MRC Hubs for Trials Methodology Research
North West Hub

UNIVERSITY OF LIVERPOOL

# Case study 1: A Bayesian clinical trial in children with polyarteritis nodosa (PAN)

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# Traditional ‘frequentist’ approach

Estimate number of patients required to detect a clinically relevant treatment effect

Phase III RCT should provide a definitive answer

Rare diseases

- Sample sizes are often unachievable
- Definitive clinical trials are impossible in very rare diseases
  - *unless the new treatment is miraculous*

# What is the alternative?

- Observational designs?
  - May be valuable
  - Comparative treatment effects prone to selection bias
- RCT provides best evidence
  - Small trial ⟹ wide CI ⟹ unconvincing for clinical decision making
  - Unethical?

*Health Technology Assessment* 1998; Vol. 2: No. 15

**Review**

# Ethical issues in the design and conduct of randomised controlled trials

SJL Edwards
RJ Lilford
DA Braunholtz
JC Jackson
J Hewison
J Thornton

# HTA report

"Given the choice between a small trial and no trial, the small trial is preferable and/or that Bayesian designs are most appropriate in such cases"

"Even then, a trial is not necessarily unethical since, given equipoise, the patient does not lose out in prospect and a more precise estimate (though not a 'definitive' answer) is obtained by going ahead with a trial than by eschewing randomisation altogether. "

# Bayesian approach

## Clinical trials and rare diseases: a way out of a conundrum

Richard J Lilford, J G Thornton, D Braunholtz

**Currently, clinical trials tend to be individually funded and applicants must include a power calculation in their grant request. However, conventional levels of statistical precision are unlikely to be obtainable prospectively if the trial is required to evaluate treatment of a rare disease. This means that clinicians treating such diseases remain in ignorance and must form their judgments solely on the basis of (potentially biased) observational studies, experience, and anecdote. Since some unbiased evidence is clearly better than none, this state of affairs should not continue. However, conventional (frequentist) confidence limits are unlikely to exclude a null result, even when treatments differ substantially. Bayesian methods utilise all available data to calculate probabilities that may be extrapolated directly to clinical practice. Funding bodies should therefore fund a repertoire of small trials, which need have no predetermined end, alongside standard larger studies.**

is because they cannot be expected to provide a "definitive" answer—that is, they cannot be expected to detect or exclude clinically worthwhile differences between treatments with standard levels of statistical confidence. Hence they are not funded by grant giving bodies.

In this article we argue that randomised trials can be expected to provide useful information, even when a definitive answer is unlikely in prospect. Standard (so called frequentist) statistical techniques are not, however, suitable in these circumstances, but bayesian methods provide a much clearer guide to action.

### An example of the problem

The evaluation of treatments applicable to congenitally abnormal fetuses (fetal surgery) is an example. The conditions for which this surgery may be contemplated are, individually, rare. For example,

BMJ. 1995 December 16; 311(7020): 1621–1625.

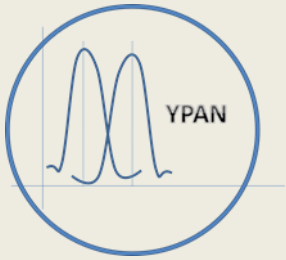
# Bayesian approach

- Define a prior distribution for the parameter of interest
  - Based on previous studies and expert opinion
- Collect some data
  - This ‘new’ data will influence and change the prior opinion about the parameter of interest
- Prior distribution updated with the new data to provide a posterior distribution
  - Assessment of where the parameter lies will change
  - Uncertainty about the parameter value will decrease

[1]BMJ. 1995 December 16; 311(7020): 1621–1625.

