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Publication Date

2022-05-01

DOI

10.1016/j.ejca.2021.12.037

European Journal of Cancer 167 (2022) 152–160

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Characteristics of clinical trials for haematological malignancies from 2015 to 2020: A systematic review

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Received 2 November 2021; received in revised form 2 December 2021; accepted 18 December 2021
Available online 27 February 2022

KEYWORDS
Neoplasms;
Hematologic neoplasms;
Clinical trials;
Randomisation;
Outcomes;
Quality of life;
Overall survival;
Drug development

Abstract ***Background:*** As the landscape of haematological malignancies dramatically changes due to diagnostic and therapeutic advances, it is important to evaluate trends in clinical trial designs. The objective of our study was to describe the design of clinical trials for five common haematological malignancies with respect to randomisation and end-points. We also aimed to assess trends over time and examine the relationships of funding source and country of origin to proportions of randomisation and utilisation of clinical end-points.

Methods: This systematic review identified haematological malignancy clinical trials starting in 2015–2020 registered at ClinicalTrials.gov as of 20th February 2021. Trial-related variables including randomisation status, type of primary end-point, and both projected and actual enrolment numbers were captured. Clinical end-points were defined as overall survival and quality of life, while surrogate end-points included all other end-points.

Results: Of 2609 relevant trials included in this analysis, only one-fifth were randomised (538, 21%), with a significant decrease in the proportion of randomised clinical trials from 26% of trials in 2015 to 19% in 2020 ($p < 0.00001$). Between the years 2015 and 2020, the proportion of randomised trials for all haematological malignancies using primary surrogate end-points remained relatively consistent, ranging from 84% in 2015 to 78% in 2020 ($p = 0.352$). Overall, only 15% of trials utilised primary end-points of overall survival or quality of life in a randomised design.

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https://doi.org/10.1016/j.ejca.2021.12.037

Conclusions: This systematic review of haematological malignancy trials found that the majority of trials are non-randomised and that there has been an increase in the ratio of non-randomised to randomised studies over time. The vast majority of randomised haematological malignancy trials use surrogate primary end-points.

1. Introduction

Despite dramatic advances in the treatment of haematological cancers, they remain a significant source of morbidity and mortality globally [1,2]. Improvement in survival over the last decade has been a result of numerous approved therapies, which have been made possible through the use of clinical trials [3]. The United States Food and Drug Administration has approved over 50 new agents for haematological malignancies over the last five years, however, most of these have been on the basis of early phase clinical trials using surrogate end-points [4,5].

Clinical end-points most relevant to patients include overall survival and quality of life [6], but these end-points are often supplanted by surrogate end-points such as progression-free survival and response rate. Although surrogate end-points allow for earlier approval of drugs and availability to patients [7], these end-points do not consistently correlate with overall survival and quality of life [8–10].

As no prior study has ever evaluated the landscape of trials for haematological malignancies in a systematic fashion, the goal of our study was twofold. First, we aimed to assess the proportion of randomised versus non-randomised trials for haematological malignancies, and second, we aimed to assess the proportion of randomised trials for haematological malignancies utilising surrogate end-points versus clinical end-points as a primary end-point.

2. Methods

2.1. Search strategy and selection criteria

The following haematological malignancies were chosen for review: multiple myeloma (MM), diffuse large B-cell lymphoma, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and acute lymphoid leukaemia.

Data were searched for on the ClinicalTrials.gov database. The key phrases 'Interventional Studies', 'Start Date from 01/01/2015 to 12/31/2020', were used, along with a key phrase for each disease, "MM", "Acute Myelogenous Leukemia", "CLL", "Acute Lymphoblastic Leukemia" and "Diffuse Large B Cell Lymphoma". The query was performed on 20th February 2021 and data were collected between 20th February 2021 and 26th April 2021.

2.2. Inclusion/exclusion criteria

Our study included all interventional trials of the five aforementioned haematological malignancies that had a start date between 1st January 2015 and 31st December 2020. Trials that were terminated early after having enrolled patients and that were not yet enrolling at collection were included in order to best represent the trial landscape available to patients. Observational or non-interventional trials were excluded. Trials that terminated without enrolling a single patient were also excluded.

2.3. End-points and variables collected

The primary end-points of the study were to determine what proportion of trials for haematological malignancies is randomised, and the proportion of randomised trials with surrogate versus clinical end-points. We defined clinical end-points as overall survival and quality of life in randomised trials, as commonly accepted [11], while surrogate end-points included dosing end-points such as maximum tolerated dose and pharmacokinetics of dosing, safety, response rate, progression free survival or derivatives of progression-free survival and adherence. The analysis of end-points was done only for randomised studies and sub-stratified for Phase III randomised studies, as early phase trials were not expected to have clinical end-points.

