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

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Abstract

Objectives

Definitive sample sizes for clinical trials in rare diseases are usually infeasible. Bayesian methodology can be used to maximise what is learnt from clinical trials in these circumstances. We elicited expert prior opinion for a future Bayesian randomised controlled trial for a rare inflammatory paediatric disease, polyarteritis nodosa (MYPAN, Mycophenolate mofetil for polyarteritis nodosa).

Methods

A Bayesian prior elicitation meeting was convened. Opinion was sought on the probability that a patient in the MYPAN trial treated with cyclophosphamide would achieve disease remission within 6-months, and on the relative efficacies of mycophenolate mofetil and

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cyclophosphamide. Expert opinion was combined with previously unseen data from a recently completed randomised controlled trial in ANCA associated vasculitis.

Results

A pan-European group of fifteen experts participated in the elicitation meeting. Consensus expert prior opinion was that the most likely rates of disease remission within 6 months on cyclophosphamide or mycophenolate mofetil were 74% and 71%, respectively. This prior opinion will now be taken forward and will be modified to formulate a Bayesian posterior opinion once the MYPAN trial data from 40 patients randomised 1:1 to either CYC or MMF become available.

Conclusions

We suggest that the methodological template we propose could be applied to trial design for other rare diseases.

Introduction

Recently, the European Commission and subsequently the UK Department of Health prioritised strategies to improve the care of patients with rare diseases (prevalence $\leq$ 5 per 10,000) [1]. Such strategies should consider alternative therapeutic trial designs for small anticipated sample sizes [2]. The Bayesian approach begins by formally characterising prior opinion which is then updated with collected data using Bayes theorem to obtain a posterior opinion to inform clinical practice. It can be particularly useful when the sample sizes required by traditional frequentist designs are infeasible [2, 3]. But what is a Bayesian prior? And how do you elicit one? Accounts have been given of Bayesian prior elicitation in the context of designing randomised controlled trials [4–5] (RCTs). The findings of a Bayesian prior elicitation exercise have been cited to motivate conduct of an RCT evaluating warfarin for the treatment of rheumatic diseases [6]. However, such methods have yet to become part of routine practice for paediatric trials. This paper describes the novel approach that was taken to elicit expert prior opinion to inform the design of an RCT for a rare disease affecting children, polyarteritis nodosa (PAN). A full account of the statistical aspects of the proposed approach is given elsewhere [7]. The aim of the current paper is to provide further practical details on the steps taken to plan and carry out the Bayesian prior elicitation meeting so this process can be replicated by clinical trialists in other rare disease studies.

Polyarteritis nodosa and the MYPAN trial

Childhood PAN is a rare and severe multi-systemic vasculitic disease that affects approximately 1 per million children [8]; a full clinical description is provided elsewhere [8, 9]. Untreated, mortality is close to 100% [10]; with aggressive immunosuppression mortality is 4% [9]. A comprehensive literature search of published and unpublished studies relating to the treatment of PAN was undertaken (full details of the search strategy and databases searched are available upon request); an important finding was that there are no published or currently recruiting RCTs relating to PAN in children. All of the paediatric reports identified were uncontrolled study designs i.e. cohort and single-case studies, that rate as low-level evidence. Conclusions based on RCTs in adults with PAN [11–14] with important implications for children are: a)

treatment of severe PAN requires corticosteroids combined with intravenous cyclophospha-
mide (CYC); b) despite therapy, mortality associated with PAN in adults remains high at
4–22%; treatment-related toxicity contributes to this; c) adverse events (disease and treatment-
related) affect 54–100% patients; and d) avoidance of CYC in children is desirable if alterna-
tives exist since complications associated with CYC include infertility and malignancy.

The MYPAN study (Mycophenolate mofetil for childhood PAN) is an open-label non-infe-
riority RCT of mycophenolate mofetil (MMF) versus CYC for the treatment of PAN in chil-
dren (4–18 years), currently being set up. Table 1 compares the design of the MYPAN trial
with that of the MYCYC trial, an RCT comparing MMF with CYC for remission induction in
ANCA-associated vasculitis. The primary endpoint of the MYPAN study is disease remission
within six months of randomisation using a standard definition [15]. Due to its lower risk of
infertility/malignancy, MMF would be favoured [16] *unless* the 6-month remission rate on
MMF was more than 10% (absolute difference) smaller than that on CYC. A definitive frequen-
tist trial would require 513 patients per arm to have 90% power to declare MMF non-inferior
to CYC at the 2.5% one-sided significance level when remission rates on both treatments equal
70%. Previous experience suggests it would take well over 30 years to reach this sample size
[9,17], thus explaining why a paediatric trial for PAN has never been performed. Early plan-
ning of the MYPAN trial estimated that recruitment of 40 children across 30–40 European cen-
tres would be achievable over four years.

Instead, the MYPAN trial adopts a Bayesian approach, first characterising expert prior
opinion about the 6-month remission rate on CYC and the relative benefit of MMF as proba-
bility distributions before the trial begins, and then updating these distributions using Bayes
theorem once data become available [2]. This paper gives an account of how expert prior opin-
ion was elicited.

Table 1. Comparison of the design of 2 randomised controlled trials for vasculitis: MYPAN versus MYCYC.

