 90% CI (0.3, 0.91)
- Prior for p_M: mode 0.65, mean 0.57, SD 0.21, and 90% CI of (0.21, 0.9)
- Prior for θ: mean -0.26, SD 0.5, and 90% CI of (-1.09, 0.56)

Experts are confident about the relative efficacies (comparing performance of interventions) of CYC and MMF in the population eligible for the MYPAN trial. Uncertainty about the absolute remission rates themselves.

This implies:

$$p_C \sim Beta(3.6, 2.1)$$

$$\theta \sim N(-0.26, 0.25)$$

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Historical data with different population

MYCYC trial, an unpublished RCT comparing MMF and CYC in a condition related to PAN

- Randomized $n = 140$ patients with ANCA-associated vasculitis to MMF or CYC arm
- 66/70 patients per arm were adults – different population than MYPAN
- Endpoint was remission within 6 months, same as MYPAN
- **Can this MYCYC data be incorporated into the prior distributions** for p_C, p_M, and θ so far developed by the expert's opinions?

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MYCYC data & notation

- Subscript V for vasculitis:
- p_{CV}: 6 month remission rate **on CYC** in MYCYC population
- p_{MV}: 6 month remission rate **on MMF** in MYCYC population
- $n_{CV} = n_{MV} = 70$
- $S_{CV} = 52$ and $S_{MV} = 51$ (via intent-to-treat principle)

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Log-odds ratios comparing studies

- If related (MYCYC) and future (MYPAN) trials are known to differ systematically, it is not realistic to regard the parameters as exchangeable nor to represent their priors as i.i.d.
- Need to link the 6 month remission probabilities in the two trial populations via log-odds ratios:

$$\lambda_C = log\Big(\frac{p_{CV}(1-p_C)}{p_C(1-p_{CV})}\Big); \quad \lambda_M = log\Big(\frac{p_{MV}(1-p_M)}{p_M(1-p_{MV})}\Big)$$

- These measure differences in treatment effects between the 2 trials
- Priors for λ_C and λ_M will represent uncertainty in the relevance of the historical MYCYC data

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Log-odds ratios priors

Let the following represent priors for the log-odds comparing studies:

$$\lambda_C \sim N(\alpha_C, \gamma_C^2); \quad \lambda_M \sim N(\alpha_M, \gamma_M^2)$$

- MYCYC trial was presented to the experts without revealing any results, then they completed a questionnaire to inform priors for λ_C and λ_M (next slide)
- Graphics were used like before to illustrate hypothetical answers to these questions (answers of 0.5 imply uncertainty)
- Experts reconvened to establish a group consensus, then priors for p_C, p_M, and θ were updated

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MYCYC questionnaire

- **7.** What is the chance that the 6-month remission rate on CYC in the MYCYC patient group exceeds that in the MYPAN patient group? 0.55
- **8.** What is the chance that the 6-month remission rate on CYC in the MYPAN patient group exceeds that in the MYCYC patient group **by more than 10%?** 0.25
- **9.** What is the chance that the 6-month remission rate on MMF in the MYCYC patient group exceeds that in the MYPAN patient group? 0.5
- **10.** What is the chance that the 6-month remission rate on MMF in the MYPAN patient group exceeds that in the MYCYC patient group **by more than 10%?** 0.25

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Log-odds ratio prior results

The consensus to questions 7-10 implies:

$$\lambda_C \sim N(0.12, 0.86); \quad \lambda_M \sim N(0, 0.6)$$

This is consistent with the opinion that remission rates on CYC might be slightly higher in adults with ANCA-associated vasculitis than in children with PAN, but remission on MMF is similar between the two populations (shown on next slide)

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Updated priors

Without MYCYC data:

- Prior for p_C: mode 0.7, mean 0.63, SD 0.19, and 90% CI (0.3, 0.91)
- Prior for p_M: mode 0.65, mean 0.57, SD 0.21, and 90% CI of (0.21, 0.9)
- Prior for θ: mean -0.26, SD 0.5, and 90% CI of (-1.09, 0.56)

With MYCYC data:

- Prior for p_C: mode 0.74, mean 0.7, SD 0.11, 90% CI: (0.51, 0.86)
- Prior for p_M: mode 0.71, mean 0.67, SD 0.12, 90% CI: (0.45, 0.85)
- MYCYC data has less impact on the θ prior because beliefs were already rather precise (results not shown in paper)
- ESS for p_C is now 17; ESS for θ is now 48.

