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Original Article

Unequal allotment of patients in phase III oncology clinical trials

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Abstract: Patient enrollment in cancer clinical trials has traditionally been limited to an equal distribution between cases and controls, however recently some clinical trials have utilized an unequal distribution between the case and control arms. Trends and proportion of phase 3 cancer clinical trials that have an unequal allocation between the years 2010 and 2019 were studied from data extracted from clinicaltrials.gov. 323 trials with two arms and 35 trials with 3 arms were identified as randomized control trials with the primary purpose of a cancer-related treatment that provided allocation data. Amongst the trials with two arms, 238 trials had equal allocation and 85 trials had unequal allocation. Therefore, cancer clinical trials with unequal allocation represent about one in four 2-arm phase 3 trials. Amongst the eligible trials with three arms, 26 trials had equal allocation and 9 trials had unequal allocation. There was no significant difference in the annual proportion of trials with unequal allocation from 2010 to 2019. The categories of cancer which had the highest number of unequally allotted two-arm clinical trials were: gastrointestinal, breast, and genitourinary malignancies. This shift may represent a new trend in clinical trial design to help enhance closer monitoring of adverse events despite higher costs and lower statistical power attached to this method.

Keywords: Unequal allotment, randomized controlled trials, trends

Introduction

Randomized controlled clinical trials (RCTs) have been the gold standard research method for evaluating treatments and interventions in oncology [1, 2]. In these trials, participants are randomly allocated into various arms to minimize selection bias and limit confounding within the clinical trial patient population [1, 3]. The majority of studies assign an equal number of participants to each study arm in order to optimize the statistical power of the study [3]. While this system of equal allocation to treatment arms has long been the standard in clinical studies, an interest in designing studies with unequal allocation schemes has recently emerged [3-8]. Distributing an uneven number of patients among the arms, or 'unequal allotment', can have many financial, ethical, and statistical implications, however the majority of reports on trial results do not discuss the specific reasons for their allocation choice [9-11].

Several studies have provided supporting evidence that unequal randomization has been an effective method utilized in clinical trials [3-5, 12-14]. In most of these cases, more study participants are found in the experimental arm in comparison to the control arm. The need for unequal allocation in clinical trials has been growing with the spread of adaptive designs, such as the investigation of multiple dose arms in phase III randomized studies [6, 7]. Some possible advantages and disadvantages of using an unequal allocation are listed in **Table 1** [11, 15-19].

Studies that are focused on collecting robust safety data but expect few novel risks with the proposed experimental intervention may benefit from the use of unequal randomization. Compared to balanced trials, however, studies with unequal allocation will likely have less statistical power to detect efficacy, especially if the ratio is 3:1 or more [13]. These studies could also expose more patients than necessary to novel study interventions, and therefore to novel risks related to the intervention [7, 20]. Moreover, the use of unequal allocation can itself be viewed as unethical in nature, depend-

Table 1. Possible advantages and disadvantages of utilizing an unequal allocation in a randomized control trial (i.e. having more participants in an experimental arm of a trial than a control arm, usually) in comparison to using equal allocation are outlined. Considerations include cost, power, flexibility, and more

Category	Advantages	Disadvantages
Cost	One arm is cheaper than the other	Often the placebo/control arm is cheaper
Power	Increased for safety data	Decreased for efficacy data
Flexibility	Allows for different dose regimens, useful in early phase trials	Increase in sample size due to decreased efficacy power
New technology/intervention	Learning curve effect is minimized	Exposure to novel risks related to intervention
Patient preference	Patients more likely to participate if chance of being in the experimental arm is higher	Scientifically, no evidence that the experimental arm is better than the control yet and therefore may violate clinical equipoise.
Ethical preference	Researchers may want to provide a higher chance of experimental treatment to the majority of participants	More participants may experience previously unknown adverse effects from experimental arm
Drop-out rate	If high drop-out rate expected in experimental arm, larger allocation allows for greater power in the intention-to-treat analysis	If high drop-out rate expected in control arm, smaller allocation results in reduced power in a per-protocol analysis

ing on the study design. For example, designating an uneven number of individuals to treatment regimens with currently unknown consequences could be seen as unfair and a violation of the tenet of clinical equipoise [3, 4].

