Article

CLINICAL TRIALS

Clinical Trials
2017, Vol. 14(1) 78–87

DOI: 10.1177/1740774516673362
journals.sagepub.com/home/ctj
SAGE

Bayesian survival analysis in clinical trials: What methods are used in practice?

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Abstract

Background: Bayesian statistics are an appealing alternative to the traditional frequentist approach to designing, analysing, and reporting of clinical trials, especially in rare diseases. Time-to-event endpoints are widely used in many medical fields. There are additional complexities to designing Bayesian survival trials which arise from the need to specify a model for the survival distribution. The objective of this article was to critically review the use and reporting of Bayesian methods in survival trials.

Methods: A systematic review of clinical trials using Bayesian survival analyses was performed through PubMed and Web of Science databases. This was complemented by a full text search of the online repositories of pre-selected journals. Cost-effectiveness, dose-finding studies, meta-analyses, and methodological papers using clinical trials were excluded.

Results: In total, 28 articles met the inclusion criteria, 25 were original reports of clinical trials and 3 were re-analyses of a clinical trial. Most trials were in oncology (n = 25), were randomised controlled (n = 21) phase III trials (n = 13), and half considered a rare disease (n = 13). Bayesian approaches were used for monitoring in 14 trials and for the final analysis only in 14 trials. In the latter case, Bayesian survival analyses were used for the primary analysis in four cases, for the secondary analysis in seven cases, and for the trial re-analysis in three cases. Overall, 12 articles reported fitting Bayesian regression models (semi-parametric, n = 3; parametric, n = 9). Prior distributions were often incompletely reported: 20 articles did not define the prior distribution used for the parameter of interest. Over half of the trials used only non-informative priors for monitoring and the final analysis (n = 12) when it was specified. Indeed, no articles fitting Bayesian regression models placed informative priors on the parameter of interest. The prior for the treatment effect was based on historical data in only four trials. Decision rules were pre-defined in eight cases when trials used Bayesian monitoring, and in only one case when trials adopted a Bayesian approach to the final analysis.

Conclusion: Few trials implemented a Bayesian survival analysis and few incorporated external data into priors. There is scope to improve the quality of reporting of Bayesian methods in survival trials. Extension of the Consolidated Standards of Reporting Trials statement for reporting Bayesian clinical trials is recommended.

Keyword

Bayesian, clinical trial, posterior distribution, prior distribution, survival modelling, systematic review, time-to-event

Introduction

Bayesian statistics are an appealing alternative to the traditional frequentist approach to the design, analysis, and reporting of clinical trials, especially when definitive levels of evidence are infeasible.[1] This challenge may arise if the disease of interest is rare, or if clinical interest lies in monitoring a rare event of a common disease, or a small patient subgroup.[2–5] How to proceed when information is scarce is a problem frequently faced by investigators; it is estimated that there are 6000–8000 rare diseases affecting in total around 30 million people in the European Union,[6] while rare

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cancers account for one fifth of all new cancer diagnoses.[7] In such cases, clinicians must make prescribing decisions informed by their own clinical experiences and/or their interpretation of underpowered clinical trials.

The merits and drawbacks of Bayesian approaches to clinical trials have been comprehensively discussed in the literature.[8–12] One promising feature is that they enable investigators to augment trial data with existing relevant evidence. On termination of a trial, remaining uncertainty about the benefits and risks of a treatment can also be quantified and fed into subsequent decision-making. There is a precedent for using Bayesian statistics for health technology assessment. In 2005, the US Food and Drug Administration (FDA) advocated the use of Bayesian statistics in the study of medical devices.[13] In this context, relevant prior information is often readily available to incorporate into new trials since the mechanism of action of medical devices is physical and not systemic and because innovations are mostly incremental. Bayesian methods may be particularly suited for the purpose of monitoring trials to ensure a trial stops early only when there is high probability of a positive and clinically relevant treatment effect.[14,15] In its guidance for industry on adaptive designs, the FDA noted the potential utility of Bayesian approaches for the planning of such trials.[16]