We measured the actual and estimated enrolment numbers of each trial as some trials in progress had not yet completed enrolment. Other variables collected included the trial start date, trial end date or projected end date, funding source (industry versus cooperative group), and whether the trial was conducted in a developed or developing country as defined by the United Nations stratification, which compiles data from World Economic Situation and Prospects (WESPS) [12]. For the purposes of this review, only countries in the category of developed economies were classified as high income, and countries that fell under economies in transition or developing economies were classified as

low/middle income. The starting year of a trial was defined as the year the trial started enrolling or was projected to start enrolling.

We evaluated randomisation proportions between high income and low/middle income countries and the percentage of randomised trial slots for each type of cancer assessed. Statistical analysis was performed using the JMP 15 suite of statistics software. A two-tailed Z-test of two proportions was used to compare the proportions of randomisation and the use of surrogate versus clinical end-points from the year 2015 to 2020 with an a priori significance level of 0.05.

3. Results

A total of 3708 clinical trials were identified through the initial search on the ClinicalTrials.gov website. From these trials, 19 were excluded as non-interventional trials, 67 were excluded for exclusively studying diseases outside the scope of this review and 286 trials were excluded as duplicates between the diseases being studied. After exclusion of non-eligible trials, 2609 trials remained for further analysis (Fig. 1).

3.1. Characteristics of included trials

Characteristics of the 2609 trials included in this review as well as the 297,623 patient slots distributed between those trials are detailed in Table 1. While Phase III trials were the minority of the included 2609 trials (272 [10%]), these trials made up the largest proportion of patient slots (114,852 [39%]). Similarly, randomised trials (comprised of Phase III trials, as well as randomised Phase II trials) made up a minority of the included 2609 trials (538 [21%]), but a majority of patient slots (154,997 [52%]). Due to the recent nature of the included trials, 196 (8%) of trials had reported results at the time of data collection. Among these 196 trials, 45 (23%) trials were randomised and 151 (77%) trials were non-randomised. From the same 196 trials, 13 (7%) trials utilised clinical end-points while 183 (93%) trials utilised surrogate end-points.

3.2. Randomisation of haematological malignancy trials and patient slots

Characteristics of the 2609 included trials are further detailed by randomisation status in Table 2. Among

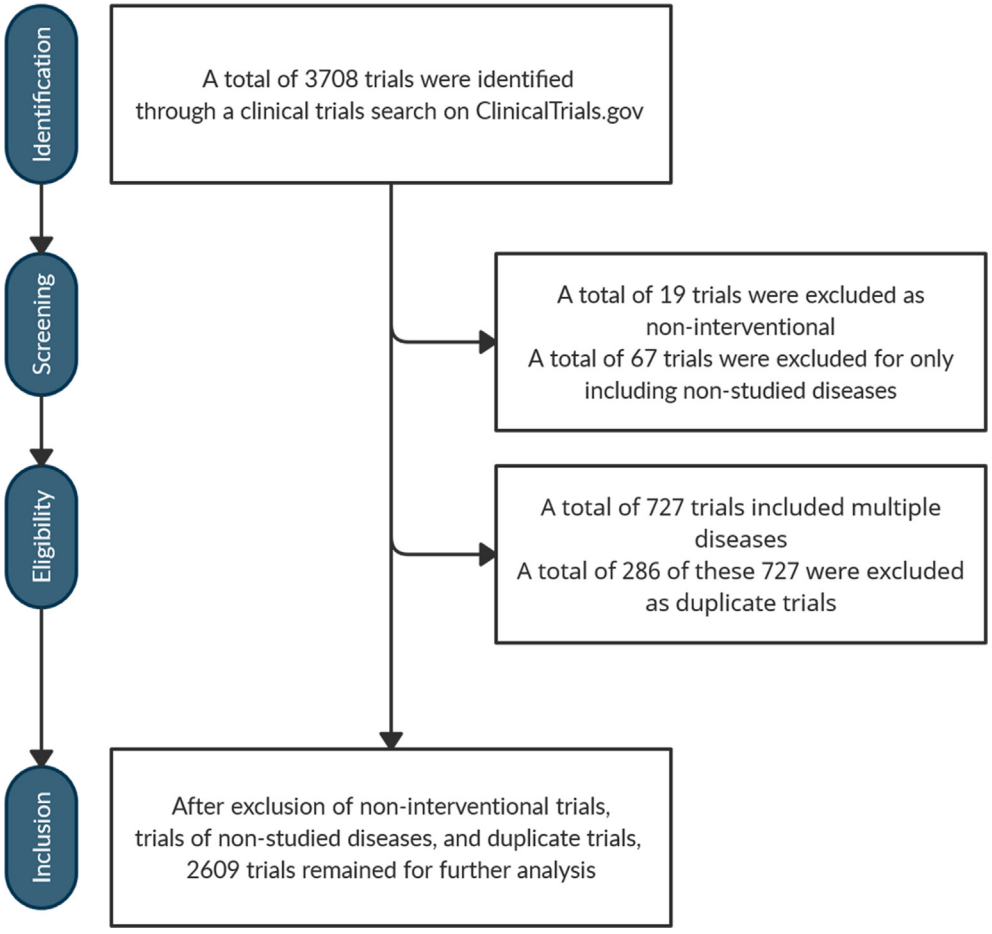

Fig. 1. Flow diagram for included trials.