While the utilization of unequal allocation in clinical trials across a variety of fields has been investigated [1, 4, 5], there does not appear to be any evidence of such evaluation in phase III oncology trials [1, 21]. It would be useful to know which fields of oncology may have adopted the unequal allotment method of study design, and whether it has increased in popularity in the last decade. Here, we investigate by a systematic review, the trend and proportion of unequal allotment in Phase III oncology clinical trials between the years 2010-2019 and the potential implications. By elucidating and analyzing its use in past studies, we hope to understand the value of unequal allocation in Phase III cancer trials as well as trends for its use in particular fields of oncology research.

Methods

Trials included within the analysis were automatically extracted from clinicaltrials.gov with the search criteria identified in **Figure 1**. Inclusion criteria represented trials using the search term "cancer"; "active, not recruiting" trials or "completed studies"; trials conducted on "adults" or "older adults" within the United States; phase 3 trials; trials funded by NIH, US Fed, industry, or other; and trials with a start date between January 1st, 2010 and December 31st, 2019. Trials were automatically restricted to randomized control trials with the primary purpose of treatment via data filtration for 'Allocation: Randomized' and 'Primary Purpose: treatment'. Trials were automatically restricted to drug and biological interventions, as defined by clinicaltrials.gov, by using data filtration to exclude other interventions (behavioral, radiation, device, procedural, etc.). These trials were narrowed further to trials that were considered cancer-related (exclusion criteria): this was done by defining a set of keywords identified in **Figure 1** and subsequently using these keywords to automatically filter the 'Conditions' column. The keywords used include "cancer", "neoplasm", "tumor", "Hodgkin", "leukemia", "oma", "myelo", "metasta", "polycythemia", "macroglobin", and "onco". Allocation information on the included trials was manually extracted from clinicaltrials.gov using the 'Study Results' section or a linked article describing the allocation. Trial results (preliminary or complete) or data on prospective methods were used to gather allocation information. Allocation was calculated by dividing the number of participants in the experimental arm with the number of participants in the control arm, and any trials with a ratio greater than 1.4 were considered unequal. Trials that had more than 3 arms and trials that were discontinued were manually excluded. Trials were then divided into those with two arms and those with three arms, and both sets were further divided into specific cancer malignancies they represented by manually filtering data from the 'Conditions' section of clinicaltrials.gov. Averages were calculated and confidence intervals were calculated using a *P* value of 0.05.

Results

812 trials were originally extracted from clinicaltrials.gov on October 20th, 2020 using the search criteria identified in **Figure 1** [22]. 500 trials met all preliminary inclusion criteria and were eligible for further manual allocation study. 90% of trials found within the time period were two-arm trials, and of those two arm trials, 323 trials had available allocation information. 74% of these two arm trials had an equal 1:1 allocation, and 26% had an unequal allocation of 3:2 or more. While the majority of unequal trials had a 2:1 ratio, 8 two-arm trials had an allocation of 3:2 and 3 two-arm trials had an allocation disparity greater than 3:1. 74% of the 35 three-arm trials with allocation information had an equal 1:1:1 allocation, and 26% had an unequal allocation. Common unequal allocations included 2:1:1 and 2:2:1.

Trials were also divided by the type of malignancy they focused on. **Table 2** illustrates the allocation of trials by specified cancer malignancy for the 323 two-arm trials. **Table 3** illustrates similar information for the 35 three-arm trials. The average number of trials with equal allocation per type of malignancy is 74% (population s.d. = 0.08, 95% confidence interval 69-79%), which is calculated by excluding the 'Other' category. Thoracic oncology and soft tissue and bone cancers have a greater number of trials with equal allocation, whereas GI, GU, and breast cancers have a significant number of trials with unequal allocation.