The review of Chevret[17] found that the uptake of Bayesian adaptive designs in practice has been slow. One challenge to implementing Bayesian methods concerns the specification of prior distributions. Regulators are cautious about incorporating prior opinion into a trial's analysis and interpretation.[3] However, no prior is completely objective. Even if priors are based on data, the investigator must decide which historical datasets should be incorporated and how to weight them.[18–24] When no relevant data exist, prior distributions can be based on opinion elicited from several experts.[25–29] However, the subjectivity of this type of prior has been strongly criticised.[8,11] Alternatively, 'archetypal' priors may be used, chosen to represent enthusiastic or sceptical opinion on the parameter of interest without the need to represent the beliefs of any single individual.[30–33]

This article will focus on the practical implementation of Bayesian methods for the design, conduct, and interpretation of trials measuring time-to-event endpoints such as overall survival, which has been considered the 'gold standard' for evaluating new therapies in many fields, in particular in oncology, or composite endpoints.[34–36] There are additional complexities to designing Bayesian survival trials which arise, in part, from the need to specify a model for the time-to-event outcome. There may be uncertainty about the shape of the true underlying survival curve and whether this is best approximated by one of a family of parametric models or a semi-parametric model. Specification of the latter may be more challenging in the Bayesian paradigm when the analyst must specify a prior distribution for the baseline hazards assuming a specific stochastic process.[37,38]

BayesWatch and Reporting Of Bayes Used in clinical Studies (ROBUST) are two checklists which have been developed for the reporting of Bayesian analyses for health technology assessment.[32,39] The aim of our article was to perform a critical systematic review of clinical trials using Bayesian survival analyses, to describe what methods and priors are used, and to assess the quality of reporting. We will conclude by making some suggestions for how reporting checklists could be tailored to Bayesian survival trials.

Methods

Search strategy

Eligible articles were those published in English which reported clinical trials incorporating Bayesian survival analyses. The criteria identifying these trials are defined by the keywords below. Bibliographic searches were performed in September 2015, with no restrictions placed on publication date.

The first part of the search strategy was to search the electronic bibliographic databases PubMed and Web of Science. For the latter database, we restricted attention to medical and statistical research fields using the Web of Science categories listed in the online Supplementary Materials 1. We searched for articles containing the following terms in their title, abstract or keywords: (Bayes* OR 'prior distribution*' OR 'posterior distribution*' OR 'credib* interval*') AND (trial* OR controlled OR randomi?ed OR 'phase*study') AND (survival OR 'time-to' OR 'time until' OR 'failure-time*'). Observational, cost-effectiveness and dose-finding studies were excluded by adding the following search conditions: NOT (observational OR epidemio* OR 'case-control') NOT (cost-effect*) NOT (dose-finding). The titles and abstracts (and the full text where necessary) of all articles identified through this process were screened by C.B. to confirm their eligibility for the systematic review. Re-analyses of clinical trials for a clinical purpose were regarded as eligible. However, re-analyses of trials performed only to illustrate a novel methodology were excluded. Statistical methodology papers as well as meta-analyses of clinical trials were also excluded. Articles with a survival endpoint considered as a binary endpoint with no censored data were also excluded.

The second part of the search strategy consisted of searching directly the online repositories of journals for which full text searches of manuscripts were possible. This enabled us to identify articles reporting Bayesian survival analyses in the main body of the paper but not in the title, abstract or keywords. We selected the five general medical journals permitting full text searches of

their online repositories with the highest impact factors in 2014; similarly, for each medical field we selected the top specialised journal allowing full text searches of articles (see Supplementary Materials 2 for a full listing of selected journals). In addition, we also considered journals contributing at least one paper to the first part of the search strategy. C.B. reviewed the full text of all articles identified by this second search strategy to confirm their inclusion in the systematic review.

A second reader (G.L.T.) independently reviewed a random 10% selection of all identified articles to verify their eligibility.