Table 1
Characteristics of haematological malignancy trials and patient slots.

Characteristic	No. (%) of Trials	No. (%) of Patient Slots
	Total (N = 2609)	Total (N = 297,623)
Disease		
Multiple myeloma	611 (23)	64,696 (22)
Acute myeloid leukaemia	707 (27)	73,932 (25)
Chronic lymphocytic leukaemia	192 (7)	20,130 (7)
Acute lymphoblastic leukaemia	309 (12)	50,766 (17)
Diffuse large B-cell lymphoma	355 (14)	37,677 (13)
Multi-Disease	435 (17)	50,422 (17)
Phase of Trial		
1	831 (32)	43,460 (15)
1,2	438 (17)	37,271 (13)
2	880 (34)	76,054 (26)
3	272 (10)	114,852 (39)
4	33 (1)	4500 (2)
Not applicable	155 (6)	21,486 (7)
Randomisation		
Randomised	538 (21)	154,997 (52)
Non-randomised	2071 (79)	142,626 (43)
Primary site economy type		
High income	2123 (81)	263,458 (89)
Low/middle income	486 (19)	34,165 (11)
Funding source		
Industry	1404 (54)	161,818 (54)
Non-industry	1205 (46)	135,805 (46)
Location of study		
US	1253 (48)	100,538 (34)
Multicenter including US	358 (14)	84,757 (28)
Non-US	998 (38)	112,328 (38)

the 2609 trials included, 538 (21%) trials were randomised and 2071 (79%) trials were non-randomised. The 2609 trials included a total of 297,623 slots for patients to be enrolled on. Among these slots, 154,997 (52%) were randomised and 142,626 (48%) were non-randomised.

Between the years 2015 and 2020, the proportion of randomised trials decreased from 26% of all trials in 2015 to 19% in 2020, $p < 0.00001$ (Fig. 2).

However, the number of patient slots for randomised trials increased modestly from 54% in 2015 to 57% in 2020, $p < 0.00001$ (Supplement Fig. 1). The median patient slots in a randomised trial increased from 139 (IQR 72.5–300) slots in 2015 to 172 (IQR 95–265) in 2020, although this was not a statistically significant increase, $p = 0.25$ (Fig. 3).

3.3. The use of surrogate end-points in randomised haematological malignancy trials

Amongst the 538 randomised trials included for analysis, 455 (85%) trials utilised surrogate primary end-points and 83 (15%) trials used clinical end-points. Of the 455 trials utilising surrogate primary end-points, 235 (44%) trials utilised response rates as a primary end-point, 205 (38%) trials utilised progression-free survival (or event-free survival/relapse-free survival) as a primary end-point, 68 (13%) trials utilised safety as a primary end-point and less than 10% of trials utilised dosing and adherence as primary end-points, respectively. Of the 83 trials that utilised a clinical primary end-point, 66 (12%) trials utilised overall survival and 17 (3%) trials utilised quality of life as a primary end-point.

When stratifying exclusively for Phase III randomised trials, the proportion of trials utilising clinical end-points as a primary end-point remained consistent between 2015 and 2020 (Supplement Fig. 2).

Between the years 2015 and 2020, the proportion of randomised trials for all haematological malignancies using primary surrogate end-points remained relatively consistent, ranging from 84% in 2015 to 78% in 2020, $p = 0.049$. The proportion of randomised slots for all haematological malignancies using primary surrogate end-points increased from 62% in 2015 to 80% in 2020, $p < 0.00001$.

3.4. Individual diseases

Information for each of the five diseases assessed is listed in the supplement.

3.5. High income versus low/middle income countries

Among the 2609 trials included, 2123 (81%) trials had at least one site in a high-income country and 486 (19%) trials took place exclusively in low/middle income countries.

There was no significant difference in the proportion of trials that were randomised as a fraction of overall trials between high income countries (21%) and low/middle income countries (19%), $p = 0.44$.

Among the 444 randomised trials that had at least one site in a high income country, 68 (15%) trials used clinical end-points as a primary end-point. Among the 94 randomised trials that took place exclusively in low/middle income countries, 15 (16%) trials used clinical end-points as a primary end-point ($p = 0.87$).

