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Publication Date

2024-04-01

DOI

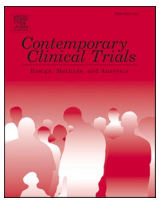
10.1016/j.cct.2024.107484

Contemporary Clinical Trials 139 (2024) 107484

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Justification for unequal allocation ratios in clinical trials: A scoping review

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ARTICLE INFO

Keywords:
Unequal randomization
Unequal allocation
Controlled clinical trials
Study design
CONSORT guidelines
SPIRIT guidelines

ABSTRACT

Objective: The objective of this review is to provide an overview of the justification reported for using unequal allocation ratios in randomized clinical trials (RCTs) testing a medical intervention.
Methods: Using the PICOS framework, we conducted a systematic search to find meta-studies within PubMed (a Medline database interface) that addressed the objective.
Results: The developed search strategy generated 525 results, of which, three studies met criteria for inclusion. These studies found that 22–43% of RCTs provided a justification for the use of unequal allocation based on publication alone, and between 38.7 and 66% after seeking input from trial authors. The most common reason given for this design was to gather increased safety data according to two reviews and to gain experience with an intervention according to the third review.
Conclusion: Reporting of justification for RCTs designed with unequal allocation appears to occur less than half the time in the included studies. The reasons given for designing clinical trials with unequal participants encompass many domains, including ethical considerations. As such, this design feature should be implemented with intentionality to maximize the ethical features of clinical trials for participants. Coupling lack of justification with lack of adjusting for sample size estimations depicts an overall landscape in which there is significant room for improvement in methodological transparency within this area of RCTs.

1. Introduction

Allocation of participants in randomized clinical trials (RCTs) is a crucial step in assuring the internal validity of a trial's results. Many design considerations must be considered, including the ratio with which patients are assigned to treatment groups. The Consolidated Standards of Reporting Trials (CONSORT) is an evidence-based and international consensus-based approach that applies methods from the Enhancing the Quality and Transparency of Health Research (EQUATOR) methodological framework to set recommendations for the reporting of clinical trial data [1]. After generating the first set of recommendations in 1996, multiple revisions have been made since.

The consensus guideline CONSORT 2010 statement was updated to include the recommendation that RCTs should "clarify the basic trial design (such as parallel group, crossover, cluster) and the allocation ratio", which remained in the 2022 update [2]. Per these guidelines, clinical trials should report the allocation ratio used; however, these guidelines do not explicitly require trials should provide rationale for this decision. These guidelines recommend rationale be given for other aspects of clinical trial design including selecting the domain of the primary outcome (e.g. pain) and timing of outcomes assessments. The decision to use unequal allocation ratios affects the number of patients enrolled, so it is important to make informed recommendations for sample size to avoid using excessive or inadequate numbers of subjects, which could result in excessive risk to subjects or not be adequately powered to address the relevant research question [3]. Similar RCT reporting guidelines such as Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) also do not explicitly recommend trials provide rationale for implementing unequal randomization [4].

Currently, no literature summarizes the landscape of studies that empirically assess the reasons given by RCT authors for using unequal allocation of participants. The purpose of this overview is to examine the justification reported for using unequal allocation ratios in clinical trials and will focus on empirically gathered justification data rather than theoretical benefits of this study design. Understanding the reasons this method is implemented will allow further study of the magnitude and direction of the effect this study design has on important issues including trial accrual, economic resources, ethical trial conduct, and any other

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https://doi.org/10.1016/j.cct.2024.107484
Received 22 November 2023; Received in revised form 13 February 2024; Accepted 28 February 2024
Available online 29 February 2024

reasons one might select this design feature.