Data extraction

Information from eligible papers was recorded using a data extraction form (see Supplementary Materials 3) comprising 100 items relating to general trial characteristics, trial design, Bayesian survival modelling, prior distributions and reporting.

Survival analyses were classified according to one of three approaches: (1) survival analysis at a fixed time point (e.g. progression-free survival at 2 years), (2) 'continuous' time-to-event analysis using a hybrid approach:[26,40] this consists of updating a prior distribution for the logarithm of the hazard ratio with the partial likelihood estimate of this parameter obtained from a frequentist analysis, and (3) 'continuous' time-to-event analysis fitting a fully Bayesian regression model (semi-parametric or parametric).

Data were extracted by C.B. and G.L.T., independently. In the case of any discrepancies or uncertainties of interpretation, M-C.L.D. and L.V.H. reviewed the article to reach a consensus.

Statistical analysis

Data were entered into a Microsoft Access® database. Statistical analyses were performed using SAS software v9.3 (SAS Institute, Cary, NC).

Results

Selection of articles

In total, 662 potentially eligible articles were identified (see Figure 1): 488 from PubMed and Web of Science (first part), and 174 from the electronic repositories of the 28 selected journals stated in Supplementary Materials 2 (second part). Following reviews of the abstract and/or the full text, we excluded 279 statistical methodology studies, 105 articles using Bayesian methods but not to analyse a time-to-event endpoint, 94 meta-analyses or systematic reviews, 63 articles that mentioned Bayesian methods but did not use them for analyses, 30 articles that were not original research (letter to the editor, commentary, review, or case report), 34 non-interventional studies, and 29 biological or environmental studies. Full agreement was observed between the first two readers, C.B. and G.L.T. We finally selected 28 articles, with 14 articles from the first part of the search and 14 from the second.[41–68]

Characteristics of selected articles are detailed in the Excel spreadsheet available online.[69]

General trial characteristics

The 28 articles were published between 1994 and 2014, including 17 in the last 5 years. Selected articles were published in eight different journals.

As detailed in Table 1, the majority of trials were in oncology, even when we restrict attention to the 14 articles selected from searches of general bibliographic databases (11/14). The disease was classified as rare for 13 trials, but this rarity was highlighted by the authors of only seven articles.

In total, 25 articles were original reports of clinical trials, whereas the 3 remaining papers described the re-analysis of a published trial. Overall, 24 of the 28 reported trials evaluated drugs, 3 considered medical devices, and 1 radiation therapy. In 10 cases, the study objective was to compare the efficacy of currently used treatments, 7 trials tested a treatment for a new indication, 6 trials evaluated a new combination of licensed treatments, 3 trials evaluated a new modality of a licensed treatment, while 2 trials considered a novel drug before marketing authorisation.

Trial design and conduct

As shown in Table 2, the majority of trials were phase III or phase II trials, and one was a phase I trial with Bayesian modelling of the survival data as a secondary analysis. The time-to-event endpoint was overall survival in 22 trials and a composite endpoint in the 6 other studies.

Overall, 14 trials included a pre-planned monitoring of efficacy data (9 with Bayesian survival analyses and 5 with a frequentist approach). In addition, five trials used Bayesian survival methods to conduct an unplanned interim analysis. Among the 14 trials conducting Bayesian interim monitoring of efficacy data, 3 planned to use Bayesian methods for the final analysis while the 11 remaining trials planned a frequentist approach for the final analysis. Only 2 of these 14 trials used overall survival for the Bayesian analysis. In total, nine trials stopped early for futility or benefit.

