Analysis of characteristics of randomized clinical trials in leukemia that are associated with how results are reported

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Abstract

Background

Since many trials are small, systematic reviews are essential for obtaining statistically reliable results. However, some trials are better-reported than others. Non-publication or delayed publication could lead to bias in a review. We identify trial characteristics affecting how quickly or widely results of randomized trials are reported, and hence how likely the trial is to be found by reviewers.

Methods

We analyzed all randomized trials in childhood acute lymphoblastic leukemia that began before 1988 and all articles for these trials published before 2000, as identified by the Childhood Acute Lymphoblastic Leukaemia (ALL) Collaborative Group secretariat. This was the set of 149 trials included in the Second International Collaborative Workshop on Childhood ALL Studies at the end of 1992, comprising 243 randomized comparisons.

We used multiple linear regression to analyze time to first mention or to first reporting of results (time to publication), logistic regression for whether a randomization was ever mentioned or reported, and Poisson regression for frequency of mentions or publications.

Results

Collectively, the articles mentioned 217 randomizations, with results reported for 188. Highly statistically significant results were published faster, each tenfold reduction in the *p*-value (e.g., going from 0.5 to 0.05 or from 0.05 to 0.005) resulting in publication on average 20 months earlier (95% confidence interval 6-34, $p=0.005$), non-statistically significant results from trials outside North America and Europe took on average 55 months longer than those without these characteristics (95% CI 22-88, $p=0.001$), and results from trials in high income countries were more likely to reach publication at some point than were results from other countries (odds ratio 7.8, 95% CI 2.4-25.3, $p=0.0006$).

Randomizations in high income countries were mentioned 73 months earlier than those in middle or low income countries (95% CI 51-94, $p<0.0001$), were more likely to ever be mentioned (OR 13.1, 95% CI 2.1-80.9, $p=0.006$), and were mentioned more frequently (incidence ratio 2.5, 95% CI 1.4-4.5, $p=0.003$), as were North American trials compared with those conducted elsewhere (IR 1.3, 95% CI 1.1-1.6, $p=0.01$).

Conclusions

Systematic reviewers should not rely solely on published reports, but should use additional ways of finding trials in order to minimize biases related to results and other trial characteristics. This relates both to published reports of trial results and to mentions of trials in the literature.

Background

The results of some randomized trials are reported quickly, widely, or both, while others remain unpublished or have delayed publication. It is important to identify factors that affect publication, since people making healthcare decisions can only be influenced by evidence they know of or can find relatively easily. Sutton et al (2000) [1] describe various biases that can cause problems when conducting meta-analyses. As part of a larger project [2] we examined 'timelag bias,' where statistically significant results are published earlier than non-significant results.

We focused on randomized trials of treatments for childhood acute lymphoblastic leukemia, and investigated which trial characteristics affect mentions of these trials and publication of their results. An earlier paper described the history of these trials, and found that most of these trials were relatively small and took place in single countries, and that many of them have been published only once [3]. In order to obtain statistically reliable results from these small trials, systematic reviews are essential, and these reviews need to include patients from as many relevant randomized trials as possible [4, 5]. Ideally, all eligible trials should be identified and included. However, some research is more quickly and widely published, and hence is easier to find. If trials that have never been published or are published more slowly are not identified for a systematic review, this can bias the review.

If reviewers aim to use data collected directly from researchers, rather than rely on published results alone, the most important aspect of their searching is to identify the existence of a trial, not necessarily a report of its results. In such circumstances, the most important factor in a trial's visibility is how quickly and widely it is referred to. We performed 'mentions analyses' to determine whether searching the published literature alone would suffice when identifying trials for inclusion, or whether other searching methods are also necessary.

Methods

In the early 1990s the Childhood Acute Lymphoblastic Leukaemia (ALL) Collaborative Group [6] began a collaborative overview of individual patient data from randomized trials of any treatments for childhood leukemia [7]. A register was compiled of randomized trials and of articles reporting the trials' results or mentioning the trials. In order to ensure complete trial coverage for the second international workshop in 1992, this list of trials was circulated to collaborating trialists and other experts along with a request for information on any trials which might have been missed. It was updated as new trials and associated articles were identified.