# Bayesian approach

- Advantages
  - Makes prior belief explicit
  - Can be more efficient
  - Produces a probability distribution
- Disadvantages
  - Priors




# MYPAN

## An open label randomised controlled trial of mycophenolate mofetil (MMF) versus cyclophosphamide (CYC) for the induction of remission of childhood polyarteritis nodosa (PAN)

UCL

VASCULITIS UK

PRINTO
Paediatric Rheumatology INternational Trials Organization

Arthritis Research UK
Providing answers today and tomorrow

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CTRC
Clinical Trials Research Centre

the Lauren Currie Twilight Foundation
FUNDING VASCULITIS RESEARCH

# PAN

- Systemic vasculitis of small- or medium-sized muscular arteries, typically involving renal and visceral vessels but sparing the pulmonary circulation
- With treatment, five-year survival is 80%
- Without treatment, five-year survival is 13%
- Annual incidence 2.0–9.0/million in adults
- Peak age onset 7–11 years

Watts et al, Vasculitis 2nd ed, Oxford 2009

Ozen et al, J Pediatrics, 2004

Dillon et al, Pediatric nephrology 2009

# There has never been a clinical trial for children with PAN

Cyclophosphamide (CYC) has become standard of care

# CYC toxicity

Durkan A et al; Non-corticosteroid treatment for nephrotic syndrome in children. Cochrane database systematic review CD002290
Coutinho et al; De novo malignancy after paediatric renal replacement therapy. ADC 85: 478 2483

- Leucopenia: 32%
- Thrombocytopenia: 2%
- Severe infections: 3%
- Alopecia: 14%
- Haemorrhagic cystitis: 4%
- Nausea and vomiting
- Bladder fibrosis
- Infertility
  - 50% of females after one year exposure
  - No safe cumulative dose threshold identified in males
- Malignancy (bladder cancer and haematological malignancies)
  - Greater than 20 mg/kg CYC in children increases risk of bladder cancer

# MMF (Mycophenolate Mofetil )

- Strong immunosuppressant with low toxicity profile
  - Superior to azathioprine for prophylaxis of renal allograft rejection in adults
  - Same efficacy as CYC in SLE
  - Similar efficacy as CYC in ANCA vasculitis in adults (MYCYC trial)
- Low-level evidence: case reports, retrospective case series, expert opinion in childhood PAN
- Could MMF be an alternative induction agent for PAN?

# Hypothesis

MMF not inferior to CYC for induction of remission of PAN within 6 months

# Recruitment

Feasibility suggested ~ 40 patients recruited from 20-30 centres across Europe over 3 years

# Traditional ‘frequentist’ approach

- Non-inferiority margin of 10%
- Type I error 5% and power of 90%

| % remission at 6 months CYC | Total patients |
|---|---|
| 70 | 884 |
| 75 | 790 |
| 80 | 674 |
| 85 | 538 |

# Traditional ‘frequentist’ approach

- Non-inferiority margin of 10%
- Type I error 5% and power of 90%

| % remission at 6 months CYC | Total patients | Years to recruit |
|---|---|---|
| 70 | 884 | 74 |
| 75 | 790 | 66 |
| 80 | 674 | 56 |
| 85 | 538 | 45 |

Not feasible for PAN !

# Bayesian approach for MYPAN

# Elicitation of prior opinion

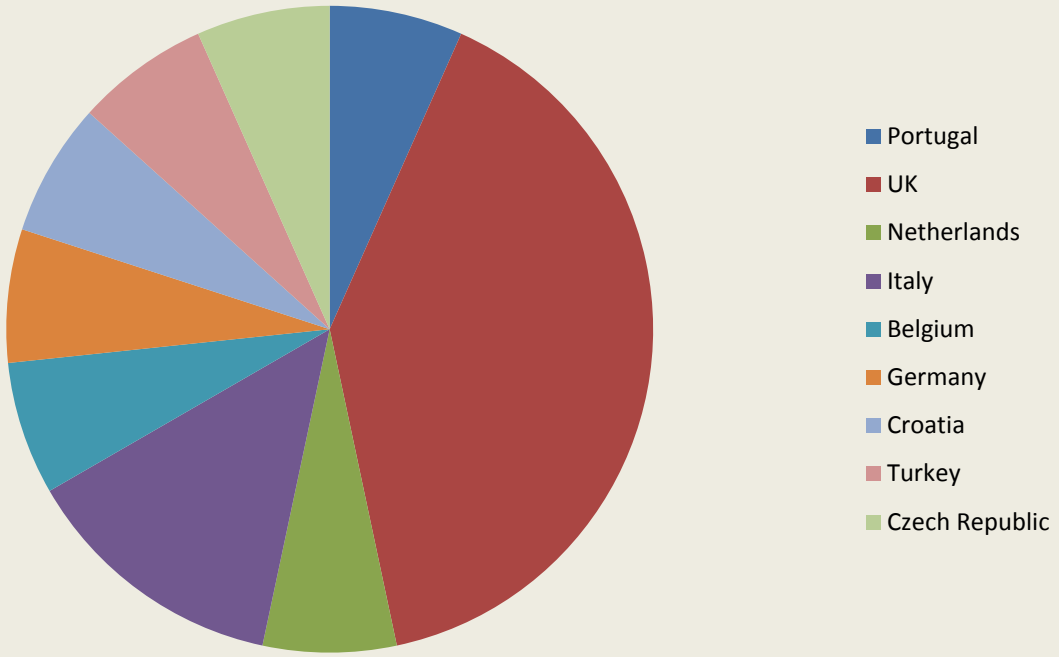
- Two day meeting, London, September 2013
- Call for participation in the meeting was circulated:
  - Paediatric consultants in rheumatology, nephrology, immunology or other allied specialisms
  - An interest in vasculitis and experience of looking after children with PAN