Bayesian survival analyses were used for the final analysis but not for interim monitoring in 14 trials. Bayesian methods were used for the primary analysis of an original trial in four cases, for a secondary analysis of a trial in seven cases, and for the re-analysis of a trial in three cases. The time-to-event endpoint upon which the Bayesian analysis was based was overall

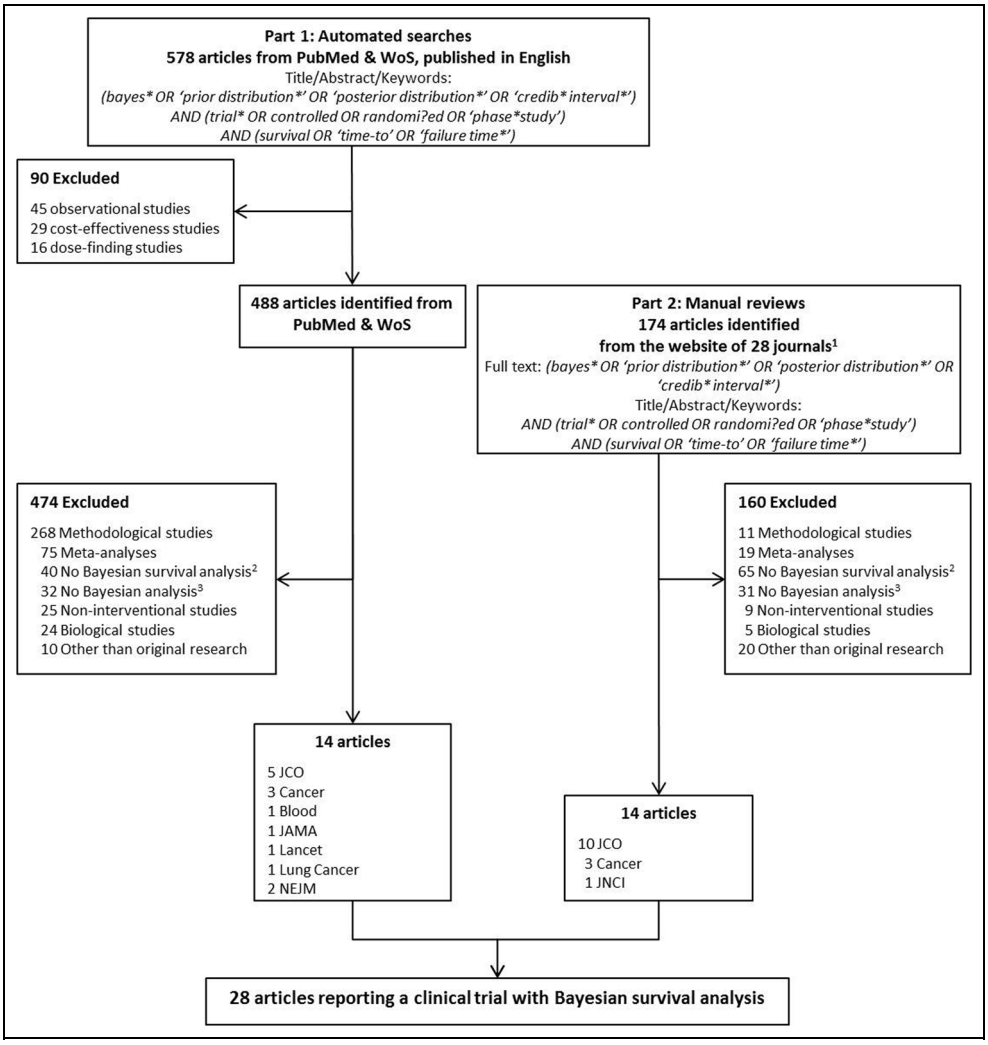

Figure 1. Flow chart of the systematic review.
[1]The selection of these 28 journals is detailed in Supplementary Materials 2.
[2]These articles included a Bayesian analysis but applied on an endpoint other than a censored endpoint.
[3]In most cases, the Bayesian approach was cited as a discussion point, whereas the trial was analysed with the frequentist approach.

survival in 10 cases. In 10 articles, the Bayesian analysis was performed in addition to a frequentist analysis.

Less than half of trials (11/28) justified the use of Bayesian statistics. Two commonly reported reasons were to overcome the challenge of small sample sizes and to quantify uncertainty about treatment effects.