Trial name and study population	MYPAN[a]: PAN[b] in children ($\geq$4 and $\leq$ 18 years)	MYCYC[c]: ANCA[d] associated vasculitis in adults & children (8 children, 132 adults)
Hypothesis	MMF[e] is not inferior (<10% absolute difference) to intravenous CYC[f] for induction of remission	MMF is not inferior (<12% absolute difference) to intravenous CYC for induction of remission
Entry criteria	i) Must fulfil classification criteria for PAN; ii) 1or more major PVAS[g] items and/or 3 or more minor PVAS items; iii) Must be newly diagnosed patients	i) Chronic inflammatory disease lasting at least 4 weeks; characteristic histology on biopsy and/or a positive ANCA; ii) 1 or more major BVAS[h] items and/or 3 or more minor PVAS items; iii) Must be newly diagnosed patients
Primary endpoint	Remission within 6 months defined as PVAS 0/63 on 2 consecutive readings at least one month apart on protocol steroid taper	Remission within 6 months defined as BVAS 0/63 on 2 consecutive readings at least one month apart on protocol steroid taper

[a]MYPAN: Mycophenolate mofetil for childhood polyarteritis nodosa;
[b]PAN: polyarteritis nodosa;
[c]MYCYC: Mycophenolate mofetil versus cyclophosphamide for ANCA associated vasculitis;
[d]ANCA: anti neutrophil cytoplasmic antibodies;
[e]MMF: Mycophenolate mofetil;
[f]CYC: cyclophosphamide;
[g]PVAS: Paediatric Vasculitis Activity Score;
[h]BVAS: Birmingham Vasculitis Activity Score.

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Materials and Methods

Identifying and inviting clinical experts

A Prior Elicitation Meeting was convened. Paediatric consultants in rheumatology, nephrology, immunology or other allied specialties were sought from across the UK and internationally, with an interest in vasculitis and experience of looking after children with PAN (having seen on average at least one case every two years). Invitations were sent to society email lists for the Pediatric Rheumatology International Trials Organisation [18] (www.printo.it), the British Society for Paediatric and Adolescent Rheumatology (www.bspar.org.uk), the British Association for Paediatric Nephrology (www.renal.org/BAPN), and the European Society for Pediatric Nephrology (http://espn.cardiff.ac.uk/), and also to 81 paediatric clinics treating PAN identified via Orphanet (www.orpha.net). Initial expressions of interest were received from 25 eligible respondents, of whom (for logistical reasons) 15 were eventually able to attend the meeting. The Expert Group comprised the following co-authors of this manuscript: MWB, CB, AC, RC, JD, PD, DE, MF, MJ, SM, NM, A-MM, JP, A van R-K and OS. Participating experts were drawn from across the EU and Turkey (see author affiliations).

No patients were involved in the Bayesian prior elicitation meeting. Instead, all participants were expert investigators who had volunteered to participate in the meeting (and are co-authors of this manuscript). Since participants were true investigators, rather than subjects involved in research, we did not require ethics approval for the elicitation exercise. We therefore followed the same process as other expert consensus exercises and did not seek written consent.

Selection of the specific quantities to be elicited

Expert opinion was sought on the probability that a patient satisfying the entry criteria of the MYPAN trial would succeed according to its primary endpoint. The probability of success for a patient treated with CYC was denoted by p_C, and expert views on the value of p_C were elicited directly. The corresponding probability of successful treatment with MMF was denoted by p_M, the value of which was derived indirectly from expert clinicians using questions about the relative merits of the two drugs. In statistical terms, this relative efficacy was expressed as the log-odds ratio defined by $\theta = \log_e\{p_M/(1—p_M)\}—\log_e\{p_C/(1—p_C)\}$. We interpret θ as a treatment effect, that is, a measure of the advantage of MMF over CYC for improving the chance of disease remission within 6-months. Positive values of θ indicate that the chances of remission are higher on MMF than CYC (superiority); values of θ close to 0 indicate equivalence of efficacy. The non-inferiority margin of $\delta = 0.1$, meaning that MMF would be preferred if $p_M—p_C \geq —0.1$, was fixed in advance of the meeting by the clinical trial management group since this difference was felt to be clinically important, and was similar to the definition of non-inferiority used in a previous vasculitis trial (see below and Table 1).