Our study included all randomized trials of the treatment of childhood leukemia beginning before January 1, 1988 and all articles referring to these trials published before January 1, 2000. This set consists of 149 **trials** comprising 243 randomized comparisons ('**randomizations**') reported in 257 published pieces (195 journal articles, 11 book chapters, and 51 meeting abstracts), representing a total of 610 separate mentions of relevant randomizations.

The randomized comparisons, rather than the trials, were of primary interest in our analyses. For example, the Medical Research Council UKALL VIII trial contained two randomizations, the first between two drug combinations used as induction treatment and the second comparing two durations of maintenance treatment (see additional file 1: Summary of trials and randomizations). If a trial was mentioned before closure (in some cases, before it had started), results would not be expected to be available for incorporation into a meta-analysis. With this in mind, we only included reports that appeared after a trial had stopped randomizing patients in our analysis of time to first mention and first reporting of results.

Randomizations were excluded if they (i) began in 1988 or more recently, (ii) appeared to be duplicates, or aborted trials (did not accrue any patients), or (iii) were exclusively for adults (since those trials were not sought systematically by the Childhood ALL Collaborative Group).

Pieces were excluded if they were: (i) published in 2000 or more recently, (ii) review articles summarizing several trials, (iii) reports of published data meta-analyses, (iv) unpublished manuscripts (since these were not collected systematically), (v) entries in Clinprot (a protocol register), or (vi) not specific about the randomized allocation, the treatments compared, or the outcomes measured.

As part of a larger study, [2] more than 70 trial characteristics were collected, relating to (i) the individual randomization (e.g., the date the randomization opened and closed and the number of patients accrued), (ii) the trial to which the randomization belonged (e.g., the funding source and level of multicentre and international participation), (iii) the results reported in a particular article (e.g., statistical significance, direction of result, and clinical significance), and (iv) the piece itself (e.g., whether it was published in a journal, book, or as a meeting abstract).

Owing to a large number of missing values, some trial characteristics were omitted from some analyses. We excluded variables from any analysis if more than 25% of the values for that variable were missing.

We collected the following data for up to two main results from each reporting of a randomization: *p*-value, clinical significance, and direction. We categorized reports as 'results reported' if they contained one or more of these, or the type of result (e.g., survival) was stated.

For statistical significance we used the main result with the smaller *p*-value.

A result was considered to be clinically significant if the authors, irrespective of the given *p*-value, stated that it clearly favored the experimental arm. For equivalence trials [8], a result was considered clinically significant if the results for the experimental arm were at least as good as those for the standard arm. A result was considered not clinically significant if it favored the standard (control) treatment. If the outcome was less clear, we designated it as 'possibly' or 'not known.'

Results were categorized as favoring the experimental treatment, the standard treatment, or with no significant difference (including results where authors did not include statistical information but stated that there was no difference). Occasionally, we found that the two main results were in opposite directions. A hierarchical system was used to select an overall value from the pairs of results. If it was unclear which treatment was 'experimental' and which 'standard,' we made some assumptions in order to make full use of the randomization in our analyses. For example, if different doses were compared, the lower dose was considered the 'standard' treatment. If two new treatments were compared, the direction was categorized as 'not reported.'

We defined time to publication as the time from the date the last patient was randomized to the date of the first reporting of results in the public domain.

We also analyzed the time to first mention. These first mentions often do not include any results. For example, a report of the results of one trial might refer briefly to another planned or open trial. This type of mention would be sufficient for identifying studies for possible inclusion in a review. Time to first mention represents how long it took for information about the study's potential availability to reach the public domain.

Our source for impact factors was the Institute for Scientific Information: Journal Citation Reports 1995 Science Edition [9]. The 1995 edition was used rather than a more recent version because only articles published before January 1, 2000 were included in our study.