A reference was specified for the Bayesian methods used in 21/28 articles, the six leading references being Fayers et al.[40] (n = 4, the hybrid approach); Gelman et al.[70] (n = 3, Bayesian analyses for different types of models), Thall and Sung[71] (n = 2, Bayesian monitoring), and Ibrahim et al.[37] (n = 2, Bayesian survival analysis), and more general papers (Berry[9] n = 3; and Brophy[72] n = 2).

Bayesian survival modelling

As described in Table 3, 24 articles reported Bayesian analyses of a 'continuous' time-to-event endpoint, of which 19 were randomised controlled trials (RCTs) and 5 were single-arm trials. Among the two RCTs that reported analyses of survival at a given time, the treatment effect was measured in terms of an absolute treatment effect (difference of survival rates at a time point between the two treatment arms).

Focusing on Bayesan analyses of RCTs with a 'continuous' time-to-event outcome (n = 19), the proportional hazards assumption was stipulated in 17 cases. Three articles fitted a semi-parametric survival model, but the model used to represent the baseline hazards was specified only in one which used a piecewise process. Of the nine articles fitting (semi-)parametric regression models in RCTs, five adjusted for baseline covariates and two of them incorporated a treatment-by-covariate interaction.

Overall, among the nine articles reporting a Bayesian parametric survival model, model selection was justified in five cases, using Bayesian Information Criterion to assess the goodness-of-fit.[73]

Table 1. General characteristics of the 28 trials.

Characteristics of the trial	N (%)
Sponsors	
Private sector only	12 (43)
Public sector only	6 (21)
Private + public sector	7 (25)
Unspecified	3 (11)
Countries	
North America only	13 (46)
Europe only	7 (25)
Asia only	2 (7)
North America + Europe	1 (4)
Worldwide	2 (7)
Unspecified	3 (11)
Trial location	
International	11 (39)
Multicentre national	11 (39)
Multicentre unspecified location	1 (4)
Single centre	3 (11)
Unspecified	2 (7)
Medical field	
Oncology	25 (89)
Cardiology	2 (7)
Obstetrics	1 (4)
Patient age	
Adults only	24 (86)
Children/teenager to adults	3 (11)
Foetus	1 (4)
Rare disease considered[a]	
Yes	13 (46)
No	15 (54)
Year of start of accrual	
Median (range)	2003 (1973–2009)
Accrual duration	
Median (range)	4 years (11 months–10 years)
Reported trial sample size	
Median (range)	228 (20–3871)

[a]The estimated prevalence of diseases studied by trials was extracted from the Orphanet website (http://www.orpha.net/consor/cgi-bin/index.php). For the purposes of this review, diseases were classified as rare if the estimated prevalence was less than 5 per 10,000 people in the European Union.[74]

Table 2. Main design and conduct characteristics of the 28 trials.

Characteristics of the trial	N (%)
Trial phase	
Phase I	1 (4)
Phase II	9 (32)
Phase III	13 (46)
Phase unspecified	5 (18)
Blind	
Open label	25 (89)
Double blind	3 (11)
Randomisation	
Randomised controlled trial	21 (75)
Non randomised trial	7 (25)
Trial design	
Parallel group[a]	18 (64)
Single arm	7 (25)
Factorial design	3 (11)
Planned adaptive design[b]	
Monitoring for efficacy	14 (50)
1–3 interim analyses planned	9
4 or more interim analyses planned	4
Number of interim analyses not specified	1
Monitoring for toxicity	1 (4)
Continual Reassessment Method	1 (4)
Adaptive randomisation	2 (7)
Non adaptive	10 (36)
Use of Bayesian survival analysis	
For the final analysis only	14 (50)
For trial monitoring only[c]	11 (39)
For trial monitoring and final analysis	3 (11)

[a]A total of 16 trials followed a two-armed parallel group design and 2 trials followed a three-armed parallel group design. One two-armed parallel group trial followed a cross-over design where treatments were switched after progression.
[b]Including Bayesian or frequentist approach for the adaptation.
[c]A total of 11 trials used Bayesian survival analysis for trial monitoring only: planned monitoring in 6 trials and an unplanned monitoring in 5 trials.