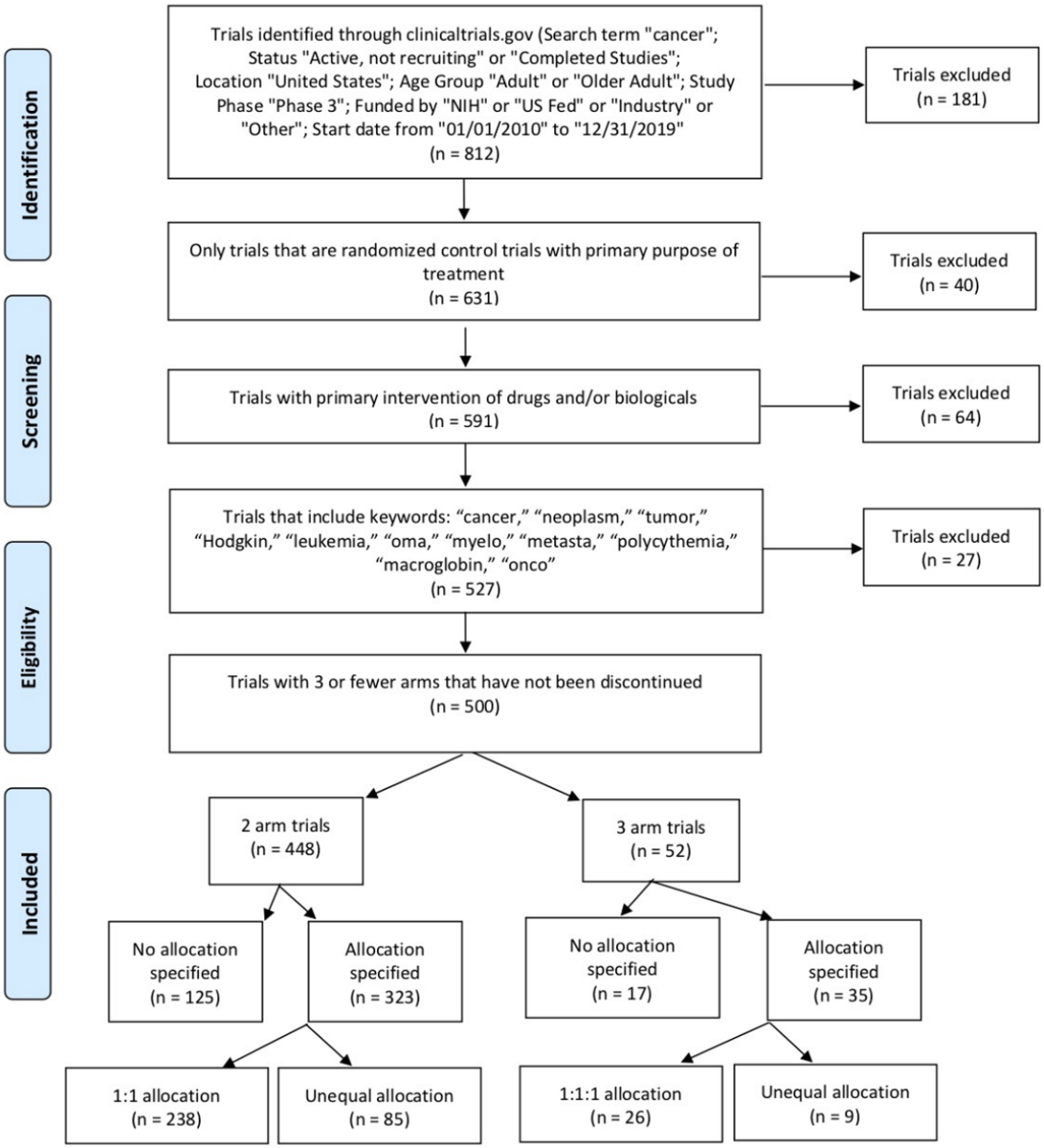

Figure 1. Process of determining phase 3 cancer clinical trials to be included in a study on trends in randomization allocations (PRISMA diagram). Data collected from clinicaltrials.gov and any linked articles on a trial's profile.

Of the total 323 two-arm trials, 41 included biologicals, five of which had unequal allocations, while the rest were drug trials. Only 12% of trials with biological treatments, therefore had unequal allocations, while 28% of the drug trials had unequal allocations. 8 of 35 three-arm trials included biologicals, of which two had unequal allocations.