2. Methods

Using the PICOS framework, we sought to identify all articles that analyzed reasons or justification for unequal randomization in RCTs on a medical topic. Search criteria were developed, and PubMed was searched on July 20th, 2023 for potential studies for inclusion based on title and abstract (with no restrictions on publication date). If it was unclear whether or not a study met inclusion criteria, the full article was obtained for further adjudication. Study selection was carried out in duplicate (JN and AH) and data were extracted by the author JN. The predefined data to be extracted was the proportion of unequally randomized RCTs providing rationale for this design and the types of rationale given. In the case that the included studies reported additional data in common or data that would be helpful for characterizing unequal allocation among RCTs, these data will also be reported. The PICOS outline and search terms are as follows:

Population: RCTs.

Intervention: Unequal allocation of subjects.

Control: Equal allocation of subjects.

Outcome: Justification given for this design (proportion of studies and rationale given).

Study design: Review.

((((((((((((((((((((Unequal Randomization) OR (Unequal Allocation)) OR (Unequal Groups)) OR (Unequal Subjects)) OR (Unequal Participants)) OR (Uneven Randomization)) OR (Uneven Allocation)) OR (Uneven Groups)) OR (Uneven Subjects)) OR (Uneven Participants)) OR (Skewed Randomization)) OR (Skewed Allocation)) OR (Skewed Groups)) OR (Skewed Subjects)) OR (Skewed Participants)) OR (Unbalanced Randomization)) OR (Unbalanced Allocation)) OR (Unbalanced Groups)) OR (Unbalanced Subjects)) OR (Unbalanced Participants))) AND (clinical trials, controlled as topic[MeSH Terms]). No additional filters were used, including article type (i.e. publication dates, publication type, etc.), to prevent potential loss of relevant studies at this step.

Included studies needed to have a review, meta-analysis, or meta-study design, have RCTs as the unit of observation, and test a medical intervention. Their primary objective involved characterizing unequal allocation/randomization ratios and assessing the justification of this design characteristic among clinical trials broadly. Included studies could stratify results by field of medicine but could not be focused solely within a particular field (i.e. cardiology, psychiatry, etc.).

Studies were excluded if they did not analyze the reasons for using unequal allocation design, as reported by RCT publications or authors. Studies were also excluded if the purpose of the study was to demonstrate the efficiency of a particular randomization method or sample size formula under different circumstances (i.e. modeling or simulation studies), if the study evaluated differences in trial arm participants in which the participants have equal likelihood of assignment to any of the trial arms, or if they solely evaluated differences in cluster sizes (i.e. the unit of allocation is the cluster of individuals) [5].

2.1. Statistical analysis

These analyses were descriptive, and results were presented as frequencies and percentages. All analyses were conducted with Google Sheets. Because data were from publicly available sources and the analysis did not use personal data, IRB approval was not required.

3. Results

Of the 525 relevant reports identified through PubMed, three review articles were selected for inclusion in this overview (Fig. 1): *Dumville* et al., *Dibao-Dina* et al., and *Peckham* et al. [6–8] Peckham (2015) is an update of the review carried out by Dumville (2006); the lead author of the latter is a co-author of both reviews. Both reviews were included in this overview as they employed different methods to address the primary objective and focused on different years of published RCTs.

3.1. Review methodologies

Key methodology characteristics of each included review are listed in Table 1 for comparison.

3.2. Design

Regarding review design, Dumville (2006) used a combination of predefined search terms in multiple databases, personal knowledge of RCTs, and bibliography searching to generate their dataset. The authors report that approximately 80% of included trials were identified "from personal knowledge and bibliographies rather than from databases" because "unequal randomisation was rarely described in paper abstracts". Peckham (2015) used a predefined search strategy in multiple databases in addition to bibliography searching, and Dibao-Dina (2014) conducted a systematic search of one database to generate their datasets. Additionally, Dibao-Dina (2014) contacted the authors of all included RCTs to collect additional justification information, Dumville (2006) contacted RCT authors if justification was unclear, and Peckham (2015) contacted RCT authors if the justification or sample size calculations were unclear.