Bayesian modelling may be different depending on whether it is used for trial monitoring or the final analysis. Considering the 14 trials using Bayesian survival analyses for the interim monitoring of efficacy data, only 1 trial implemented a Bayesian semi-parametric model, whereas a simpler approach was adopted in the 13 other trials. Among the 14 trials using Bayesian methods for the final analysis only, 7 fitted a fully Bayesian regression model.

Choice of prior distribution

Non-informative priors for the treatment effect were used to analyse 11 of the 21 trials which were RCTs (complemented or not by archetypal priors). Four trials incorporated historical data into prior distributions, with all these trials using the available data to formulate an informative prior for the treatment effect. Three of the trials provided references to the historical trials used and one listed the number of patients included in the historical trials. The method used to incorporate historical data into the current trial was specified in three of the articles: they pooled the historical and contemporary datasets without down-weighting the historical data. Two of the four trials incorporating historical data performed analyses to assess the sensitivity of results to the choice of prior distribution. Only 1 article elicited expert opinion to formulate a prior for the treatment effect, based on a mathematical aggregation of the opinions of 17 experts. None of the nine articles reporting Bayesian regression models placed informative priors on the treatment effect (non-informative prior used in seven trials; prior unspecified in two).

Of the 19 RCTs analysing a 'continuous' time-to-event endpoint, 16 considered the relative treatment effect parameter. Among those, seven used a normal

Table 3. Specification of the Bayesian survival analysis, overall and according to its purpose (monitoring or final analysis only).

	Monitoring, N = 14[a]	Final analysis only, N = 14	Total, N (%)
Bayesian modelling in RCTs (N = 21)	**10**	**11**	**21**
Survival at a fixed time point[b]	1	1	2 (10)
Hybrid approach[c]	5	5	10 (48)
Semi-parametric model[d]	1	2	3 (14)
One parameter exponential model	3	–	3 (14)
Log-normal model	–	2	2 (10)
Parametric model unspecified	–	1	1 (5)
Bayesian modelling in single-arm trials (N = 7)	**4**	**3**	**7**
Survival at a fixed time point[b]	2	–	2 (29)
One parameter exponential model	1	–	1 (14)
Log-normal model	–	2	2 (29)
Unspecified model of a 'continuous' time-to-event endpoint	1	1	2 (29)
Prior distribution of the treatment effect (RCT, n = 21)	**10**	**11**	**21**
Historical data + experts + non-informative	–	1	1 (5)
Historical data + archetypal + non-informative	1	–	1 (5)
Historical data only	–	2	2 (10)
Archetypal + non-informative	1	–	1 (5)
Non-informative only	4	6	10 (48)
Unspecified	4	2	6 (29)
Prior distribution of the model parameter (Non-RCT, n = 7)	**4**	**3**	**7**
Non-informative	–	2	2 (29)
Unspecified	4	1	5 (71)
Minimum important efficacy effect pre-specified			
Yes	11	5	16 (57)
No	3	9	12 (43)
Decision rule pre-specified			
Yes	8	1	9 (32)
No	6	13	19 (68)

[a]Among the 14 trials performing Bayesian survival analyses for trial monitoring, three also planned and conducted a Bayesian final analysis of the survival endpoint.
[b]Survival at a fixed time point: for example, progression-free survival at 2 years.
[c]Hybrid approach: this consists of updating a prior distribution for the logarithm of the hazard ratio with the partial likelihood estimate of this parameter obtained from a frequentist analysis.
[d]Bayesian semi-parametric model: this consists of using the full data likelihood under a survival regression model with the baseline hazard function specified. The values given in Boldface represent totals and subtotals for each main category.