Upon review, all experts kept the MYCYC data in their priors.

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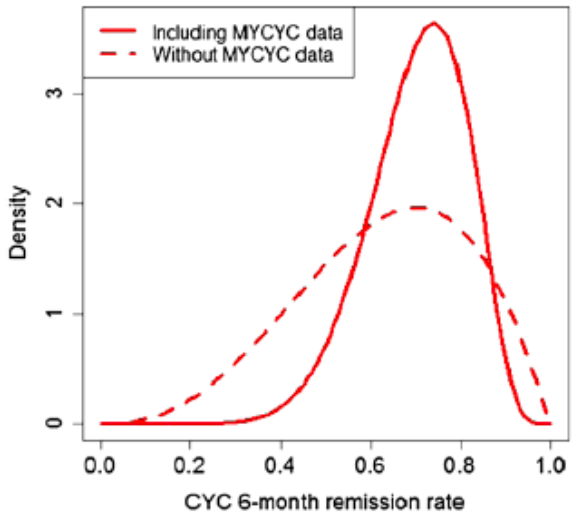
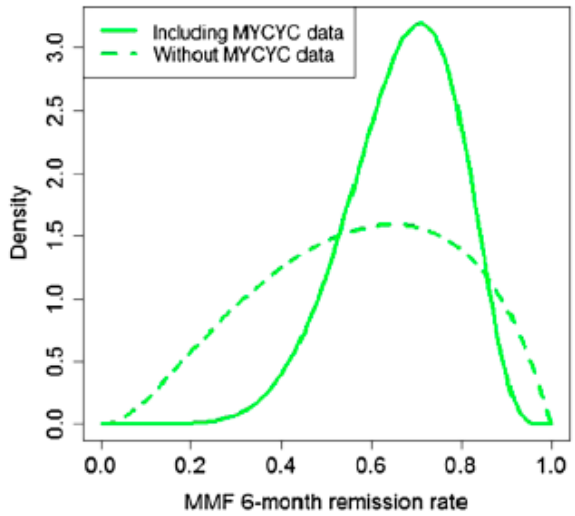
Priors with and without historical data