Having chosen the possibly informative explanatory variables, the best subsets were identified using both backward and forward stepwise regression methods. If a variable was highly correlated with another but had far fewer missing values or was more meaningful, it would be preferred. Finally, possible interactions were tested.

After selecting the best-fitting model we checked that the association between the response and the explanatory variables was linear and fit the assumption of constant variance by plotting the standardized residuals against the fitted values.

We used logistic regression to examine why some randomizations were never published and Poisson regression to investigate why some are published more frequently than others. Data specific to an individual publication could not be used in these analyses. Again, the best subsets were identified using both backward and forward stepwise regression methods.

Results

A summary of trials and randomizations is given as additional file 1. This provides the number of patients recruited for each randomization, dates of the accrual period, date of publication of the article in which the randomization was first mentioned and results first reported, and number of articles in which the randomization was mentioned. Additional file 2 provides summary statistics and the results of univariate analyses for all trial characteristics investigated. Additional file 3 lists those characteristics excluded from all analyses due to a high proportion of missing values.

Time to publication

Of the 243 randomizations, 188 were published at least once. Of these, we excluded 18 first results because of missing values for date of close of randomization, date of publication, or both. A further 16 were not used because the results were published before accrual to the trial had stopped.

A longer time to publication was associated with earlier randomizations (7 months (95% CI 2-12, p=0.01) longer per ten years earlier close of randomization); results of lower statistical significance (each tenfold increase in the *p*-value

resulting in an average of 20 months delay, 95% CI 6-34, p=0.005); reports with no clear indication of clinical significance (16 months delay, 95% CI 6-27, p=0.003); reports where a clear indication is given as to whether the main question(s) as stated in the paper are answered in that paper (11 months delay, 95% CI 1-20, p=0.03); publication in a journal with an impact factor (17 months delay, 95% CI 5-28, p=0.005); and publication in a journal with a lower impact factor (11 months delay, 95% CI 5-17, p=0.0007) (Table 1). The following interactions were associated with very long delays: randomizations conducted outside North America and Europe with non statistically significant results had an additional time lag of 55 months (95% CI 22-88, p=0.001), and randomizations conducted by European trialists and reported in a journal with a higher impact factor had an average delay of 27 months (95% CI 15-39, p<0.0001).

How widely published

We found that results were less likely to be published for more recent randomizations compared to those that began earlier (p=0.005), and for randomizations in low or middle income countries (Poland, India, South Africa, Argentina, Peru, Brazil, Taiwan and Israel) compared to high income countries (Italy, Germany, the Netherlands, France, Spain, Austria, UK, USA, Japan and Australia) (p=0.0006) (Table 2).

Since some observations were excluded from the analysis due to missing values, we repeated the analysis using p=0.2 rather than p=0.05 as the significance level, and found two additional significant variables: results from randomizations with fewer treatment arms (or asking fewer therapeutic questions) and trials conducted in North America (controlling for country income) were less likely to be published.

Characteristics associated with less frequent publication were research into chemotherapy, immunology or antibiotics, as opposed to radiotherapy (p=0.001), taking place in low or middle income countries (p=0.0008), earlier trials as opposed to those closing ten years later (p<0.0001), trials accruing fewer patients (p=0.0007), and those involving multi-center participation (p<0.0001) (Table 3).

When a 0.2 significance level was used, trials with fewer randomizations, superiority rather than equivalence trials, and randomizations with fewer treatment arms (or asking fewer therapeutic questions) were also found to be associated with less frequent publication.

Time to first mention

Of the 243 randomizations, 217 were mentioned at least once. Of these, 22 first mentions were excluded because of missing values for the date of close of randomization, date of first mention, or both. A further 32 were not used because the ‘mention’ was published before accrual to the trial had closed.