3.3. Key exclusion criteria

The reviews differed in several important ways regarding the trials they included. Peckham (2015) and Diboa-Dina (2014) restricted RCTs to only 2-arm studies, whereas Dumville (2006) did not. Peckham (2015) allowed cluster trials, of which at least one cluster RCT was identified for inclusion, whereas the other reviews excluded cluster trial designs.

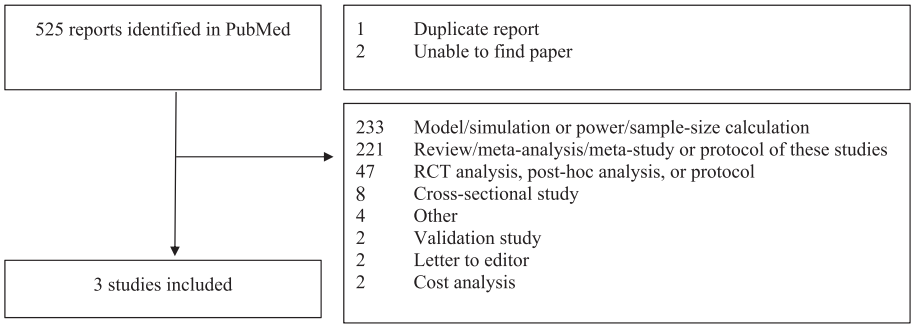

Fig. 1. PRISMA flow diagram [9].

Table 1
Review methodologies.

	Dumville et al. (2006)	Dibao-Dina et al. (2014)	Peckham et al. (2015)
Objective	"To examine reasons given for the use of unequal randomisation in randomised controlled trials"	"To assess the reporting of the unequal randomization ratio in reports of trials with this design and to identify the justification for the design"	"To update a 2005 review of the reasons researchers have given for the use of unequal randomisation in randomised controlled trials"
Sources of Data	Medline Pubmed Cochrane Library Science Citation Index "Papers from this literature search were also supplemented by the authors' detailed personal knowledge of trials that had unequal group sizes and from the bibliographies of papers discussing unequal randomization"	Medline core clinical journals via PubMed[a]	Ovid Medline CINAHL Cochrane Library Embase "We also conducted bibliographic searches and examined the reference lists from papers discussing unequal randomisation to obtain details of other potentially relevant studies."
Additional Data Gathered	"If the reason for unequal randomisation was not given in the paper, where possible, authors were e-mailed to gain further information about why they used unequal randomisation."	"Corresponding authors of all selected reports were contacted (via… email…) to collect additional information on their justification for unequal randomization"	"Authors… were contacted once by e-mail if it was unclear whether the unequal randomisation had been taken into account in the sample size calculation or if the reason for the unequal randomisation was unclear"
Search Strategy	"unequal or unbalanced, randomis(z)ation, allocation or ratio"	"core clinical journals" and "randomized controlled trials"	1. Randomi(?)ation OR allocation OR ratio AND unequal OR uneven 2. 1:2 randomi* ratio OR allocation 3. 1:3 randomi* ratio OR allocation
Key Exclusion Criteria	Trials using cluster design	Trials using cluster design Trials with >2 arms	Trials with >2 arms Trials with randomization ratios of 1:4 or above

[a] Core clinical journals are a PubMed journal subset of 121 English language clinical journals whose selection is based on scientific policy and quality.

3.4. Allocation justification

The percentages of trials providing justification for unequal allocation design based on the publication alone were 22.6% and 43% in Dibao-Dina (2014) and Dumville (2006), respectively. Peckham (2015) did not specify the number of trials providing justification prior to receiving author clarification. After receiving author clarification, these percentages increased to 66% [6], 38.7% [7], and 45.3% [8]. Table 2 includes this information and the RCT publication years analyzed.

The most common rationale for designing RCTs with unequal allocation is displayed in Table 3 and Fig. 2. Among two reviews, the most common justification was to gather increased safety data, whereas Peckham (2015) found this to be the second most common reason behind gaining experience (i.e. overcoming unfamiliarity with an intervention or a "learning curve"). Some RCTs provided multiple reasons for using unequal allocation; Peckham (2015) reported 41 justifications for 39 trials, Dibao-Dina (2014) reported 63 justifications for 41 trials, and Dumville (2006) reported one justification per trial, resulting in 43 justifications for 43 trials.