Mathematical modelling of beliefs and uncertainties

Opinion on the value of p_C was uniquely defined by two parameters designed to elicit the experts' choice for the most likely value of p_C, and their level of uncertainty about this value. These values were sought by asking the experts two questions (Q1 and Q2 in S1 Table). Opinion on the relative efficacy of CYC and MMF (θ) was modelled as a normal distribution, the parameters of which were determined by asking experts two questions (Q3 and Q4 in S1 Table). From the resulting opinions about p_C and θ, treated as independent, a consistent opinion about p_M was derived. The nature and strength of stated beliefs were characterised through the mean and mode of the distributions of p_C and p_M. To illustrate this, Fig 1 summarises the prior
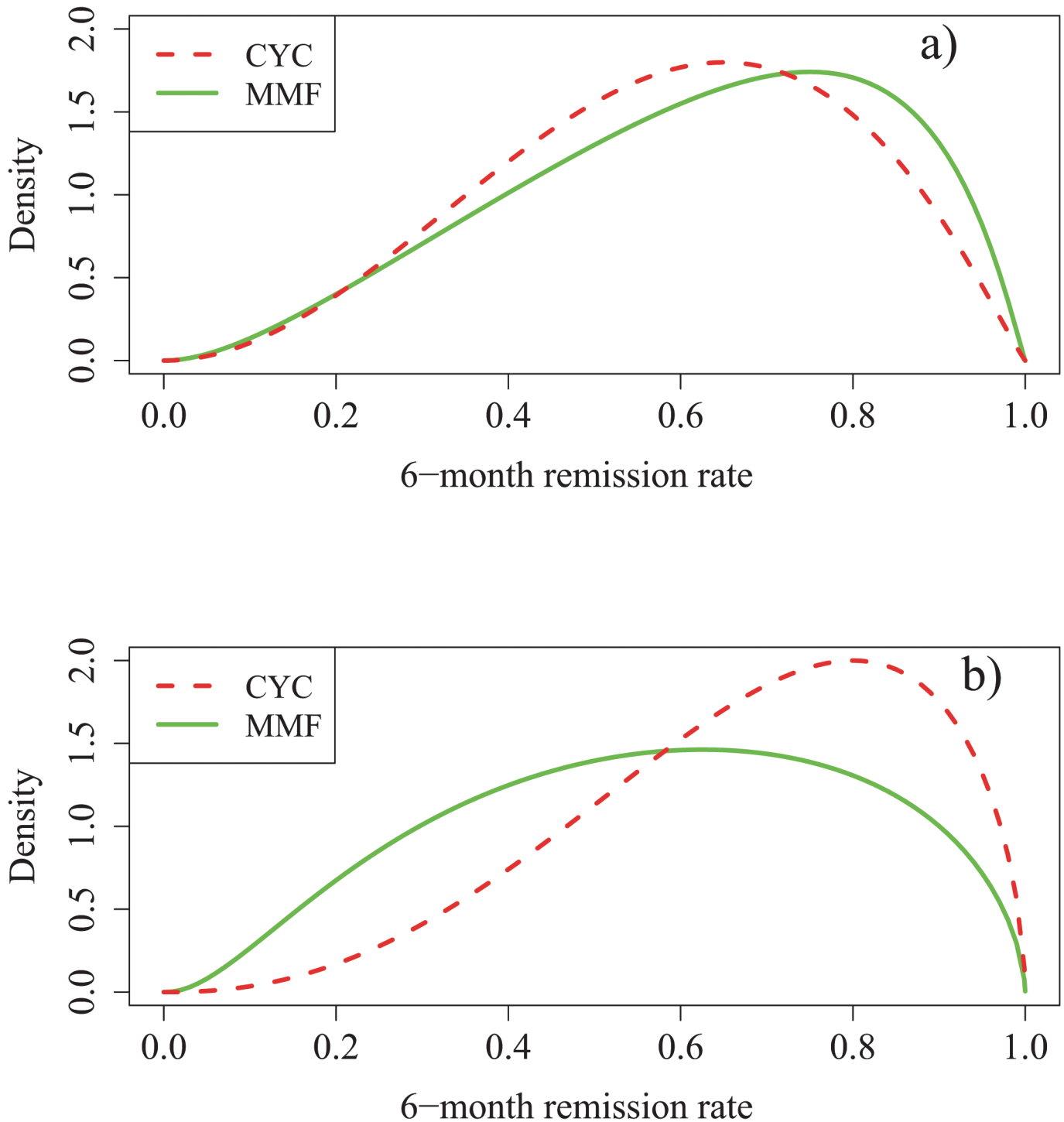
Fig 1. Range of prior opinions elicited before introduction of the MYCYC data. Fig 1A) Comparison of Expert A's prior densities for p_C and p_M. Expert A thought the most likely value of p_C is 0.65 and was 75% confident that p_C exceeds 0.45. Expert A was optimistic about the relative efficacy of MMF stating that the chance that MMF is superior to CYC is 63% while the chance it is inferior to CYC is 5%. Fig 1B) Comparison of Expert B's prior densities for p_C and p_M. Expert B thought the most likely value of p_C is 0.8 and was 75% confident that p_C exceeds 0.55. Expert B was more sceptical about the benefits of MMF, stating that the chance that MMF is superior to CYC is 10% while the chance it is inferior to CYC is 50%. Given each expert's prior opinion about p_C and the relative efficacies of MMF and CYC, a consistent prior for p_M is derived.

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distributions for two experts with extreme opinions about p_C and p_M relative to the rest of the group. Experts were asked two further questions to verify that the elicited opinion reflected their personal beliefs. Especially useful to the clinicians when considering their prior belief was the calculation of the *effective sample size* [19] (ESS) of a prior distribution; in other words, providing clinicians with the numbers of patients in a hypothetical clinical trial that would be required to statistically generate that level of certainty they had expressed for the parameters. For further details about these calculations, see [7]. The elicitation process was iterative, and the mathematical models and bespoke computer software allowed for quick and clear graphical representations of their densities. The consequences of adding hypothetical data sets to form posterior distributions were also shown. The computer program [7] was written in R [20] using the Shiny package [21] to create a user-friendly, interactive, interface. Software was tested on statistics students (seeking opinions on quantities that they understood) and clinical experts (PB, DE), which led to improvements and modifications.
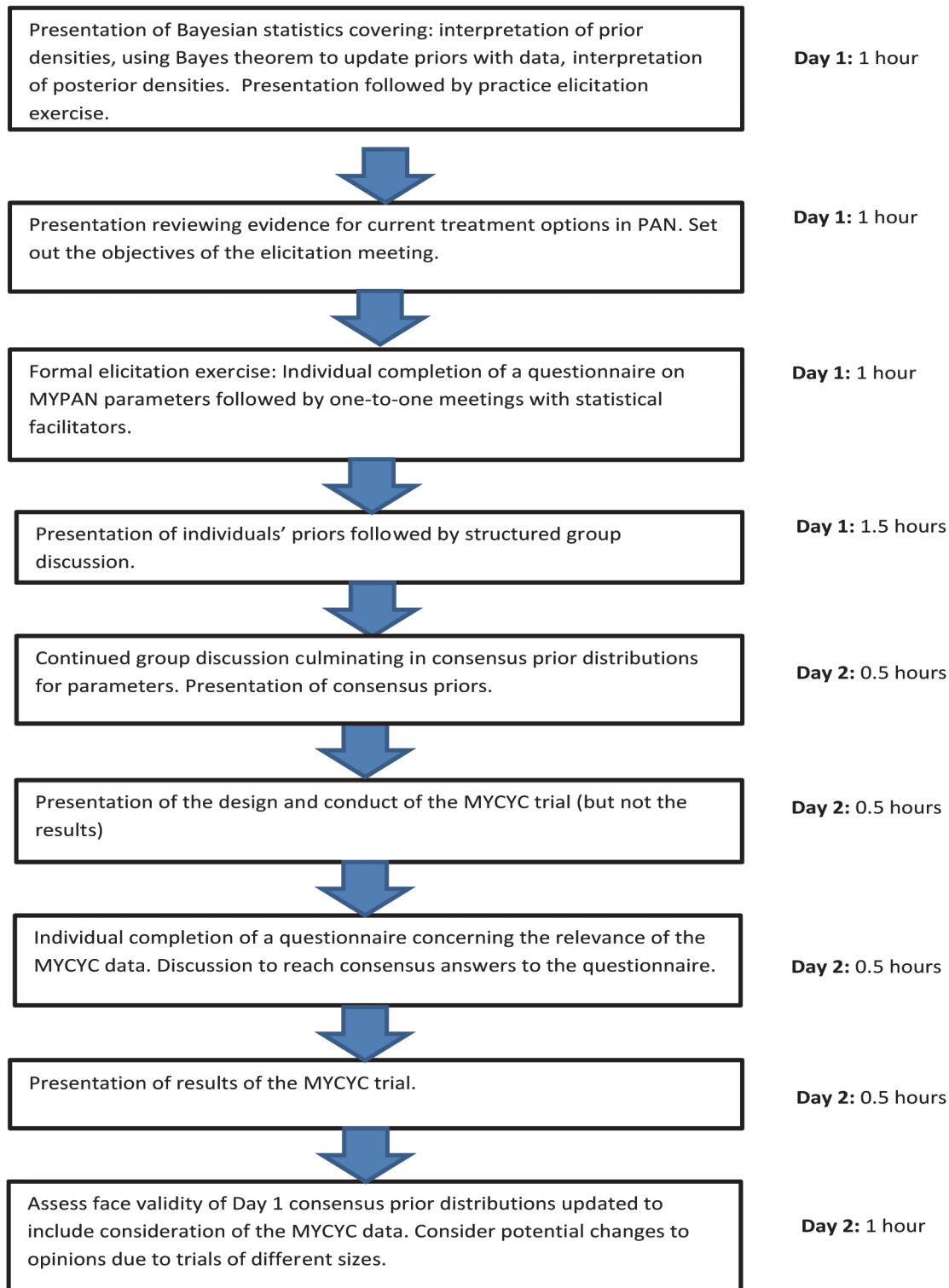
Training of the expert participants