3.6. Funding source

Among the 2609 trials included, 1404 (54%) trials were funded by industry sponsors whereas 1205 (46%) trials were funded by non-industry sponsors (cooperative groups, and so on).

Among the 1404 trials funded by industry sponsors, 258 (18%) trials were randomised. Among the 1205 trials funded by non-industry sponsors, 280 (23%) trials were randomised, a significant increase over their industry counterparts ($p = 0.0022$).

Table 2
Characteristics of randomised and non-randomised haematological malignancy trials.

Characteristic	No. (%) of Trials	No. (%) of randomised trials	No. (%) of non-randomised trials
	Total (N = 2609)	Total (N = 538)	Total (N = 2071)
Disease			
Multiple myeloma	611 (23)	161 (30)	450 (22)
Acute myeloid leukaemia	707 (27)	154 (29)	553 (27)
Chronic lymphocytic leukaemia	192 (7)	37 (7)	155 (7)
Acute lymphoblastic leukaemia	309 (12)	54 (10)	255 (12)
Diffuse large B-cell lymphoma	355 (14)	75 (14)	280 (14)
Multi-disease	435 (17)	57 (11)	278 (18)
Phase of trial			
1	831 (32)	33 (6)	798 (39)
1,2	438 (17)	41 (8)	397 (19)
2	880 (34)	164 (30)	716 (35)
3	272 (10)	224 (42)	48 (2)
4	33 (1)	15 (3)	18 (1)
Not applicable	155 (6)	61 (11)	94 (5)
Treatment type			
Chemotherapy	1704 (65)	363 (67)	1341 (65)
Cell therapy	431 (17)	34 (6)	397 (19)
Combination therapy	271 (10)	51 (9)	220 (11)
Supportive care	138 (5)	75 (14)	63 (3)
Procedure	52 (2)	9 (2)	43 (2)
Device	9 (0)	5 (1)	4 (0)
Radiation therapy	4 (0)	1 (0)	3 (0)
End-points			
Safety	922 (35)	68 (13)	854 (41)
Response	1098 (42)	235 (44)	863 (42)
Progression/relapse	445 (17)	205 (38)	240 (12)
Dosing	645 (25)	44 (8)	601 (29)
Adherence	58 (2)	15 (3)	43 (2)
Quality of life	34 (1)	17 (3)	17 (1)
Survival	134 (5)	66 (12)	68 (3)
Primary site economy type			
High income	2123 (81)	444 (83)	1679 (81)
Low/middle income	486 (19)	94 (17)	392 (19)
Funding source			
Industry	1404 (54)	258 (48)	1146 (55)
Non-industry	1205 (46)	280 (52)	925 (45)

Among the 258 randomised trials that were funded by industry sponsors, 38 (15%) trials used clinical end-points as a primary end-point. Among the 280 randomised trials funded by non-industry sponsors, 45 (16%) trials used clinical end-points as a primary end-point. This difference was not statistically significant ($p = 0.67$).

4. Discussion

As the landscape of haematological malignancies dramatically changes due to diagnostic and therapeutic advances, it is important to evaluate trends in clinical trial designs. The results of our systematic review demonstrate that only a minority of trials for common haematological malignancies are randomised and that the proportion of randomised trials as a fraction of all trials has decreased over time. As randomised trials have accrued larger sample sizes, the overall proportion of randomised patients' slots as a fraction of all available clinical trial slots has increased modestly over time. Overall, this trend suggests that modern trials are either non-randomised or randomised in design but testing surrogate end-points or testing marginal gains using a larger sample size.

Early phase, non-randomised clinical trials have critical roles in the evaluation of novel approaches and combinations of treatments, as well as determination of the safety in new compounds [13,14]. This role should not be minimised, as demonstrating safety is the groundwork for any new therapy. However, the definitive measure of efficacy of a treatment in relation to the prevailing standard of care is best taken through a randomised controlled trial, as phase I trials efficacy rates translate poorly to real-world efficacy as well as efficacy in larger randomised trials [15,16]. While a randomised controlled trial may incur higher costs in time and money than early phase trials, randomisation offer three advantages over observational studies [17]. Randomisation minimises differences in measured and unmeasured confounders, it sets time-zero equally in both arms, and it minimises multiple hypothesis testing and selective reporting [18]. For these reasons, randomised trials are considered the gold standard to inform treatment decisions [19–21].

We demonstrate that independent of funding source (industry versus non-industry), the proportion of randomised trials and use of clinical end-points is low. The United States Food and Drug Administration instituted *Accelerated Approval* regulations in 2012, allowing the approval of drugs for unmet medical needs, based on measurement of surrogate end-points [22]. By utilising surrogate end-points, drug manufacturers can gain easier approval and access to the market [8,23]. The usage of surrogate end-points such as overall response and event-free survival can thus provide quicker results with respect to the 'efficacy' of a drug but unfortunately do not capture the true goals of treatment – improvements to quality of life and improving overall survival [24].