# Elicitation of prior opinion

- Circulated through
  - PRINTO (Pediatric Rheumatology INternational Trials Organisation)
  - British Society for Paediatric and Adolescent Rheumatology
  - British Association for Paediatric Nephrology
  - European Society for Paediatric Nephrology
  - Child-only clinics treating PAN identified via Orphanet
- Expressions of interest from 25 eligible respondents

# Elicitation of prior opinion

- 15 experts attended the elicitation meeting



# Elicitation Meeting

- ‘Bayesian’ training provided
- Practice questions discussed
- Clinical, and trial associated background presented
- Formal elicitation

# Elicitation Meeting

- Each expert was asked six questions to elicit prior opinion about $p_{CYC}$ and $\theta_1$
  - responses requested using visual analogue scales ranging from 0 to 1
- Experts completed independently
- Met individually with "statistical facilitators"
  - Important that experts understood the questions and that their answers reflected their opinion
  - Answers were displayed graphically using R software developed by Lisa Hampson

[1] Hampson LV, Whitehead J, Eleftheriou D, Brogan P. Bayesian methods for the design and interpretation of clinical trials in very rare diseases. *Statistics in Medicine* 2014 33:4186-4201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http://www.research.lancs.ac.uk/portal/en/publications/r-software-to-accompany-bayesian-methods-for-th
design-and-interpretation-of-trials-in-rare-diseases(350b8e33-dca7-470b-9cee-f93eab812fa5).html





# R software to accompany "Bayesian methods for the design and interpretation of trials in rare diseases".

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*Non-textual form › Software*

Published



Overview | Cite this

Lisa Hampson (Photographer)
John Whitehead (Photographer)

Department of Mathematics and Statistics

## Associated organisations

Medical and Pharmaceutical Statistics Research Unit



## Download

R software to accompany "Bayesian methods for t...
122 KB, application/x-zip-compressed