Fig 2 illustrates the sequence of activities undertaken during the two day meeting and the time allocated to each. Four statistical facilitators were available throughout the two days to support the elicitation process. The meeting began with an overview of PAN [9] and the evidence supporting treatment options including the findings of RCTs in adults [11–14] (S2 Table). A talk by one of the statistical facilitators (JW) introduced Bayesian reasoning, credibility intervals and representation of treatment differences as log-odds ratios. A practice session was then held. A glass jar containing 60 small wooden blocks, coloured either pink or black, was briefly shown to the experts who were then asked for their opinions about the proportion of pink blocks in the jar. Specifically, they were asked for the most likely proportion of pink blocks (interpreted as the most likely value of their prior distribution) and for a value, p_L, between 0 and 1, which they believed the true proportion of pink blocks exceeded with probability 0.75. Using software similar to that to be used for the real elicitation, opinions were represented through graphics, summaries and ESSs. Having chosen a prior, the wooden blocks were transferred to a black bag, and four volunteers in turn each drew a sample of five, announced the number of pinks, and replaced them. The emerging posterior distribution was displayed. This exercise allowed the principles of the elicitation process and of the Bayesian method to be rehearsed in a neutral setting. The purpose of the statistical training was to standardise the experts' understanding of Bayesian methods so that they could interpret and check the goodness-of-fit of the prior distributions determined during the formal elicitation process.

Elicitation of opinions

Each expert was given a structured questionnaire designed to systematically ascertain prior opinion regarding outcomes for treatment with CYC and MMF (S1 File). Experts completed their questionnaires independently, and then met individually with statistical facilitators to discuss their answers. The R program was used to display the consequences of the answers provided. Changes to answers were allowed following discussion with facilitators, until the expert was happy that the model truly reflected their opinion.

Consensus prior distributions for θ and p_C were then sought, allowing the group to decide how to weight competing opinions. This was preferred to an automatic mathematical aggregation of individual prior distributions that would require the relevant competencies of participating experts to be quantified, or to working with multiple priors that would lead to multiple posterior distributions and no clear trial conclusion. A nominal group technique process of reaching consensus began with each expert individually commenting to the group on their

Presentation of Bayesian statistics covering: interpretation of prior densities, using Bayes theorem to update priors with data, interpretation of posterior densities. Presentation followed by practice elicitation exercise.	**Day 1:** 1 hour
Presentation reviewing evidence for current treatment options in PAN. Set out the objectives of the elicitation meeting.	**Day 1:** 1 hour
Formal elicitation exercise: Individual completion of a questionnaire on MYPAN parameters followed by one-to-one meetings with statistical facilitators.	**Day 1:** 1 hour
Presentation of individuals' priors followed by structured group discussion.	**Day 1:** 1.5 hours
Continued group discussion culminating in consensus prior distributions for parameters. Presentation of consensus priors.	**Day 2:** 0.5 hours
Presentation of the design and conduct of the MYCYC trial (but not the results)	**Day 2:** 0.5 hours
Individual completion of a questionnaire concerning the relevance of the MYCYC data. Discussion to reach consensus answers to the questionnaire.	**Day 2:** 0.5 hours
Presentation of results of the MYCYC trial.	**Day 2:** 0.5 hours
Assess face validity of Day 1 consensus prior distributions updated to include consideration of the MYCYC data. Consider potential changes to opinions due to trials of different sizes.	**Day 2:** 1 hour

Fig 2. Flow diagram illustrating the sequence of activities undertaken during the MYPAN prior elicitation meeting and the time allocated to each activity.

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answers to the structured questionnaire, starting with those with extreme values. Technical misunderstandings were identified and corrected. Lengthy and constructive discussions took place, with the ESS for the opinion about θ being particularly influential in leading to a reduction in the certainty expressed for this parameter. Potential results for the 40 patients in the MYPAN study were considered, and the corresponding posterior distributions displayed to show the relative influence of the prior and the data. Overnight reflection was allowed, and a final consensus (agreed by the majority as reflecting their opinion) was reached on the morning of the second day of the meeting.