Table 2
Percentages of RCTs providing justification for unequal allocation design.

	Dumville (2006)	Dibao-Dina (2014)	Peckham (2015)
Included Clinical Trials			
Publication Years Considered	Database inception - June 2005[a]	2009 – 2010	2005 - June 2014
Total Trials Included	65	106	86
Pharmacological Trials	61.5%	62.3%	64.0%
Nonpharmacological Trials	38.5%	34.0%	36.0%
Justification for unequal allocation reported in publication	43%	22.6%	Not given
Justification for unequal allocation reported following author clarification	66%	38.7%	45.3%
Sample size calculation adjusted for unequal allocation	21.5%	42.5%	44.2%

[a] Mean publication year 1998 according to Peckham (2015).

3.5. Sample size calculation

Each of the included reviews looked for the prevalence of accounting for unequal allocation in the RCT sample size calculation. Of all included trials, the percentage that adjusted for unequal allocation was 21.5% [6], 42.5% [7], and 44.2%)[8] (Table 2). The reviews report percentages of studies that were unclear or did not adjust for unequal allocation in more granular detail, however, it is difficult to make direct comparisons between reviews in these categories because the Dumville (2006) and Dibao-Dina (2014) reviews used a different denominator than [8]. The former reviews used the number of RCTs that outlined a sample size calculation as the denominator, whereas the latter review used the total number of unequally allocated RCTs as the denominator, so there is not enough detail in the Peckham (2015) review to adjust this denominator, and for the other two reviews it would be unclear whether the RCTs excluded from the denominator (i.e. RCTs that did not outline a sample size calculation) did not account for unequal allocation.

The methods were slightly different between reviews for assessing whether RCT sample size calculations were adjusted for unequal allocation, not adjusted for, or were unclear. Dumville (2006) recorded that unequal randomization had been taken into account in the sample size calculation "if the authors explicitly stated they had accounted for unequal randomisation or we were able to repeat and confirm the sample size calculation for the proposed ratio". Dibao-Dina (2014) reported they "recorded whether the unequal randomization was taken into account in sample size calculation(s)", which gives less detail on the exact methods that were used. Peckham (2015) reported "Where authors had explicitly mentioned the unequal randomisation in the sample size calculation we recorded that unequal randomisation had been taken into account. If there was no mention of the unequal randomisation in the sample size calculation and we were not able to follow the calculation from the details supplied we recorded the calculation as being unclear".

4. Discussion

4.1. Methodologic differences

We found three studies assessing the justification of using unequal randomization in RCTs testing a medical intervention. The percent of

Table 3
Justification given for unequal allocation design in RCTs.

	Safety Data	Increase Recruitment	Cost	Ethics	Statistical Reason[a]	Gain Experience[b]	Dropout Concern[c]	Other[d]
Review								
Dumville	30.2%	14.0%	14.0%	7.0%	7.0%	2.3%	11.6%	14.0%
Dibao-Dina	31.7%	17.5%	15.9%	11.1%	7.9%	–	–	15.9%
Peckham	22.0%	12.2%	0%	7.3%	22.0%	24.4%	–	12.2%

Percentage calculation: number of times a justification was given divided by the total number of justifications (i.e. when justification for unequal allocation is provided, this method gives the percentage a particular reason is provided). These values include justifications acquired through author correspondence.
– indicates this review did not comment on this rationale.