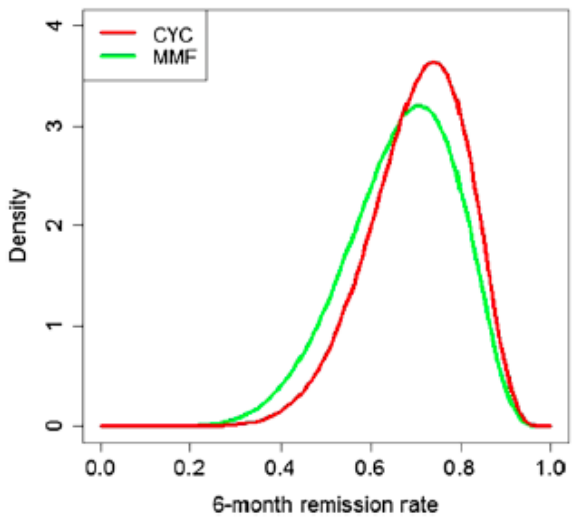
(a) Prior density for p_C



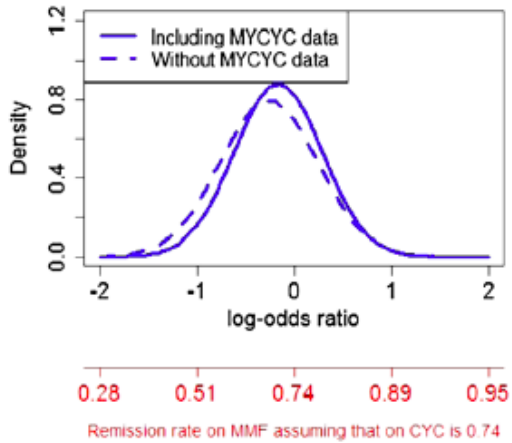
(b) Prior density for p_E



(c) Comparison of prior densities for p_C and p_E



(d) Prior density for θ



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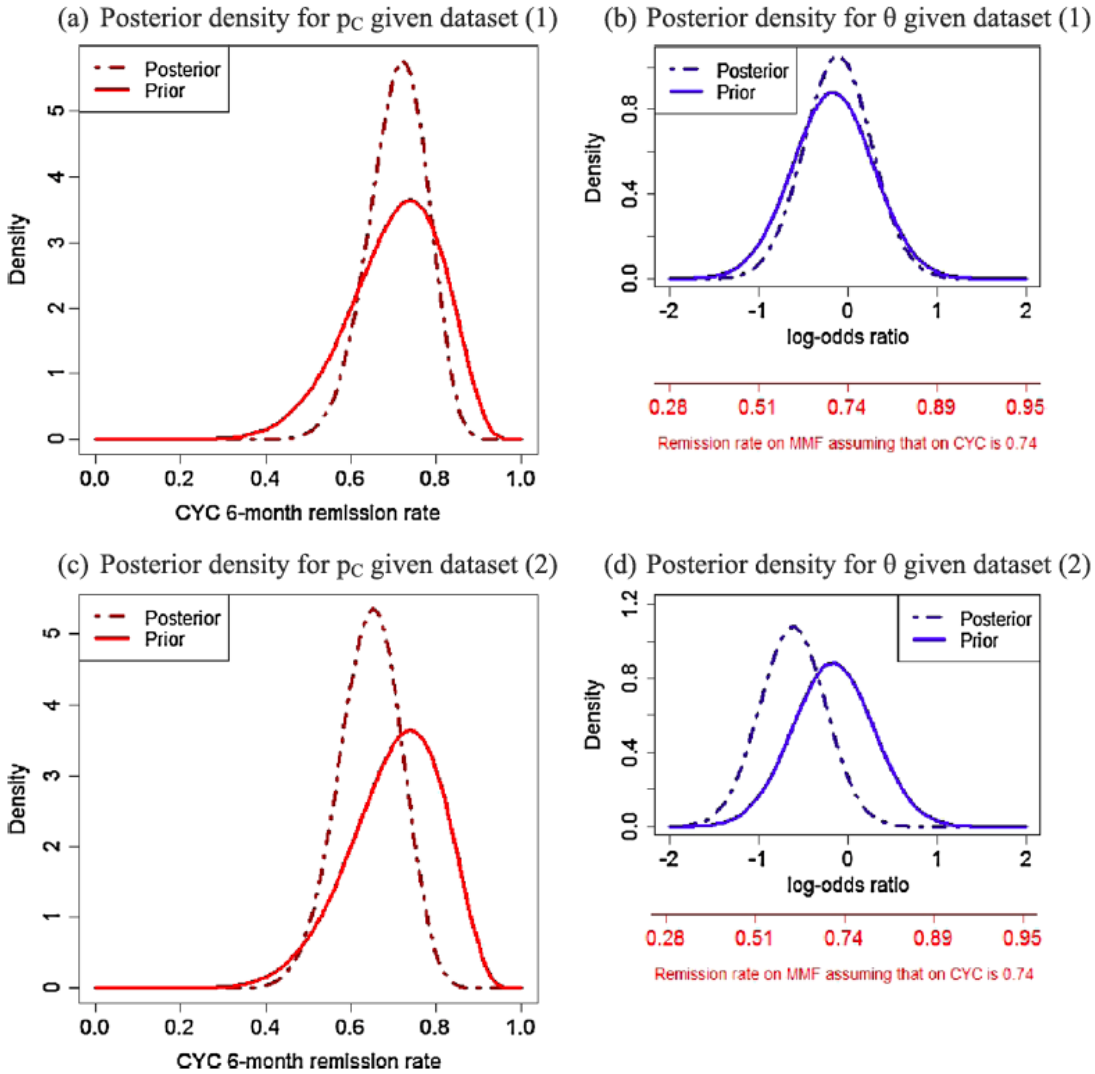
Posteriors with hypothetical MYPAN data