distribution to present prior opinion on the treatment effect parameter. This contributed to a hybrid analysis in four trials, a parametric analysis based on a log-normal survival model in one case, a parametric analysis without more details in one case, and a semi-parametric analysis assuming baseline hazards follow a piecewise process in one case. The latter article placed non-informative Gamma prior distributions on the parameters of the baseline hazards model. Nine trials (six using a hybrid approach, two fitting a semi-parametric model, and one fitting a parametric model) did not specify the prior distribution used. In total, 3 of the 19 RCTs fitted separate one-parameter exponential models to data from the control and experimental treatment groups; one placed Gamma prior distributions on the hazard in each treatment group while the two remaining trials did not specify the priors.

Of the five single-arm trials analysing a 'continuous' time-to-event endpoint, two defined non-informative normal priors for the effects of covariates in survival models while the other three trials did not report priors for model parameters.

The definition of the prior may be different when the Bayesian approach is used for the final analysis rather than interim monitoring. Historical data were more commonly used to formulate prior distributions when Bayesian methods were used for the final analysis. Among the 14 trials with Bayesian monitoring, most did not specify the prior used for the parameter of interest and only 1 made use of historical data.

Decision rules

A higher proportion of trials using a Bayesian approach for trial monitoring pre-specified a minimum important efficacy effect and decision rule than trials using Bayesian methods for the final analysis (Table 3). Most trials using Bayesian methods for monitoring framed

Table 4. Reporting and characterisation of the prior and posterior distributions.[a]

Reporting	N (%)
Prior distribution	
Definition of the distribution	7 (25)
Graphical representation	2 (7)
Measure of location	8 (29)
Credibility intervals	1 (4)
Not reported	20 (71)
Posterior distribution	
Definition of the distribution	3 (11)
Graphical representation	3 (11)
Credibility/HPD intervals	10 (36)
Posterior/predictive probabilities	24 (86)
Measure of location	12 (43)
Not reported	3 (11)

HPD: highest posterior density.
[a]Numbers do not sum to 28 because the different items are not exclusive.

their decision rules in terms of predictive probabilities. The majority of trials using Bayesian methods for the final analysis only did not define the Bayesian decision rule at the design stage of the trial (see details in Supplementary Table 1).

Reporting of Bayesian survival analyses

Of the 25 articles that reported Bayesian analyses in the original trial report, 7 did not mention Bayesian survival analysis in the 'Methods' section of the paper: 5 of them used Bayesian methods to monitor the trial, and 2 used them as a secondary final analysis.

In 18 articles, the results of Bayesian analyses were not cited in the abstract. As detailed in Table 4, most articles did not report any information about prior distributions, and the full specification of the distribution was given in only seven papers. In general, posterior distributions were more comprehensively reported, with some summaries of these distributions given in 25 articles. However, less than half reported a measure of location of the posterior distribution and the associated credibility intervals.

Most articles (20/28) did not specify the software used for Bayesian analyses. WinBUGS or OpenBUGS was used in five cases (always to fit a Bayesian regression model), while SAS was used in two cases, although Bayesian survival analyses have been possible in SAS since 2009.

Discussion

Despite the potential benefits of Bayesian statistics for evaluating new medicines and medical devices, and the many recent methodological developments in this area,[75] few survival trials have implemented Bayesian methods and even fewer have used a Bayesian approach for their primary analysis. Surprisingly, Bayesian methods were used for monitoring but not for the trial analysis in 11 articles (39%), likely because Bayesian techniques offer more flexibility and an easier interpretation in the decision-making process compared to the frequentist approach. Bayesian methods have been much vaunted for their potential to aid the interpretation of clinical trials in small populations, in particular by augmenting the trial data with historical data.[1–5] However, this review found only 13 trials in rare diseases conducting Bayesian survival analyses and of these, 1 trial incorporated historical data into the prior for the treatment effect. Different approaches exist for incorporating historical data,[20–24] but they are scarcely used in practice and, despite their advantages, authors seem to prefer non-informative priors. The small number of trials identified by this review is consistent with the findings of Pibouleau and Chevret[76] who reviewed the use of Bayesian methods in medical device trials and found 12 clinical studies. A review of trials conducted at the MD Anderson Cancer Center, known for a particular interest in Bayesian trials, found that Bayesian methods tended to be used more in early phase trials but were rarely used in seamless phase II/III or phase III trials where time-to-event endpoints are more typically measured.[77]