[a] The terms supplied by Dumville (2006) "statistical need" and "increase power for secondary analysis" were combined into one "statistical reason" category. Peckham (2015) incorporated the following reasons into a statistical reason category: 1. "Statistical" 2. "Needed to be able to detect events related to safety that occurred at least 3% of the time" 3."To enable future secondary analysis of targeted treatment mechanisms" 4."Large reduction in high grade lesions was expected in the HPV revealed arm so ratio chosen to give a high power to detect this difference" 5."To allow comparison between intermittent NRT and and constant NRT" 6."Need to randomise within the intervention group" 7."To allow between acupuncturist effects to be compared" and 8. "Statistical" (no further elaboration). Dibao-Dina (2014) did not detail specific reasons included within the statistical justification category.

[b] "Gain Experience" refers to overcoming a learning curve for an intervention, such as a new surgical technique. Dumville (2006) reported a category "gaining experience of treatment" and explains that this encompassed one trial (2.3%) overcoming a learning curve and 13 trials (30.2%) gathering increased safety data; these are separated in this table.

[c] "Dropout Concern" refers to "anticipated differences in drop-out or treatment cross-over rates between groups", allowing preservation of statistical power for a per protocol analysis.

[d] Other" category Dumville (2006): intervention more available compared to control (4.7%), late start of one arm (2.3%), limited variability of control group (2.3%), more participants required in treatment group for next phase of study (2.3%), ensure maximum use of available counseling intervention (2.3%). "Other" category Dibao-Dina (2014) not detailed in review. "Other category" Peckham (2015): logistical reasons (7.3%) and "other" (4.9%).

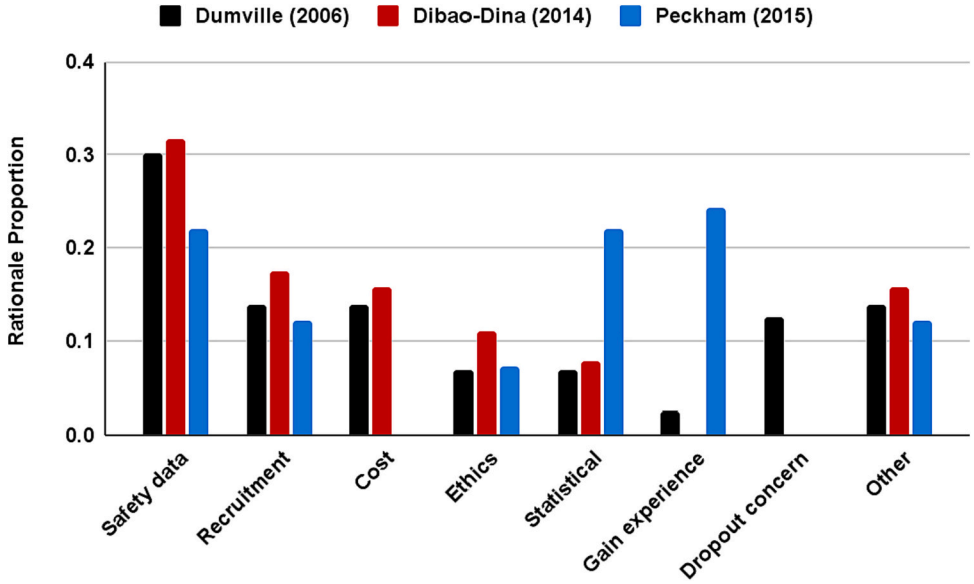

Fig. 2. Graphical representation of justification given for unequal allocation.

studies reporting justification in their publications ranged between 23% and 43%. The most common reason for using an unequal randomization design was for safety. There was notable heterogeneity in the methodologies of the included reviews. Each study employed some systematic elements including a predefined search strategy and multiple, independent reviewers for data extraction. Dumville (2006) justified their search strategy based on "unequal randomisation was rarely described in paper abstracts". Nevertheless, given that approximately 80% of trials included in Dumville (2006) were identified "from personal knowledge and bibliographies rather than from databases", this greatly increased the risk of selection bias.