$S_M = S_C = 14$ (top row); $S_M = 7, S_C = 14$ (bottom row)



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Alternative priors

Vague priors for λ_C and λ_M as a result of questions 7-10:

- 7. 0.5; 8. 0.45; 9. 0.5; 10. 0.45
- MYCYC data results would be discounted almost entirely; prior would return to the expert opinion only prior

If experts had been **more** confident that $p_{CV} > p_C$:

- 7. 0.65; 8. 0.1; 9. 0.5; 10. 0.25
- $\lambda_C \sim N(0.21, 0.3)$; p_C has mode 0.72, mean 0.7
- $\lambda_M \sim N(0, 0.6)$; p_M has mode 0.7, mean 0.66

If experts had been confident that $p_C > p_{CV}$:

- 7. 0.2; 8. 0.5; 9. 0.5; 10. 0.25
- $\lambda_C \sim N(-0.51, 0.37)$; p_C has mode 0.8, mean 0.77
- $\lambda_M \sim N(0, 0.6)$; p_M has mode 0.76, mean 0.72

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Overview of allocation ratio

- When designing a rare-disease trial, it may be optimal to deviate from randomizing equal numbers of patients to treatments M and C if relatively little is known about p_M
- Pocock, for example, chooses the optimal M:C allocation ratio in the presence of historical controls to minimize posterior variance of a probability difference, thus increasing power
- We will form some decision criteria based on values we already have available

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Notation for decision criteria

Denote:

- $\Gamma = P(p_M > p_C)$
  - Answer to Question 3: What is the chance that the 6-month remission rate on MMF is higher than that on CYC?
- $\Pi = P(p_M > p_C – 0.1)$
  - Complement to answer to Question 4: What is the chance that the 6-month remission rate on CYC exceeds that of MMF by less than 10% OR the remission rate of MMF exceeds that of CYC?
  - In other words, what is the chance that MMF is not inferior to CYC by at least the non-inferiority margin?

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Decision criteria

- **MMF is recommended as non-inferior to CYC** iff the posterior value of $\Pi = P(p_M > p_C – 0.1)$ exceeds some large value ν
- Alternatively, there exists the scenario where Π does not exceed the large value ν but $\Gamma = P(p_M > p_C)$ is large, implying that MMF is sufficiently non-inferior to CYC
  - Need another metric to identify these cases!
- Consider all sets of data (S_M, S_C) for which $\Pi \leq \nu$. Find $\Gamma^* = max(\Gamma)$ for each one, where Γ^* is the maximum value of Γ with which the trial can terminate without recommending MMF by way of the criterion $\Pi > \nu$
- The allocation ratio M:C is chosen by finding which dataset generates the minimal Γ^*

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Choosing an allocation ratio

- Evaluate the Bayesian prior power of a non-inferiority trial as $p_0(\Pi > \nu | p_M - p_C > -0.1)$, the probability that MMF will be correctly recommended, for each hypothetical MYPAN dataset where $n = 40$ is fixed
- Suppose MMF will be recommended as non-inferior to CYC if $\Pi > 0.8$ with $\eta = 0.1$. We seek the allocation ratio that both attains high Bayesian prior power AND achieves a low Γ^*