Presentation of related trial results: the MYCYC trial

Once prior distributions had been determined for the parameters of interest, further information was presented to the experts. This concerned the soon-to-be published MYCYC trial (http://www.clinicaltrials.gov/show/NCT00414128) involving 132 adults and 8 children. The design, treatment arms, and primary endpoint for MYCYC were similar to that planned for MYPAN (Table 1), but the final results were not yet published.

## Influence of MYCYC trial results on the prior opinion

Following the presentation of the MYCYC trial design, but before mention of any results, the experts were asked their opinions of the relevance of the MYCYC results to those of MYPAN. Individually they were tasked with completing another structured questionnaire (S2 File) designed to elicit opinion about the relationship between probabilities of response for MYPAN and MYCYC patients on CYC or MMF. Individuals' answers were displayed on flip charts. Consensus was reached after each expert had explained their views. After consensus had been reached on the relationship between the results of the two trials, key results from MYCYC were presented and key points of comparison between the MYCYC and MYPAN trials were further highlighted. Prior distributions from the first day were then updated by including the influence of the MYCYC results; a full account of the statistical approach used to incorporate these historical data into the prior distributions is provided in [7]. Revisions to opinions about the relationship between the two trials were invited. A final consensus about beliefs in the response probabilities in the MYPAN population was then reached. Opinion about the allocation ratio that should be used in the MYPAN trial was sought but views about the total sample size were not since this number was considered fixed by the maximum feasible number of patients that could be recruited within the timeframe of the trial.

Results

Experts' final responses to the first structured questionnaire are available online (S1 Table). Group discussion led some experts to change their initial answers, either because they had misinterpreted the questions, or because they accepted suggestions made by their colleagues. Based on the consensus answers of the experts (Fig 3), the most likely value of the remission rate for CYC was 0.70 (90% probability that p_C lies between 30% and 91%); this opinion equated to an ESS of 5 patients on CYC. The most likely remission rate on MMF was 0.65 (with 90% probability that p_M lies between 21% and 90%). The strength of prior opinion concerning θ corresponded to an ESS of 39 patients on each treatment.

The results of the MYCYC trial, in which 70 ANCA associated vasculitis patients were treated with CYC and 70 with MMF, were that 74% of patients on CYC achieved remission within 6 months, compared with 73% of patients on MMF. Incorporating the consensus relevance of these data (S3 Table) resulted in the modified opinions summarised in Fig 4. The most likely remission rates on CYC and MMF changed to 0.74 and 0.71 respectively. In terms of ESS, prior
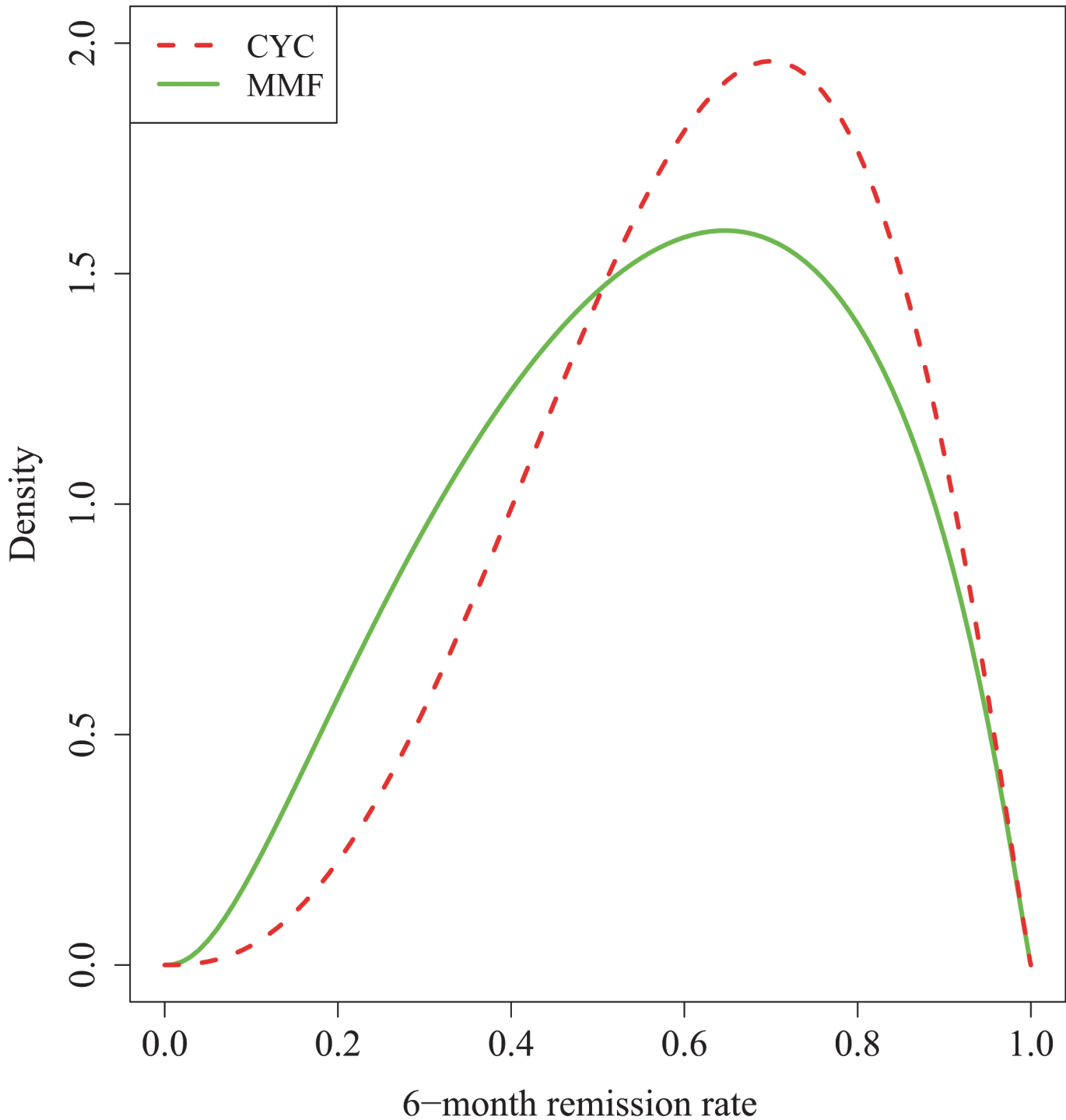
Fig 3. Expert prior opinion before introduction of the MYCYC data regarding 6-month remission rates using treatment with CYC or MMF for children with PAN. Reprinted from [7] under a CC BY license, with permission from the authors, original copyright 2014. Prior opinion was that the most likely value for p_C was 0.7; 90% and 50% credibility intervals were (0.30, 0.91) and (0.50, 0.78), respectively. The effective sample size was 5 patients on CYC. The prior for p_M is derived from those for p_C and θ. It had mode = 0.65; 90% and 50% credibility intervals were (0.21, 0.90) and (0.41, 0.74), respectively.