Guidelines for reporting Bayesian analyses already exist (e.g. BayesWatch[32] and ROBUST[39]), but their recommendations were rarely adhered to by the articles included in this review. The ROBUST and BayesWatch frameworks stipulate that articles should report prior distributions, statistical models, computational techniques, and posterior distributions. In our review, three articles specified, justified, and reported sensitivity analyses of the stated prior distribution. Details of the survival model (justification/model definition/model checking) were frequently lacking. Three trials did not define the survival model used (one unspecified parametric model; two completely unspecified). Meanwhile, two of the three trials fitting a Bayesian semi-parametric model did not define the stochastic process used to model the baseline hazards. In terms of model selection, five of the nine trials fitting parametric survival models described the process by which the final model was selected. Only four trials mentioned the use of a Markov Chain Monte Carlo algorithm to make posterior inferences, and two of these specified the number of chains and length of burn-in. We speculate that space constraints on journal articles may prohibit this level of detail. Of the 17 trials using Bayesian methods for the final analysis (final analysis only, n = 14, or monitoring with a Bayesian final analysis, n = 3), 12 reported a measure of the central tendency and the standard deviation or credibility interval for the posterior distribution.

One limitation of this review is that only half of the included articles were found via our searches of the electronic bibliographic databases PubMed and Web of Science. We tried to extend our searches using the clinicaltrials.gov registry but failed to find any additional trials. However, despite our best efforts to be comprehensive, it is likely that we missed reports of trials which performed Bayesian survival analyses but did not explicitly cite them in the title, abstract, or keywords. It is also possible that some articles have been omitted because the survival analysis was referred to using other terms other than those used in our search strategy. In addition, the second step of our search strategy focused on oncology journals. We decided to focus more attention on oncology journals due to the fact that 11 of the 14 articles identified by our initial searches described cancer trials. Regarding the stated exclusion criteria, it is possible that some papers describing clinical trials may mention 'epidemiology' or 'case-control' in the introductory part of the abstract and thus been erroneously excluded from our review. However, we have checked all of the articles satisfying our stated exclusion criteria and found no such papers. Despite the stated limitations of our review, we would claim that it still provides an overview of the methods currently used in practice to monitor and analyse clinical trials in a Bayesian context when a censored endpoint is considered.

In conclusion, few clinical trials have used Bayesian statistics with censored data. Gönen[12] has suggested that not only clinicians but also statisticians have little or no exposure to Bayesian approaches. We think that more study is needed to identify barriers to using Bayesian methods through discussions with trial investigators, statisticians, ethics review boards, and regulators. The findings of this review lead us to suggest that the reporting of Bayesian analyses in clinical trials could be improved upon in the following ways: defining the prior distribution and clarifying the information used to formulate it, clarifying what survival models are fitted and how they are used, and clarifying the planned decision rules. Guidelines for reporting Bayesian analyses already exist but our review suggests they are not often adhered to. Extension of the Consolidated Standards of Reporting Trials (CONSORT[78]) statement for reporting Bayesian clinical trials could be developed, comprising points specific to Bayesian survival modelling. We speculate that more training and guidance on Bayesian methods would increase the quality of reporting of Bayesian survival analyses in clinical trials.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by PhD grant from doctoral School of Public Health, Paris-Sud University, Paris-Saclay University; the UK Medical Research Council (grant MR/J014079/1); and the European Community's Seventh Framework Programme under grant agreement no. 261474 (project ENCCA).

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