The 323 two-arm trials were broken down further by year of the start date to discern any potential changes in trend towards equal or unequal allocation (Table S1; **Figure 2**). Because of the limited data for 2018 and 2019 currently on clinicaltrials.gov, results from these years were excluded from further analysis. The mean percentage of two-arm trials with equal allotment in any given year is 74% (population s.d. = 8%, 95% confidence interval 68-80%). In the same way, unequal allotment data was analyzed. The mean percentage of two-arm trials with unequal allotment is 26% (population s.d. = 8%, 95% confidence interval 20-32%). There is a statistically significant devi-

Table 2. Number and percentage of two-arm phase 3 cancer randomized control trials with equal or unequal allocation shown by malignancy type

Type of Malignancy	*Equal allocation n (%)*	*Unequal allocation n (%)*	*Total Studies*
Gastrointestinal cancer	26 (63)	15 (37)	41
Breast cancer	27 (66)	14 (34)	41
Genitourinary cancer	37 (67)	18 (33)	55
Head and Neck cancer	8 (73)	3 (27)	11
Hematological malignancies	68 (76)	21 (24)	89
Skin cancer	16 (80)	4 (20)	20
Thoracic Oncology	43 (83)	9 (17)	52
Soft Tissue and Bone cancer	6 (86)	1 (14)	7
Other	7 (100)	0 (0)	7
Total	238	85	323

323 two-arm cancer trials with a primary purpose of treatment with information on allocation were included. Data collected via clinicaltrials.gov from 2010 to 2019. While the use of equal allocation is more common, some oncology fields utilize unequal allocation more than other fields (such as GI, breast, and GU).

Table 3. Number of three-arm phase 3 cancer randomized control trials with equal or unequal allocation shown by malignancy type

Type of Malignancy	*Equal allocation*	*Unequal allocation*	*Total*
Breast cancer	3	1	4
GI cancer	5	4	9
GU cancer	7	1	8
Hematologic cancer	1	0	1
Lung cancer	7	1	8
Skin cancer	2	0	3
Head and Neck cancer	1	2	3
Other	0	0	0
Total	26	9	35

35 three-arm cancer trials with a primary purpose of treatment with information on allocation were included. Data collected via clinicaltrials.gov from 2010 to 2019. While the use of equal allocation is more common, some oncology fields may utilize unequal allocation more than other fields (such as GI and head and neck)

ation from the mean number of equal allocation two-arm trials compared to the total every year in the years 2010, 2012, 2014, and 2015. In 2010 and 2014, more unequal allocations were utilized than average.

Discussion

The purpose of this study was to illustrate the utilization of unequal allocation schemes specifically in Phase III cancer randomized-controlled trials by assessing the prevalence, trends, and proportion of studies that use unequal allotment.

Prevalence of studies with unequal allotment

This study found 85 two-arm studies (26% of total two-arm studies) and 9 three-arm studies (26% of total three-arm studies) that had used unequal allocation in ratios greater than 1:1 or 1:1:1. The overall proportion of studies that utilized unequal randomization in three-arm studies was noted to be similar to those of two-arm studies. The categories of cancer which had the highest number of two-arm clinical trials with unequal allotment were: gastrointestinal, breast, genitourinary malignancies. For three-arm trials, gastrointestinal cancer had four studies with unequal allocation and head and neck cancer had two studies with unequal allotment.

Dumville *et al.* reviewed studies that utilized unequal allotments and provided the following advantageous reasons for this choice: (i) reduction in overall financial costs or increased statistical power with greater recruitment to the less expensive arm; (ii) improved acceptability and recruitment rates for the trial with higher potential for allocation in the treatment group; (iii) increased exposure to the experimental treatment; (iv) a way to offset a higher dropout in one of the groups; (v) increased power for secondary analyses; and (vi) ethical patient beneficence to provide more experience of a treatment, resulting in increased safety and toxicity data [10]. In each case of unequal allotment, the randomized allocation favored more patients in the experimental arm. This phenomenon suggests that the financial cost of novel treatments may not be the motivating factor for unequal allotment. By favoring more patients in the experimental arm, these unequal allotment studies were able to provide more patients exposure to the experimental treatment as opposed to placebo or standard of care. These two-arm trials with unequal allotment may be for patients with cancer refractory to otherwise standard of care treatment who may not have