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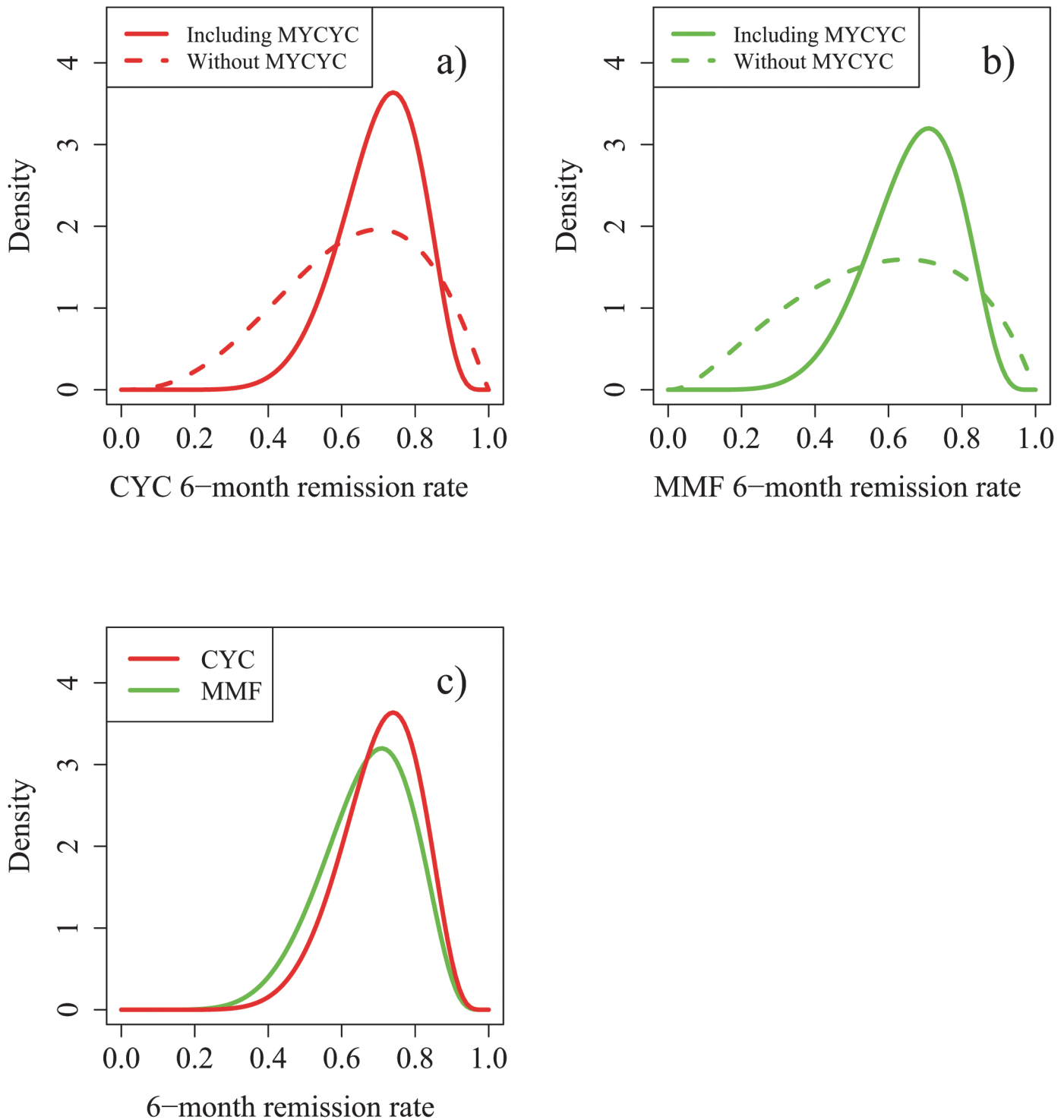
Fig 4. Influence of the MYCYC trial results on expert prior opinion regarding 6-month remission rates using treatment with CYC or MMF for children with PAN. Reprinted from [7] under a CC BY license, with permission from the authors, original copyright 2014. Fig 4A): Influence of MYCYC results on prior opinion for p_C. The modified prior distribution for p_C after considering the MYCYC results had mode = 0.74; 90% and 50% credibility intervals were (0.51, 0.86) and (0.63, 0.78), respectively. This level of certainty is equivalent to what would be obtained from a clinical trial involving 17 patients treated with CYC (effective sample size). Fig 4B): Influence of MYCYC results on prior opinion for p_M. The modified prior for p_M after considering the MYCYC results had mode = 0.71; 90% and 50% credibility intervals were (0.45, 0.85) and (0.59, 0.76), respectively. Fig 4C): Comparison of the final expert prior opinions for p_C and p_M incorporating the MYCYC data.

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information on p_C was now worth 17 patients on CYC and that on θ worth 48 patients on each treatment. The effect of 70 real patients per treatment arm in MYCYC was to increase the former ESS by 12 and the latter by 9, showing how the new information from MYCYC was downweighted in the context of MYPAN. The MYCYC data had a substantial influence on opinions of the absolute values of remission rates on the two treatments, but much less influence on their relative merits (data not shown). Fig 5 shows how these final prior opinions would change after two hypothetical outcomes of MYPAN itself.