30/04/13

# $p_{CYC}$

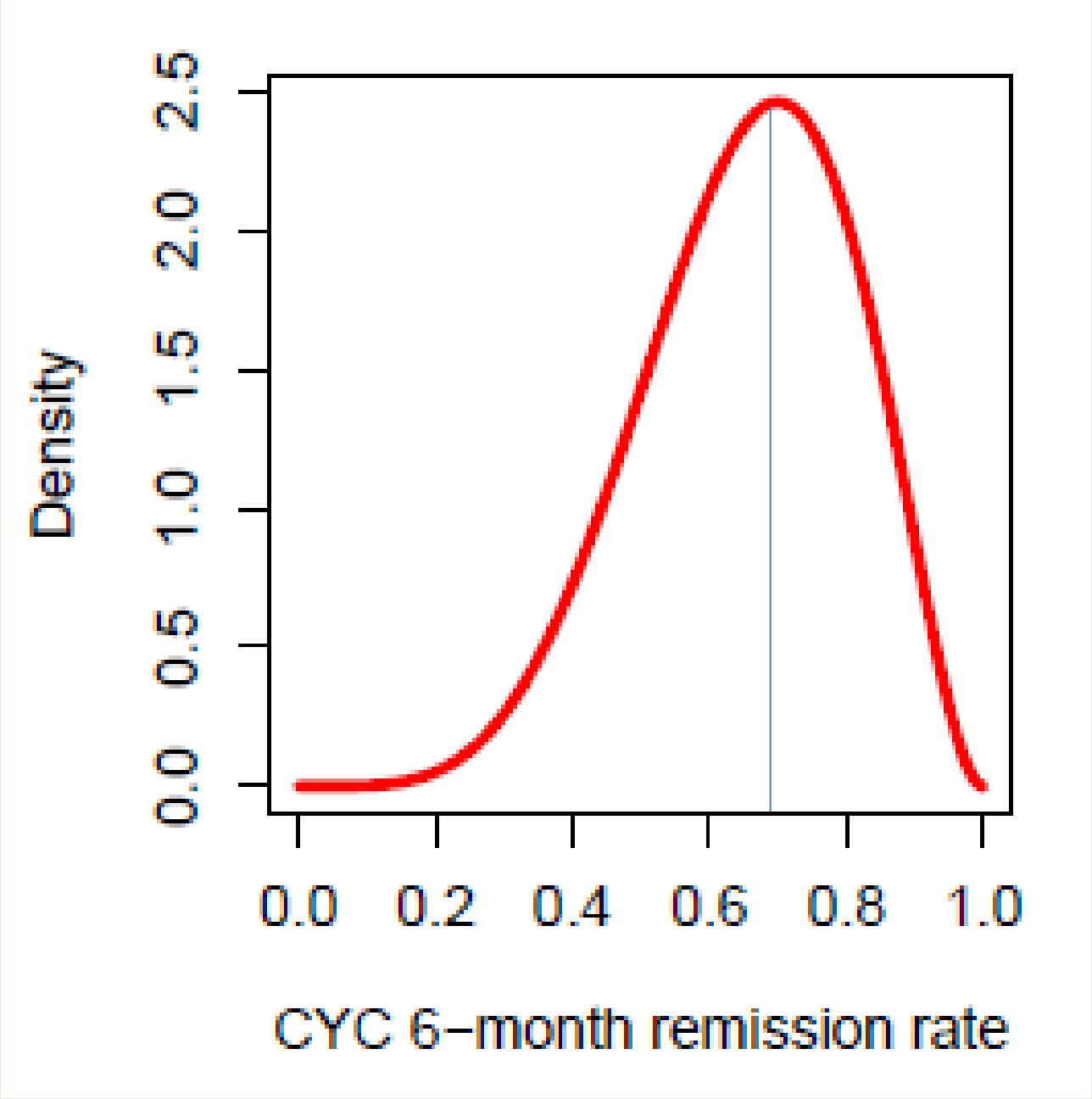
- Q1: What do you think the 6-month remission rate for children with PAN treated with CYC/steroids ($p_{CYC}$)?