Our analysis of low/middle income countries merits a comparison to a recent review of oncology trials stratified based on whether the primary author was from a low/middle income country or high income country [25]. In their analysis of all published oncology Phase III trials from 2014 to 2017, randomised clinical trials from low/middle income countries were more likely to identify effective therapies and have a larger effect sise than trials from high income countries [25]. While our study differs from the study by Wells *et al.* in various ways, our

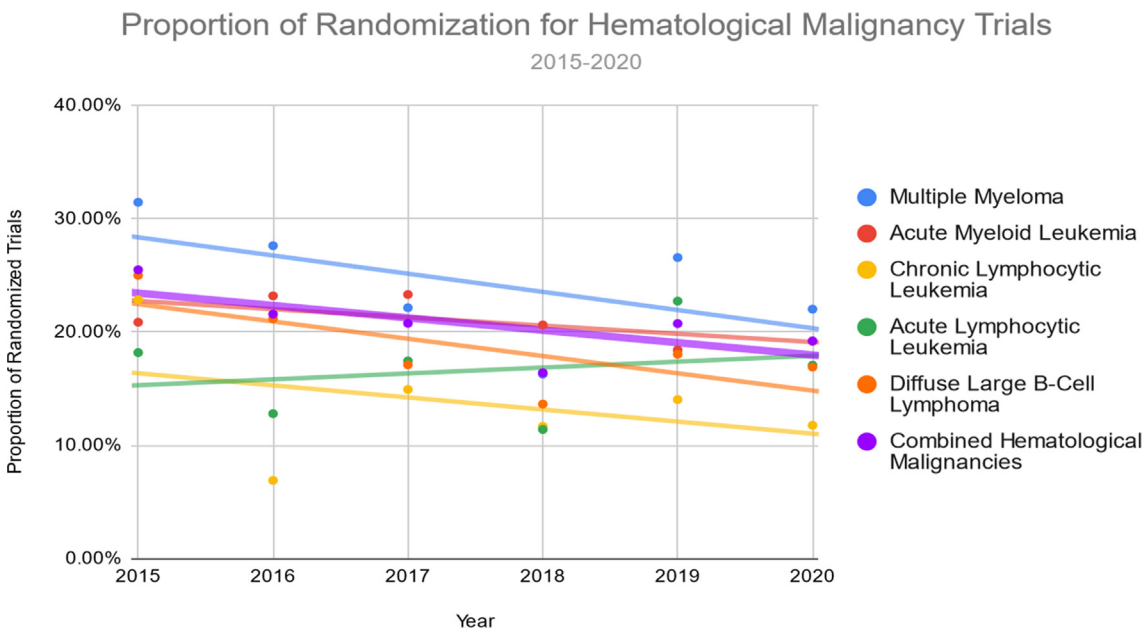

Fig. 2. Proportion of randomisation for haematological malignancy trials over time.

findings concur that there is a paucity of randomisation and preponderance of surrogate end-points present in trials from both low/middle income and high income countries, with only 15% of randomised trials utilising clinical end-points as the primary end-point. This is a concerning finding with important implications for patients, regulatory authorities and clinicians alike, as the true benefit to patients of new interventions can be hard to elucidate. Our findings have similarities to what has been observed with solid tumours, in which recent randomised trials have also predominantly used surrogate end-points like progression-free survival as a primary end-point [26].

Some surrogate end-points such as progression free survival and efficacy have been shown to correlate with a number of domains of quality of life in patients with AML [27]. However, direct measurement of improvement of quality of life is of the paramount importance