Discussion

A major challenge in rare diseases is conducting clinical trials with sufficient power to inform best clinical practice when anticipated sample sizes are small. Historically, this has been a major barrier in rare paediatric autoimmune diseases and almost certainly explains why a clinical trial for PAN in children has never been undertaken. We have adopted a Bayesian clinical trial design to overcome this barrier, and describe the process for elicitation of expert prior opinion to inform the design of the MYPAN trial, the first RCT for childhood PAN.

Recently, guiding principles in relation to good practice for prior opinion elicitation have been suggested [22], and where possible we have adopted these. Using a formal Bayesian prior elicitation exercise we have established that the most likely rates of disease remission within 6 months on CYC and MMF are 74% and 71%, respectively. These findings are likely to remain the state of knowledge until they can be updated with data received from MYPAN. Posterior distributions will quantify the uncertainty about disease remission rates that remains once the MYPAN data are available. This uncertainty means that conclusions about whether MMF is non-inferior to CYC are unlikely to be definitive. However, it would take a prospective randomised trial recruiting over 500 patients per arm to achieve that. That said, for a rare disease like PAN, clinically informative results can still be obtained.

Our results revealed that experts can be quite uncertain of absolute effects of treatments, but more convinced of their relative merits. In other words, for MYPAN, experts were uncertain about the precise value of p_C but more confident that p_M would not be too dissimilar. If the actual data from MYPAN confirm the prior, then confidence in those opinions will grow and this in turn would have an appreciable impact on the treatment approaches that would subsequently be adopted. If the data are at odds with the prior, this will be reflected in a clear and documented change in opinion: the prior is not so strong that contradictory evidence is dismissed.

In the prior elicitation meeting, experts accepted the Bayesian paradigm as a framework for representing their prior knowledge and uncertainty. We canvassed opinion from a pan-European group of experts. However, as the experts were volunteers, their views may not be representative of those who did not accept the invitation to participate.

In conclusion, the methodology developed for this exercise allows formal and structured learning about the treatment of childhood PAN to begin, and to be updated by MYPAN and studies beyond that. We suggest that this methodological template could be applied to trial design for other rare diseases, and is of particular relevance to rare autoimmune conditions that currently lack a good evidence base for treatment.
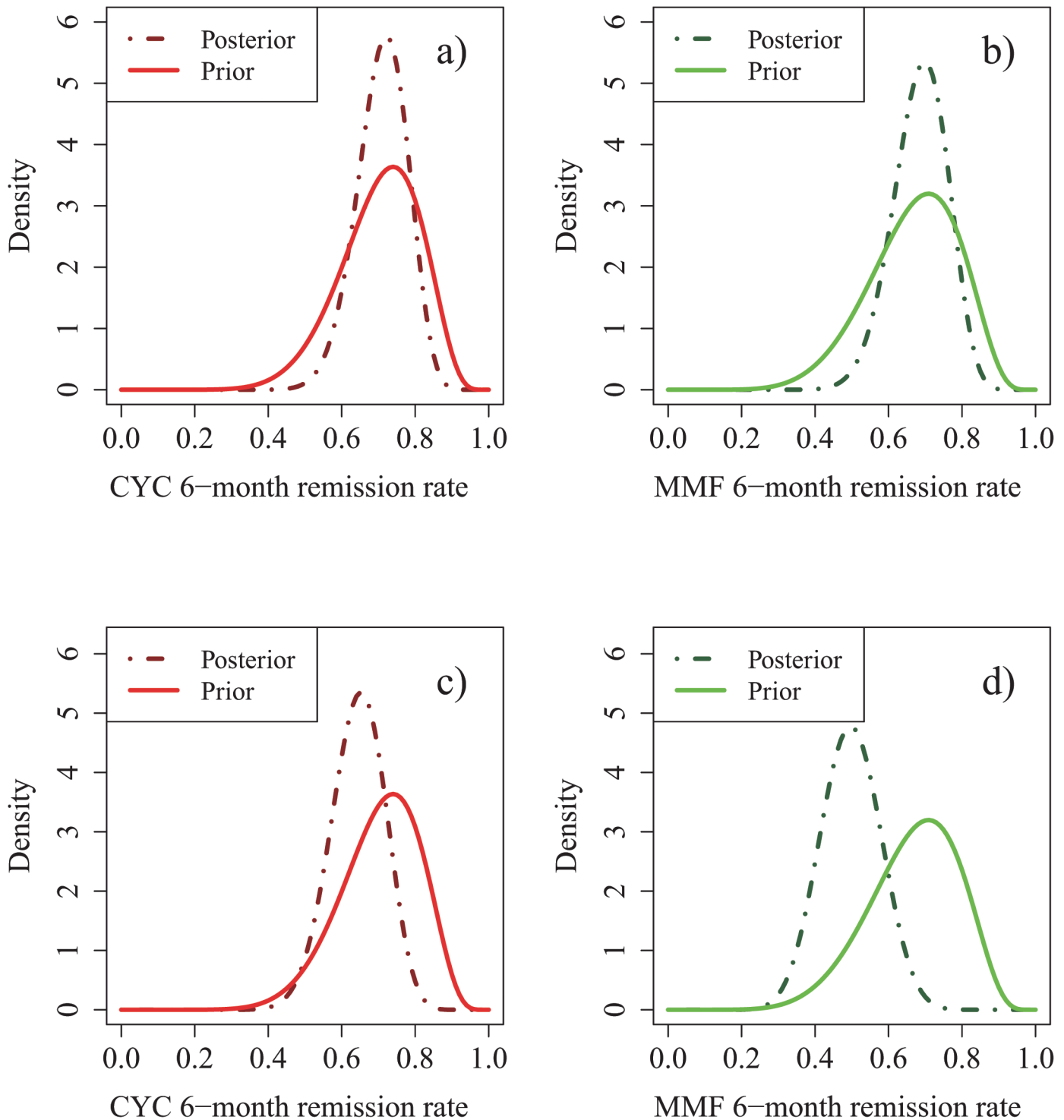
Fig 5. Posterior densities for p_C and p_M based on the prior of [Fig 4](#) following observation of 20 patients treated on each study arm, with 14/20 successes on CYC and 14/20 successes on MMF (Hypothetical Scenario 1), or with 14/20 successes on CYC and 7/20 successes on MMF (Hypothetical Scenario 2). Fig 5A) and 5C) are reprinted from [7] under a CC BY license, with permission from the authors, original copyright 2014. Fig 5A): Prior and posterior densities for p_C in Hypothetical Scenario 1. Fig 5B): Prior and posterior densities for p_M in Hypothetical Scenario 1. Fig 5C): Prior and posterior densities for p_C in Hypothetical Scenario 2. Fig 5D): Prior and posterior densities for p_M in Hypothetical Scenario 2.