A1: 0.7

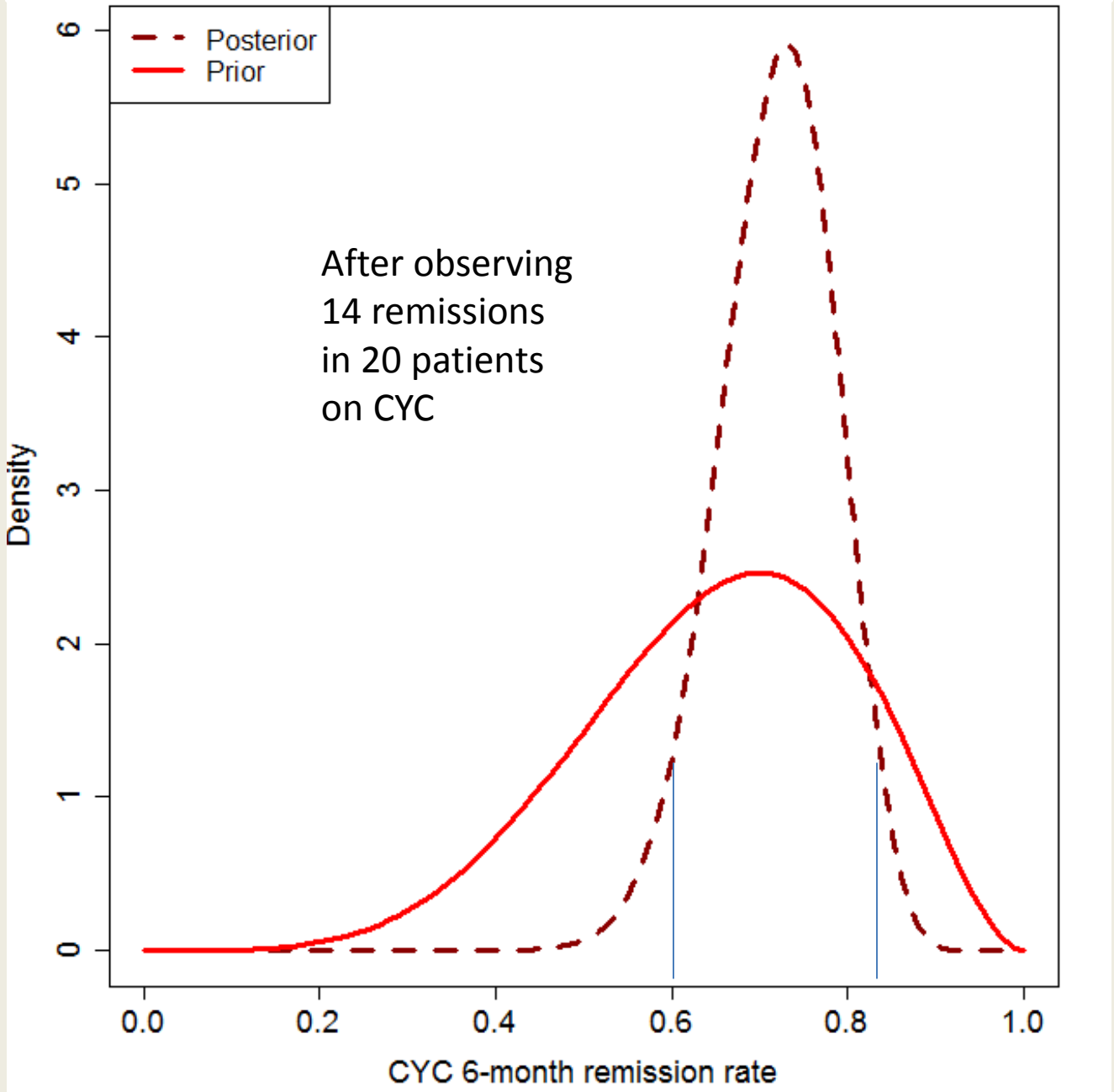
- Q2: Provide a proportion such that you are 75% sure that the true 6-month remission rate on CYC/steroids exceeds this value.

A2: 0.55

Prior distribution for $p_{CYC}$



# Prior and posterior distribution for $p_{CYC}$



# Elicitation Meeting

- Nominal group technique used to arrive at consensus
- Effective sample size of prior distribution
- MYCYC trial in ANCA associated vasculitis presented
- Elicitation of relevance of the trial
- MYCYC trial results presented
- Slight modifications made to consensus prior