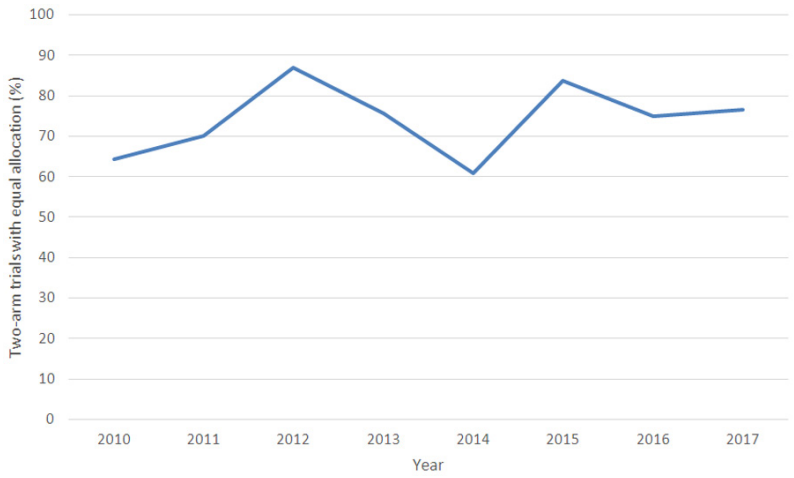

Figure 2. Percentage of phase 3 cancer clinical trials with equal allocation (1:1) in comparison to the total number of two-arm trials from 2010 to 2017. While no particular pattern emerges on use of equal or unequal allocation trial design, overall about 1 in 4 trials may be using unequal allocation in the past decade.

another chance at survival. These trials may also be more focused on capturing safety data, as efficacy may already be well-understood. More research needs to be done to determine possible reasons for these trials to pursue unequal allocations.

Trends of utilization

Given the trends shown in **Figure 2**, it is evident that unequal allocation has become a commonly utilized study design in cancer research for about one in every four two-arm trials. About every three in four trials utilize a standard 1:1 allocation protocol. Trials that started in the years 2010 and 2014 had a significantly higher number of trials with unequal allocations as opposed to equal allocations, while the years 2012 and 2015 had a significantly lower number of trials with unequal allocations.

Of the original 323 two-arm trials, data from more recent years, particularly 2018 and 2019, was more difficult to obtain, which could have led to a limited understanding of the unequal allotment trend in those years. In the future, it may be beneficial to compare trends for studies earlier than 2010 to discern long-term changes and to increase power of the statistical model.

Limitations

While this study looked at the trends in the utilization of unequal allocation in cancer clinical trials, we did not further explore the underlying reasons for why each method was used for those respective studies. Many manuscripts detailing results of these studies did not elaborate on the reasoning behind utilizing unequal allocation of patients. Moreover, these results account for only those studies for which we were able to find allocation data through clinicaltrials.gov and linked articles. This proved more difficult for clinical trials from recent years such as 2018 and 2019. We also limited the search to only include cancer trials from 2010 and 2019, thus preventing further study of trends in study design over the past decades.

Conclusions

As unequal allocations are receiving more attention in clinical trial design, the use of this scheme in cancer clinical trials has not been investigated. This study investigates the trends and proportions of cancer trials that utilize unequal allocation over the time period of 2010-2019. Our results indicate that one in four two- or three-arm trials in cancer research involve unequal allotment in the past ten years. Each trial with unequal allocation favors more patients in the experimental arm than the control arm. The fields of gastrointestinal, breast, and genitourinary cancers have embraced trials with unequal allocations the most. While the study does not delve into the specific reasons behind this growing trend, this may represent a new trend in clinical trial design to help increase exposure to a novel treatment or enhance closer monitoring of adverse events despite higher costs attached to this method.

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Disclosure of conflict of interest

None.

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Table S1. Number of two-arm phase 3 cancer clinical trials with equal allocation as opposed to unequal allocation of trials by year

Year	*Equal Allocation of Total*	*Equal Allocation of Total (%)*
2010	27 of 42	64%
2011	28 of 40	70%
2012	33 of 38	87%
2013	31 of 41	76%
2014	28 of 46	61%
2015	36 of 43	84%
2016	21 of 28	75%
2017	26 of 34	76%
2018	5 of 8	63%
2019	3 of 3	100%

Data collected for a total of 323 trials from clinicaltrials.gov from 2010 to 2019. Use of unequal allocations was common in 2010 and 2014 and uncommon in 2012 and 2015. Overall, only about 3 in 4 trials used a standard study design with equal allocation.