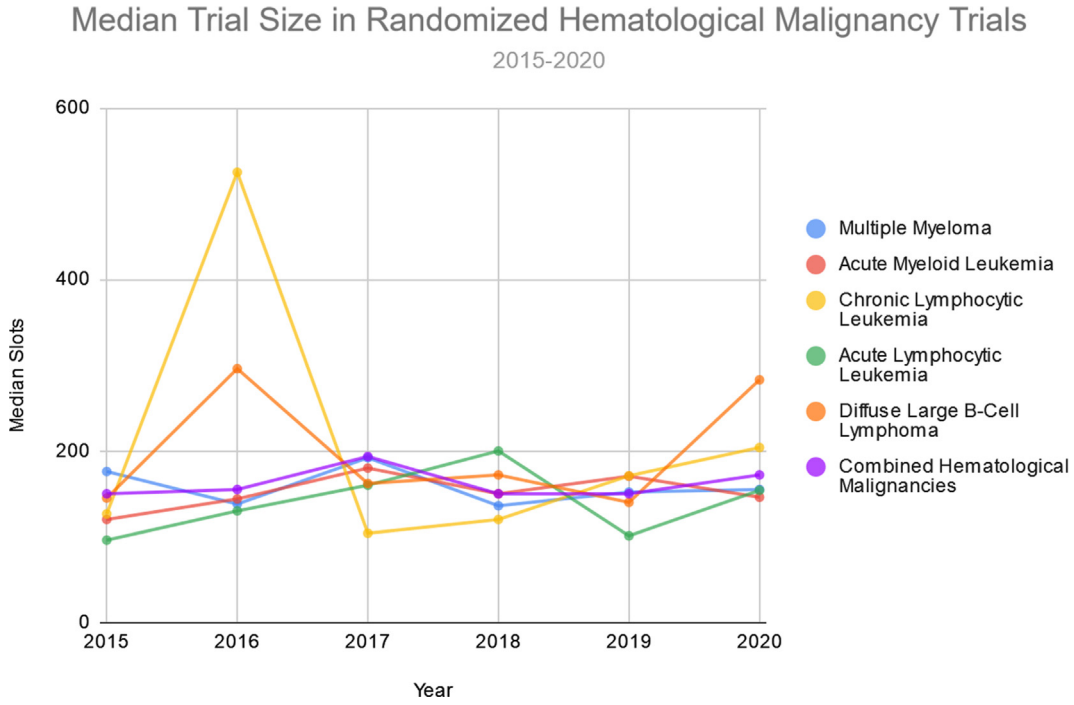

Fig. 3. Median trial size in randomised haematological malignancy trials over time.

for cancer treatments. Despite the measure's importance, many clinical trials lack quality of life as an end-point and most enter the market without showing any indication of quality of life or overall survival improvement [28]. Of all the trials we evaluated, only 17 (3%) of randomised trials used quality of life as a primary end-point.

Amongst the five diseases we assessed, we found that the proportion of randomised trials as a fraction of all trials decreased the most for MM, CLL and diffuse large B-cell lymphoma whereas it remained relatively stable for AML and acute lymphoid leukaemia. We hypothesise that this is due to several potential reasons. We hypothesise that the relative abundance of early phase trials is proportional to the interest of the biotech and pharmaceutical industry in the field. This is evident in MM where in addition to multiple drugs that are in development targeting numerous targets, there is also a plethora of agents in development targeting just a single target (BCMA) across several different classes of drugs, such as chimeric antigen receptor therapy, bispecific immune engagers and so on [29]. This may also be a result of the cultural norms within the academic community in each haematological malignancy. As an example, the standard of care has historically been clearly defined for AML and hence there have likely been an increased proportion of randomised trials aiming to assess it against the standard of care, relative to other haematological malignancies [30]. There may also be a different regulatory burden for approval of drugs in each haematological malignancy, leading to different incentives for clinical trial design.

Despite the identified issues facing the clinical trial landscape of haematological malignancies, there are potential solutions. Public funding of clinical trials could help to minimise the influence of profits on the design of clinic trials and lead to clinical trial design that better serves patients within an affordable public health infrastructure [31,32]. Regulatory agencies can correct the trends observed in our study by requiring overall survival and randomisation prior to the full market approval. Although we recognise that quality of life may not be a primary end-point for trials seeking to approve a new drug or evaluate the efficacy of a new drug, quality of life remains a highly relevant end-point for many other strategies – such as in de-escalation or escalation trials or in trials designed to evaluate supportive care interventions [33]. The measurement and reporting of quality of life have previously been shown to be heterogeneous and incomplete in clinical trials, and there is an urgent need for standardisation and consistent reporting [34].

Early phase studies are essential to identify novel compounds, pathways and combinations, and a well-designed early phase study can advance the field substantially further than a poorly designed randomised study. However, when early phase studies are considered adequate for regulatory approval, incentives are skewed towards non-randomised studies, and the ratio of randomised studies decreases, as observed in our analysis.

Our study has limitations. Our study relied on data provided by sponsors to ClinicalTrials.gov. Although this information is provided in English, language-related or typographic errors may have led to corresponding errors in this analysis. Many of the trials that were started towards the end of the studied date range have not completed enrolment or reported results, thus necessitating the use of 'trial slots' or 'projected enrolment' in our analysis, as opposed to actual patients enrolled. This may ultimately skew the data collected in either direction – by under or overestimation, depending on actual enrolment on these trials in the future. Furthermore, we did not assess the adequacy of surrogacy by the type of tumour or of each individual surrogate, as the strength of surrogacy may vary widely depending on what end-point is used, and what disease state it is being considered in the study by Shi et al. [35] and Gyawali et al. [36]. Many of the trials we included are ongoing and do not have results publicly available, and hence our ability to draw inferences on the results and effect size was limited.