# Consensus prior

$P_{CYC}$ 74%

$P_{MMF}$ 71%

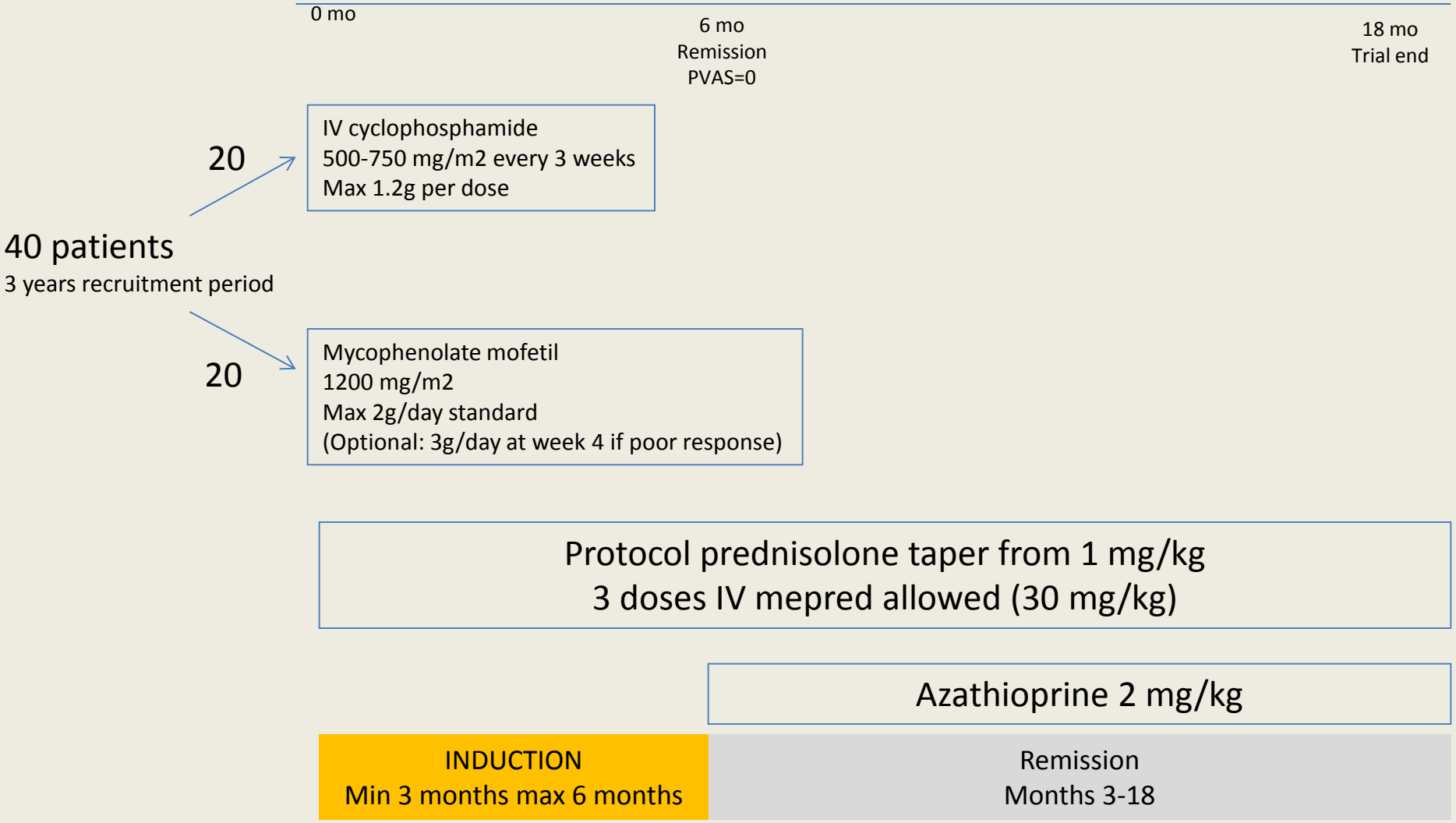
PLOS | ONE

RESEARCH ARTICLE

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

**Citation:** Hampson LV, Whitehead J, Eleftheriou D, Tudur-Smith C, Jones R, Jayne D, et al. (2015) Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa. PLoS ONE 10(3): e0120981. doi:10.1371/journal.pone.0120981

# Trial overview



# Concluding remarks

- Trials in very rare diseases are challenging
- Some randomised evidence is better than none
- Bayesian methodology may help

**BUT**

  - Replaces data with prior opinion
  - Robust approach to elicitation
  - Use of expert prior opinion is not a substitute if adequate sample size is available

# Questions…

1. How many experts do we need?
2. Other methods to elicit prior opinion?
3. Other design options for MYPAN?

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# Thank you

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