A longer time to first mention was associated with being a superiority rather than an equivalence trial (36 months, 95% CI 18-55, p=0.0002); being conducted in a low or middle income country (73 months, 95% CI 51-94, p<0.0001); earlier randomizations (10 months (95% CI 5-16, p=0.0001) longer per ten years earlier start of randomization); failing to indicate whether the results were clinically significant (23 months, 95% CI 10-35, p=0.0005); giving a clear indication as to whether the main questions as stated in the paper are answered in that paper (34 months, 95% CI 22-46, p<0.0001); not having been presented at a meeting (18 months, 95% CI 7-29, p=0.002); and the number of trials reported in the article (12 months, 95% CI 7-16, p<0.0001) (Table 4).

How widely mentioned

Randomizations conducted in low or middle income countries (p=0.006), those conducted more recently (p=0.004), and those accruing a smaller number of patients (p=0.0003) were less likely to have been mentioned in an article (Table 5).

Trial characteristics associated with a lower frequency of mentions were research in refractory or relapsed disease compared to first line therapy (p=0.007), superiority rather than equivalence trials (p=0.01), trials in low or middle income countries (p=0.003), trials conducted outside North America (p=0.01), multi-center trials (p=0.0004), earlier trials as opposed to those starting ten years later (p<0.0001) and trials accruing a smaller number of patients (p<0.0001) (Table 6).

When a 0.2 significance level was used, trials with fewer randomizations and those investigating treatments other than radiotherapy were also found to be associated with a lower frequency of mentions.

Discussion

Highly statistically significant results were published faster, with a tenfold reduction in p-value resulting in publication on average 20 months earlier, non-statistically significant results from trials outside North America and Europe took 55 months longer, and results from trials in high income countries were more likely to be published at some point.

Randomizations in high income countries were mentioned 73 months sooner than others, were more likely to ever be mentioned, and were mentioned more frequently, as were North American trials.

Strengths and weaknesses of the study

Two major strengths of this study are the wide range of variables considered and the analyses of 'mentions' in addition to publication of results.

One possible weakness of this study relates to the generalisability of results. The history of trials of childhood ALL is fairly unusual in that most trials have been performed by large well-established co-operative groups, and relatively few by smaller groups or single centers. This is rather different from the situation in many other disease areas, and may affect our results because major groups will publish all their trials at some point, whereas smaller groups may be less likely to.

Perhaps our most striking finding in regard to trial mentions is that randomizations from low or middle income countries had a much longer time to first mention than those from elsewhere. This variable has a large coefficient, which has a wide 95% confidence interval (51-94 months). Furthermore, only 15 of the 243 randomizations were conducted in low or middle income countries. Although this is an important explanatory variable, its effect is likely to have been heightened by the inclusion of one particular outlier [2]. This should be borne in mind when interpreting the findings. However, excluding this outlier did not affect the variables selected for the model.

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Other studies of pipeline bias have examined different areas: acute stroke [10], passive smoking [11], cystic fibrosis [12], studies submitted to a hospital ethics committee [13], papers published in a particular journal [14], various health-related research projects [15], manuscripts rejected by a radiology journal [16], and HIV [17]. Although our findings may be specific to childhood lymphoblastic leukemia, any similarities to the other studies may suggest some generic features of bias in the publication of health research.

A variety of starting points have been used by others to calculate time to publication: like us, Liebeskind et al [10] and Ioannides [17] used the start of the accrual period; Misakian and Bero [11] used the year funding began; and Stern and Simes [13] used time from approval by the ethics committee.

Although the total number and type of variables used in the analyses in all the other studies is not always stated, it is likely that we used the largest number of variables (additional file 2).

We used two variables to categorize statistical significance and a third variable for the direction of the results (i.e., statistical significance and direction of results are two distinct one-dimensional variables). In three of the other studies [10, 11, 17], one variable was used in a two-dimensional capacity to specify both statistical significance and direction. In retrospect the latter may have been preferable. Different definitions are used in two of the other studies [12, 15]. The only 'two dimensional' results variable we used is 'clinical significance.' This combines the direction of the result with our opinion of the 'strength of the impression given by the article,' regardless of any *p*-values reported. This is similar to the definition of 'significance' used by Dickersin and Min: *"judged by investigator to be either statistically significant or 'of great importance'* " [15].