Dibao-Dina (2014) also employed a fundamentally different search strategy than the other reviews by looking at all published trials during a specified period of time, whereas the other two reviews specifically searched for RCTs utilizing unequal allocation. This allowed the authors to consider RCTs at-large, and they estimate the proportion of two parallel-group RCTs using unequal allocation ratios to be 4.7% (106 of 2246 trials). All reviews selected reports based on the title and abstract, however, only Dibao-Dina (2014) reported searching full-text reports "when it was unclear from the abstract whether randomization was unequal". Peckham (2015) acknowledged "it may be that there are more studies that have used unequal randomisation that did not describe this in their abstract and were therefore not identified in [our] searches".

A final methodological consideration is that none of the included studies commented on whether the allocation ratios were instituted at the outset of the trials or were the result of a protocol amendment, which may be done for different reasons.

4.2. *Published and post-hoc rationale*

The authors of each review attempted to get justification clarification from the RCT authors if the rationale for using unequal allocation was unclear, except for Dibao-Dina (2014), who reached out to all authors. The percentage of studies providing rationale for unequal allocation

increased with author correspondence from 43% to 66% (23% increase) in the Dumville (2006) review and from 22.6% to 38.7% (16.1% increase) in the Dibao-Dina (2014) review. 15 out of 37 authors replied to correspondence in the Dumville (2006) review, resulting in 15 new responses, 30 out of 106 RCT authors responded to the Dibao-Dina (2014) review, resulting in 17 new responses, and Peckham (2015) did not report this information. The response rate among RCT authors that did not provide clear rationale in the initial publication was 40.5% (15 new responses of 37 new inquiries) in the Dumville (2005) review and 20.7% (17 new responses of 82 new inquiries); this difference between reviews calls into question the potential for response bias. It is unclear how the authors of Dumville (2006) had acquired "personal knowledge" of many of the RCTs included in their dataset, however, a prior relationship with study authors may have resulted in greater author response compared to the other review. Reaching out to RCT authors allowed reviewers to gather more comprehensive data on the different rationale given for using unequal allocation in clinical trials while also introducing flexibility and uncertainty into estimating the true prevalence of each unique justification. The difference between the prevalence of rationale given in the original publication and following author correspondence suggests lack of reporting by study authors.

4.3. Favoring the treatment arm

The majority of RCTs allocated more patients to the treatment arm at 86.2% [6], 96.2% [7], and 95.3% [8]. Of the seven trials in [6] that favored the control group, five of these cited cost rationale, one had unclear reasoning but the authors thought this was likely due to cost as well, and one study cited statistical need. Similarly, Dibao-Dina (2014) reported that of the four trials favoring the control group, two cited cost rationale and one cited patient acceptability (i.e. to increase recruitment). Peckham reported four trials favoring the control group, with one study citing increased safety data and recruitment, another study recruited too many participants so they defaulted to the control group, and two did not provide rationale.

4.4. Trial positivity rate

The positivity rate of unequally randomized trials was not assessed in any of the included studies and, therefore, was unable to be compared to the positivity rate of equally randomized trials during the same time period. However, in a separate study, the authors of [7] employed the same search criteria as the currently considered review to identify unequally randomized RCTs, which were then compared to a maximum of four equally randomized trials addressing the same clinical question. The authors found that unequally randomized trials are more likely to be positive in favor of the new treatment (Odds Ratio, 2.38; 95% confidence interval: 1.23, 4.63) [10].

4.5. Assessing justification

Given the variety of reasons RCT authors provided to justify unequal allocation of participants, there exists some flexibility in each study in terms of categorizing these reasons, especially for testing unique interventions or when the stated reason is somewhat unclear. Consider the "logistical" rationale. Peckham (2015) classified the rationale given for three trials as logistical in nature due to needing a certain number of participants in one arm of the study for it to be viable, in the case of a support group, or the trial arm needed to recruit quickly to use blood within a short time frame to avoid expiration when comparing blood storage times prior to transfusion. Neither of the two other studies categorized any RCT rationale as logistical in nature, though the case could be made that "intervention more available compared to control" or "ensure maximum use of available counseling intervention", as extracted in Dumville (2006), could be considered logistical in nature depending on data extraction criteria. All studies utilized multiple authors for independent data extraction, however, no interrater reliability measure was reported, such as the kappa statistic. Categorization is likely less of an issue when the RCT publication or authors cite the more common rationale such as safety data or cost, but it is important to be mindful of the flexibility in these studies as authors lump different rationale into each category, including the "other" category.