5. Conclusions

Our systematic review of haematological malignancy trials found that the majority of trials are non-randomised and that there has been an increase in the ratio of non-randomised to randomised studies over time. The vast majority of randomised haematological malignancy trials use surrogate end-points rather than clinical end-points most relevant to patients such as overall survival and quality of life. Given the widespread use of surrogate end-points and non-randomised studies, it is important to be cognizant of their limitations, and further efforts are needed to prioritise trial design that translates most directly to improving clinical outcomes for patients.

Data sharing

The data set used collected for this systematic review is publicly available on ClinicalTrials.gov. Included data can be made available upon request with investigator support and approval through a signed data access agreement. Data to be shared include aggregate study-level data and the statistical analysis plan. These data will be made available from the time of publication.

Funding

This study recieved no funding.

Author contributions

WW, VG, VP and GM contributed to the study conception and design. WW planned the statistical analysis. WW and VG collected data. WW, VG, and GM did data quality assessment. WW and SA analysed the data. WW, VG and GM wrote the first draft of the manuscript. DS, BM, AG, BG, SA and VP critically revised the manuscript for important intellectual content. All authors commented on the drafts and approved the final draft. WW and GM are the guarantors.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests, although the study did not recieve any funding from these sources: Vinay Prasad reports royalties from Johns Hopkins Press, Medscape, MedPage, consulting for UnitedHealthcare, and speaking fees for Evicore. Vinay Prasad has a plenary session podcast that has Patreon backers. Vinay Prasad is funded to study low value drugs through a grant from Arnold Ventures. The funder had no role in the design of this study. Aaron Goodman reports consulting for Seattle Genetics and EUSA Pharma. Douglas Sborov reports consulting for Janssen, SkylinDx, GlaxoSmithKline, Legend Biotech, Amgen and Celgene. None of the authors have any other conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.12.037.

References

[1] Pulte D, Jansen L, Brenner H. Changes in long term survival after diagnosis with common hematologic malignancies in the early 21st century. Blood Cancer J 2020;10:56. https://doi.org/10.1038/s41408-020-0323-4.

[2] Keykhaei M, Masinaei M, Mohammadi E, Azadnajafabad S, Rezaei N, Saeedi Moghaddam S, et al. A global, regional, and national survey on burden and Quality of Care Index (QCI) of hematologic malignancies; global burden of disease systematic analysis 1990–2017. Exp Hematol Oncol 2021;10:11. https://doi.org/10.1186/s40164-021-00198-2.

[3] Islami F, Ward EM, Sung H, Cronin KA, Tangka FKL, Sherman RL, et al. Annual report to the nation on the status of cancer, Part 1: national cancer statistics. JNCI J Natl Cancer Inst; 2021djab131. https://doi.org/10.1093/jnci/djab131.

[4] Al Hadidi S, Ramos CA. Level of evidence for FDA drug approvals in pivotal clinical trials of hematological malignancies. Leuk Lymphoma 2021;62:1522–4. https://doi.org/10.1080/10428194.2021.1876872.

[5] Prasad V, Lindner S. Why is research in early-stage cancer research so low? J Cancer Policy 2018;17:4–8. https://doi.org/10.1016/j.jcpo.2018.07.003.

[6] Mohyuddin GR, Koehn K, Abdallah A, Sborov D, Rajkumar SV, Kumar S, et al. Use of endpoints in multiple myeloma randomized controlled trials over the last 15 years: a systematic review. Am J Hematol 2021;96:690–7. https://doi.org/10.1002/ajh.26166.

[7] Chen EY, Joshi SK, Tran A, Prasad V. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. JAMA Intern Med 2019;179:642. https://doi.org/10.1001/jamainternmed.2018.8351.

[8] Sherrill B, Kaye Sandin, Cappelleri Chen. Review of meta-analyses evaluating surrogate endpoints for overall survival in oncology. OncoTargets Ther 2012;287. https://doi.org/10.2147/OTT.S36683.

[9] Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of overall survival, quality of life, and safety benefits associated with new cancer medicines. JAMA Oncol 2017;3:382. https://doi.org/10.1001/jamaoncol.2016.4166.

[10] Gyawali B, Prasad V. Combining drugs and extending treatment — a PFS end point is not sufficient. Nat Rev Clin Oncol 2017;14:521–2. https://doi.org/10.1038/nrclinonc.2017.72.

[11] Sullivan Eugene J. Clinical trial endpoints. United States Food and Drug Administration; 2012.

[12] UN/DESA. World economic situation and Prospects 2014. Development Policy and Analysis Division of the Department of Economic and Social Affairs of the United Nations Secretariat; 2014.

[13] Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. Postgrad Med 2011;123:194–204. https://doi.org/10.3810/pgm.2011.09.2475.

[14] Lawrence TS, Runowicz C, Turner S, Wade III JL. Critical role of phase I clinical trials in cancer treatment. J Clin Oncol 1997;15:853–9.