A major strength peculiar to this study is that analyses of 'mentions' were performed in addition to those of publication of results.

Other studies have shown a shorter time to publication for trials with statistically significant results favoring the experimental treatment compared to those with statistically significant results favoring the standard treatment, which in turn are published more quickly than trials with non-significant results [10, 11, 13, 17, 18]. Statistical significance was also associated with faster publication in this analysis. This phenomenon was most marked for trials from countries outside North America and Europe, where there was a considerable delay in the publication of non-significant results. However, this was not a pre-planned subgroup analysis and may be a chance finding, rather than a real difference. Unlike most other studies, we found that whether results favored the experimental or the standard treatment was not a significant predictor of time to publication. Another important factor associated with faster publication was the importance trialists attached to their results, irrespective of the direction.

We found time to publication to be longer when results were published in a journal with an impact factor. This is in part because the group of publications without an impact factor included meeting abstracts and book chapters. It is not unusual for results to be reported early as a meeting abstract, before being published as a full paper in a journal [19]. Generally, for publications in journals with impact factors, we found (like Chew [16]) that the lower the impact factor, the longer the time to publication. This may be because manuscripts were submitted first to a prestigious journal with a high impact factor, and then rejected and re-submitted to a journal with a lower impact factor. We found, as did

Liebeskind et al [10], Misakian and Bero [11], Cheng et al [12], Stern and Simes [13], and Ioannides [17], that sample size did not appear to be a significant predictor of time to publication.

Possible mechanisms and implications for clinicians or policymakers

Systematic reviewers should use additional ways of finding trials rather than relying solely on published reports, in order to minimize publication bias related to results and other trial characteristics.

Unanswered questions and future research

The model for characteristics associated with results ever being published fits the data fairly well, but contains only two explanatory variables if significance is set at $p<0.05$. All other variables not specific to a particular report were tried, and none were significant. A possible explanation is that the results of the randomization have a greater than anticipated effect on their publication. Potential alternative models would require the creation of new variables covering statistical significance, direction of results, clinical significance, and whether the main questions of the randomization were ever answered. These would need to draw on all publications for each randomization, rather than the results within each single article. This would also allow the analysis to be restricted to the most statistically significant result obtained for each randomization.

Conclusions

We found 'pipeline bias' in the reporting of first results of these childhood leukemia trials, which supports the findings from other health fields [18] that statistically significant results are published faster than others.

Location was also an important predictor of whether a randomization was ever mentioned in an article, the time to first mention, and the frequency of mentions. We found that trials from low and middle income countries were associated with a particularly long delay. This suggests that contacting researchers and other strategies to find trials that have closed but not yet been published is worthwhile, especially outside of North America and Europe.

Our study identified several variables that are likely to make it difficult for reviewers and others to find an unbiased sample of randomized trials. In order to minimize bias, systematic reviewers need to search in a variety of ways, and not rely solely on published reports of trial results.

Competing interests

The authors have no competing interests.

Authors' contributions

DL provided the statistical expertise and participated in the development of the methodology and the interpretation of results. JAB collected, analyzed, and interpreted the data and drafted the manuscript.

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Tables

Table 1 - Trial characteristics significantly associated with time to publication of first results

Trial Characteristic	**Additional time to publication (months) (95% CI)**	***p*-value**
Main effects:		
For each ten years earlier close date of accrual period	7 (2-12)	0.01
Lower statistical significance (for each tenfold increase in the *p*-value)	20 (6-34)	0.005
No clear indication of whether clinically significant or not	16 (6-27)	0.003
A clear indication is given as to whether the main questions in the paper are answered in that paper	11 (1-20)	0.03
Reported in a journal with an impact factor associated with it	17 (5-28)	0.005
Published in a journal with a lower impact factor	11 (5-17)	0.0007
Interactions:		
Non statistically significant results from a randomization conducted outside North America and Europe	55 (22-88)	0.001
European randomization reported in a journal with a higher impact factor	27 (15-39)	<0.0001