4.6. Adverse events

The most common rationale for using unequal allocation was to gather increased safety data, among Dumville (2006) and Dibao-Dina (2014); this was the second most common reason given in Peckham (2015). This rationale is based on the idea that by having more participants in the experimental group, more adverse events will occur, allowing for improved detection of adverse events compared to an equal allocation design with fewer people in the treatment group. Dibao-Dina (2014), expecting this to be a prominent reason based on the previous review, recorded whether authors who justified unequal randomization for safety data reported adverse events in their report, and if so, whether they reported severity data and withdrawals. This review found that 20% (4 out of 20) of trials citing obtaining safety data as rationale for unequal allocation did not report any data on adverse events and 35% (7 out of 20) of trials did not describe one or more of the adverse events per group, severity data, or withdrawals due to adverse events; ultimately, they report 55% (11 of 20) of trials using this rationale did not fully report adverse events, according to their criteria.

4.7. Increase recruitment

The prevalence of using unequal allocation to increase patient recruitment was fairly similar between reviews (12.2–17.5%). Dumville (2005) and Dibao-Dina (2014) also refer to this category of rationale as "patient acceptability". This rationale is based on the idea that patients prefer to participate in trials when they have a higher chance of receiving an intervention. It should be noted that the most recent review of strategies to increase recruitment to randomized trials found "patient preference design increased total participation but made little or no difference to recruitment to the randomised trial" [11]. Peckham (2015) raised the concern that this strategy "might increase the risk of differential attrition among those allocated to the control group" post-randomization, given the increased expectation of being assigned to the intervention group. Dibao-Dina also raised a concern that "the placebo response could… be exaggerated (as compared with trials with balanced randomization), thus introducing a bias in the treatment effect estimate".

4.8. Cost

Utilizing unequal allocation due to cost consideration comprised 14.0% and 15.9% of rationale for Dumville (2006) and Dibao-Dina (2014), respectively. The authors of Peckham (2015) remarked in the discussion that "in contrast to Dumville's previous review we found no studies which cited cost effectiveness as a reason for using unequal randomisation. The disparity may be because one of the authors (DT) of the reviews is a health economist by background and the previous review included trials personally known to him". The Dumville (2006) review analyzed trials from database inception to June 2005, whereas the Peckham (2015) review included trials from 2005 to June 2014, so there is not much data overlap; however, Dibao-Dina (2014) included trials published in 2009 and 2010, which the Peckham (2015) review also covers. This discrepancy may be due to differences in search strategy, as Dibao-Dina (2014) utilized very broad search terminology to look at all RCTs published in a two year period and generated 4923 initial reports and 106 final reports, whereas the Peckham (2015) review searched for trials using unequal allocation and entered three specific allocation ratios, resulting in 4701 initial reports and 86 final reports

generated for almost a ten year period.

4.9. Ethics

Justifying unequal allocation design in RCTs based on ethical reasons occurred between 7.0 and 11.1% of RCTs. This is based on the principle that this design may minimize participant exposure to the inferior treatment arm. However, presupposing that one arm is likely better than the other invalidates the concept of equipoise as articulated by Freedman, involving "genuine uncertainty within the expert medical community – not necessarily on the part of the individual investigator – about the preferred treatment" [12]. Therefore, as discussed by Peckham (2015) "citing minimising exposure to an inactive placebo or no treatment may not be adequate reasoning for carrying out unequal randomisation".