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Supporting Information

S1 File. Structured questionnaire designed to systematically ascertain prior opinion regarding outcomes for treatment with CYC and MMF.
(PDF)

S2 File. Structured questionnaire designed to ascertain expert opinion on the relevance of the MYCYC results to those of MYPAN.
(PDF)

S1 Table. Individual experts' final answers to Q1-Q4 and consensus answers agreed by the group before results from the MYCYC trial were revealed.
(PDF)

S2 Table. Clinical trials in adults with polyarteritis nodosa.
(PDF)

S3 Table. Individual experts' answers to four questions eliciting their beliefs about the relevance of the MYCYC trial results for informing opinion about 6-month remission rates in the MYPAN trial.
(PDF)

Acknowledgments

Author Contributions

References

1. Department of Health. Consultation on the United Kingdom Plan for Rare Diseases. 2013. Available: www.gov.uk/government/uploads/system/uploads/attachment_data/file/215141/dh_132883.pdf. Accessed 2014 Mar 30.

2. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. BMJ 1995; 311:1621–1625. PMID: 8555809

3. Gupta S, Faughnan ME, Tomlinson GA, Bayoumi AM. A framework for applying unfamiliar trial designs in studies of rare diseases. J Clin Epidemiol 2011; 64:1085–1094. doi: 10.1016/j.jclinepi.2010.12.019 PMID: 21530171

4. Tan S-B, Chung Y-F A, Tai B-C, Cheung Y-B, Machin D. Elicitation of prior distributions for a phase III randomized controlled trial of adjuvant therapy with surgery for hepatocellular carcinoma. Control Clin Trials 2003; 24: 110–121. PMID: 12689733

5. Hiance A, Chevret S, Levy V. A practical approach for eliciting expert prior beliefs about cancer survival in phase III randomized trial. J Clin Epidemiol 2009; 62: 431–437. doi: 10.1016/j.jclinepi.2008.04.009 PMID: 19010642

6. Johnson SR, Granton JT, Tomlinson GA, Grosbein HA, Hawker GA, Feldman BM. Effect of warfarin on survival in scleroderma-associated pulmonary arterial hypertension (SSc-PAH) and idiopathic PAH.

Belief elicitation for Bayesian priors. J Rheumatol 2011; 38:462–469. doi: 10.3899/jrheum.100632 PMID: 21159827

7. Hampson LV, Whitehead J, Eleftheriou D, Brogan P. Bayesian methods for the design and interpretation of clinical trials in very rare diseases. Stat Med 2014; 33:4186–4201. doi: 10.1002/sim.6225 PMID: 24957522

8. Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. Pediatr Nephrol 2010; 25:1641–1652. doi: 10.1007/s00467-009-1336-1 PMID: 19946711

9. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. Arthritis Rheum 2013; 65:2476–2485. doi: 10.1002/art.38024 PMID: 23754739

10. Bagenstoss AH, Shick RM, Polley HF. The effect of cortisone on the lesions of periarteritis nodosa. Am J Pathol 1951; 27:537–559. PMID: 14846911

11. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. Br J Rheumatol 1997; 36:1290–1297. PMID: 9448590

12. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Généreau T et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum 1995; 38:1638–1645. PMID: 7488285

13. Guillevin L, Cohen P, Mahr A, Arène JP, Mouthon L, Puéchal X et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. Arthritis Rheum 2003; 49:93–100. PMID: 12579599

14. Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Puéchal X et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010; 62:1186–1197. doi: 10.1002/art.27340 PMID: 20131268

15. Dolezalova P, Price-Kuehne FE, Özen S, Benseler SM, Cabral DA, Anton J et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2013; 72:1628–1633. doi: 10.1136/annrheumdis-2012-202111 PMID: 23100606

16. Hiemstra TF, Jones RB, Jayne DR. Treatment of Primary Systemic Vasculitis with the Inosine Monophosphate Dehydrogenase Inhibitor Mycophenolic Acid. Nephron Clin Pract 2010; 116:c1–c10. doi: 10.1159/000314543 PMID: 20484933

17. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010; 69:798–806. doi: 10.1136/ard.2009.116657 PMID: 20413568

18. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch Dis Child 2011; 96:596–601. doi: 10.1136/adc.2010.188946 PMID: 21317432

19. Morita S, Thall PF, Müller P. Determining the effective sample size of a parametric prior. Biometrics 2008; 64:595–602. PMID: 17764481

20. R Core Team. R: A language and environment for statistical computing; 2013. R Foundation for Statistical Computing, Vienna, Austria.

21. RStudio and Inc. Shiny: Web Application Framework for R; 2013. R package version 0.7.099.

22. Johnson SR, Tomlinson GA, Hawker GA, Granton JT, Feldman BM. Methods to elicit beliefs for Bayesian priors: a systematic review. J Clin Epidemiol 2010; 63:355–369. doi: 10.1016/j.jclinepi.2009.06.003 PMID: 19716263