Table 2 - Trial characteristics significantly associated with the results of a randomization ever being reported

Trial Characteristic	**Odds ratio (95% CI) for results of randomization ever being reported**	***p*-value**
Conducted in a high vs. in a low or middle income country	7.8 (2.4-25.3)	0.0006
For each ten years earlier start date of accrual period	2.3 (1.3- 4.1)	0.005

Table 3 - Trial characteristics significantly associated with the results of a randomization being reported in more articles

Trial characteristic	**Incidence ratio[a] (95% CI)**	***p*-value**
Treatment type: radiotherapy vs. chemotherapy, immunotherapy or antibiotic	1.4 (1.2-1.8)	0.001
Conducted in a high vs. in a low or middle income country	4.6 (1.9-11.1)	0.0008
For each ten years more recent close date of accrual period	1.6 (1.4-1.9)	<0.0001
log_{10} (number of patients accrued)	1.6 (1.2-2.0)	0.0007
Single-centre vs. multi-centre participation	2.1 (1.6-2.7)	<0.0001

[a]Ratio of number of publications of a randomization with a certain trial characteristic to the number of publications of a randomization without that trial characteristic.

Table 4 - Trial characteristics significantly associated with time to first mention

Trial Characteristic	**Additional time to first mention (months) (95% CI)**	***p*-value**
Main effects:		
Superiority vs. equivalence trial	36 (18-55)	0.0002
Conducted in a low or middle income country	73 (51-94)	<0.0001
For each ten years earlier start date of accrual period	10 (5-16)	0.0001
No indication is given as to whether the results are clinically significant or not	23 (10-35)	0.0005
A clear indication is given as to whether the main questions in the paper are answered in that paper	34 (22-46)	<0.0001
Not presented at a meeting vs. presented	18 (7-29)	0.002
Reported in articles which mention a greater number of trials	12 (7-16)	<0.0001
Interaction:		
Equivalence trial where a clear indication is given as to whether the results are clinically significant or not	33 (8-59)	0.01

Table 5 - Trial characteristics significantly associated with whether a randomization is ever mentioned in an article

Trial Characteristic	Odds ratio (95% CI) for randomization ever being mentioned	*p*-value
Conducted in a high vs. low or middle income country	13.1 (2.1-80.9)	0.006
For each ten years earlier start date of accrual period	7.1 (1.9-27.0)	0.004
log_{10} (number of patients accrued)	18.3 (3.8-88.3)	0.0003

Table 6 - Trial characteristics significantly associated with a randomization being mentioned in more articles

Trial characteristic	Incidence ratio[a] (95% CI)	*p*-value
First-line vs. relapse/refractory disease treatment	1.8 (1.2-2.8)	0.007
Equivalence trial vs. not	1.3 (1.1-1.6)	0.01
Conducted in high vs. low or middle income country	2.5 (1.4-4.5)	0.003
Conducted in North America vs. elsewhere	1.3 (1.1-1.6)	0.01
Single-center vs. multi-center participation	1.6 (1.2-2.1)	0.0004
For each ten years more recent start date of accrual period	1.6 (1.4-1.9)	<0.0001
log_{10} (number of patients accrued)	1.9 (1.5-2.4)	<0.0001

[a]Ratio of number of mentions of a randomization with a certain trial characteristic to the number of mentions of a randomization without that trial characteristic.

Additional files

Additional file 1 – Summary of trials and randomizations

File name: key_findings_additional_file_1.doc
File format: Word document
Title of data: Summary of trials and randomizations
Description of data: table plus comments

Additional file 2 – Summary statistics and the results of univariate analyses for all trial characteristics investigated

File name: key_findings_additional_file_2.doc
File format: Word document
Title of data: Summary of trials and randomizations
Description of data: table plus comments

Additional file 3 – Characteristics excluded from all analyses

File name: key_findings_additional_file_3.doc
File format: Word document
Title of data: Summary of trials and randomizations
Description of data: table plus comments