[15] Tao DL, Kartika T, Tran A, Prasad V. Phase I trials and therapeutic intent in the age of precision oncology: what is a patient's chance of response? Eur J Cancer 2020;139:20–6. https://doi.org/10.1016/j.ejca.2020.04.037.

[16] Roberts TG. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA 2004;292:2130. https://doi.org/10.1001/jama.292.17.2130.

[17] Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: study design: randomised controlled trials. BJOG An Int J Obstet Gynaecol 2018;125. https://doi.org/10.1111/1471-0528.15199. 1716–1716.

[18] Prasad V. Reliable, cheap, fast and few: what is the best study for assessing medical practices? Randomized controlled trials or synthetic control arms? Eur J Clin Invest 2021;51. https://doi.org/10.1111/eci.13580.

[19] Shore BJ, Nasreddine AY, Kocher MS. Overcoming the funding challenge: the cost of randomized controlled trials in the next decade. J Bone Jt Surg 2012;94:101–6. https://doi.org/10.2106/JBJS.L.00193.

[20] Dekkers OM, Elm Ev, Algra A, Romijn JA, Vandenbroucke JP. How to assess the external validity of therapeutic trials: a conceptual approach. Int J Epidemiol 2010;39:89–94. https://doi.org/10.1093/ije/dyp174.

[21] Rief W, Barsky AJ, Glombiewski JA, Nestoriuc Y, Glaesmer H, Braehler E. Assessing general side effects in clinical trials: reference data from the general population: GASE IN clinical trials. Pharmacoepidemiol Drug Saf 2011;20:405–15. https://doi.org/10.1002/pds.2067.

[22] United States Food and Drug Administration. Accelerated approval program. 2020.

[23] Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med 2017;15:134. https://doi.org/10.1186/s12916-017-0902-9.

[24] Svensson S, Menkes D, Lexchin J. Surrogate outcomes in clinical trials: a cautionary tale. JAMA Intern Med 2013;173:611–2.

[25] Wells JC, Sharma S, Del Paggio JC, Hopman WM, Gyawali B, Mukherji D, et al. An analysis of contemporary oncology

randomized clinical trials from low/middle-income vs high-income countries. JAMA Oncol 2021;7:379–85. https://doi.org/10.1001/jamaoncol.2020.7478.

[26] Del Paggio JC, Berry JS, Hopman WM, Eisenhauer EA, Prasad V, Gyawali B, et al. Evolution of the randomized clinical trial in the era of precision oncology. JAMA Oncol 2021;7:728. https://doi.org/10.1001/jamaoncol.2021.0379.

[27] Alibhai SMH, Leach M, Gupta V, Tomlinson GA, Brandwein JM, Saiz FS, et al. Quality of life beyond 6 months after diagnosis in older adults with acute myeloid leukemia. Crit Rev Oncol Hematol 2009;69:168–74. https://doi.org/10.1016/j.critrevonc.2008.07.015.

[28] Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ 2017:j4530. https://doi.org/10.1136/bmj.j4530.

[29] Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. J Hematol Oncol 2020;13:125. https://doi.org/10.1186/s13045-020-00962-7.

[30] Estey E, Othus M, Gale RP. New study-designs to address the clinical complexity of acute myeloid leukemia. Leukemia 2019;33:567–9. https://doi.org/10.1038/s41375-018-0363-y.

[31] Schilsky RL. Publicly funded clinical trials and the future of cancer care. Oncologist 2013;18:232–8. https://doi.org/10.1634/theoncologist.2012-0423.

[32] Bressler LR, Schilsky RL. Collaboration between cooperative groups and industry. J Oncol Pract 2008;4:140–1. https://doi.org/10.1200/JOP.0834601.

[33] Costa DSJ, Mercieca-Bebber R, Rutherford C, Tait M-A, King MT. How is quality of life defined and assessed in published research? Qual Life Res 2021;30:2109–21. https://doi.org/10.1007/s11136-021-02826-0.

[34] Chakraborty R, Cannella L, Cottone F, Efficace F. Quality of patient-reported outcome reporting in randomised controlled trials of haematological malignancies according to international quality standards: a systematic review. Lancet Haematol 2020;7:e892–901. https://doi.org/10.1016/S2352-3026(20)30292-1.

[35] Shi Q, Schmitz N, Ou F-S, Dixon JG, Cunningham D, Pfreundschuh M, et al. Progression-free survival as a surrogate end point for overall survival in first-line Diffuse Large B-Cell lymphoma: an individual patient-level analysis of multiple randomized trials (SEAL). J Clin Oncol Off J Am Soc Clin Oncol 2018;36:2593–602. https://doi.org/10.1200/JCO.2018.77.9124.

[36] Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. EClinicalMedicine 2020;21:100332. https://doi.org/10.1016/j.eclinm.2020.100332.