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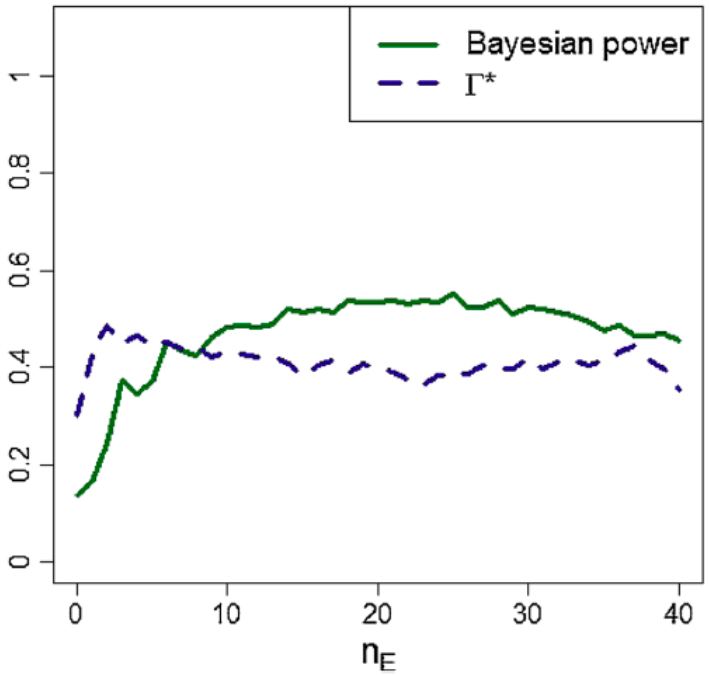
Choosing an allocation ratio, cont.



- Both curves plateau quickly - there are many acceptable designs
- Bayesian power is maximized at 0.55 by randomizing $n_M = 25$, $n_C = 15$, at which $\Gamma^* = 0.38$ (Γ^* is close to the global minimum of 0.3 achieved at $n_M = 0$, $n_C = 40$)

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MYPAN design conclusion

- The MYPAN trial will randomize equal numbers to MMF and CYC assuming n=40
- Bayesian decision rule that recommends MMF as non-inferior to CYC if $\Pi > 0.8$ has a Frequentist type 1 error rate of 0.29 under $p_M = 0.6$ and $p_C = 0.7$
- Type 1 error is high because prior opinion is confident that MMF is non-inferior to CYC - the prior distributions chosen stipulate $\Pi = P(p_M > p_C - 0.1) = 0.77$.

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Final remarks

- A drawback of the proposed approach is that there is no simple representation of the prior distributions for p_C, p_M, and θ because they incorporate both opinion and related data. Unfortunately, we have to run numerical integration routines to obtain prior densities.
- It should be noted that such related data we used could be in the form of data generated in a related population (as it was here) or more generally data on a related endpoint or drug with a similar mechanism of action to the new medicine.

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Final remarks, cont.

- Equal allocation between CYC and MMF is stipulated for the MYPAN trial because MYPAN will be the first RCT in children with PAN; estimating remission rates on both treatments is of interest because neither treatment has been scrutinized in an RCT despite the fact that CYC is the current standard.
- Acceptance of prior distributions by the clinical community will be important if posterior recommendations are to change practice because in trials of very rare diseases, sample sizes will not be large enough to dilute strong prior opinion. Regulators are therefore cautious about using Bayesian methods with informative priors to support new drug applications.

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Final remarks, cont.

- It is a common regulatory requirement that studies supporting the development of medicines for children should follow a prospectively agreed pediatric investigation plan (PIP). In this setting, priors for parameters linking success rates in adults and children could be pre-specified in the PIP before adult efficacy studies are completed.
- The approach of providing secondary funding for the trial only if the prior opinion supported clinically relevant levels of uncertainty about treatment effects is sensible because it avoids the risk of wasting money on a fruitless trial that is unlikely to generate an influential posterior opinion.

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Questions?

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