4.10. Statistical justification

Statistical justification for using unequal allocation design in RCTs is a heterogeneous category. Dumville (2006) identified RCTs citing "statistical need to reduce the exposure of difficult to treat patients to the experimental treatment", as well as "increased power for a secondary analysis", and chose not to categorize these reasons into one category; however, we chose to combine these rationale into one statistical reason category because of shared similarities with Peckham (2015), which noted that RCTs cited statistical reasons "primarily to allow enough power for secondary analyses to be carried out". Dibao-Dina (2014) created a category of "for statistical justification" without any elaboration as to what this included.

It could be argued that using unequal allocation based on concern for differential dropout of the intervention arm to preserve statistical power for a per-protocol analysis should also be considered statistical justification. Ultimately, we did not choose to include "dropout concern" rationale in the statistical justification category. This is another example of how the reasons cited by RCT authors are subject to interpretation when categorized for analysis.

4.11. Overcoming learning curves

The most common rationale in Peckham (2015) was gaining experience with a treatment, which refers to overcoming a learning curve. Only one trial was identified in the Dumville (2006) review cited this rationale and no trials in Dibao-Dina (2014). Peckham (2015) commented that "any additional analysis to the standard intention to treat (ITT) analysis is likely to be complex and needs to be carefully considered to avoid introducing bias. For instance, excluding the intervention patients that were part of the learning curve in an analysis is likely to introduce a temporal bias as the control patients recruited at the same time would remain in the trial."

4.12. Sample size calculations

Each study assessed the prevalence of adjusting for unequal allocation in the sample size calculation. This was included in this overview to further characterize unequally randomized trials. While only Peckham (2015) incorporated a significant number of RCTs after the publication of the CONSORT 2010 statement, which recommends RCTs report allocation ratios, looking at the sample size calculation provides further insight into the intentionality of using unequal allocation, or lack thereof. Sample size calculations take place prior to enrolling patients in a clinical trial and are nearly ubiquitous, whereas the reporting of allocation ratios is more variable among trials, especially shortly after the publication of new guidelines. If the allocation ratio was not reported and the sample size calculation was not correctly adjusted in a RCT using unequal allocation, this calls into question the overall reliability of this trial's design.

5. Limitations

There is significant heterogeneity in the methodologies of the few included reviews, from a systematic review to a hybrid review whose database was built mostly from personal knowledge and bibliographies. Additionally, it is possible the prevalence of justification or the rationale for unequal allocation has changed since the update of the CONSORT 2010 statement to include that RCTs should report allocation ratios, so inferences drawn from this review concerning more recent clinical trials using unequal allocation may not apply to some domains, such as the estimation of prevalence for RCTs adjusting the sample size calculation. Alternatively, the reasons given by RCT authors for using this design may share similarities to those found in this review.

6. Conclusion

The allocation of subjects and the reason for this decision are important aspects of clinical trial design. Reporting of justification for this design consideration appears to occur in less than half of RCTs in the included studies. The reasons given for designing clinical trials with unequal participants encompassed many domains, including ethical considerations. As such, this design feature should be implemented with intentionality to maximize the ethical features of clinical trials for participants. While CONSORT and SPIRIT guidelines do not explicitly require this explanation be provided, they do so for similarly relevant questions of design, and as such, we believe the guidance should be extended. Coupling lack of justification with lack of adjusting for sample size estimations depicts an overall landscape in which there is significant room for improvement in methodological transparency within this area of RCTs. Further study of the empirical evidence for each unique justification for this design is a logical next step.

Author contributions

JN and VP contributed to the conception. JN and AH assessed studies for inclusion and exclusion. JN conducted data extraction and statistical analyses. JN and AH wrote the first draft of the manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Funding

This project was funded by Arnold Ventures, LLC through a grant paid to the University of California, San Francisco. The funders had no role in the design and conduct of the study.

CRediT authorship contribution statement

Joshua Nay: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Alyson Haslam:** Investigation, Supervision, Writing – review & editing. **Vinay Prasad:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. All other authors have no financial or non-financial conflicts of interest to report.

Data availability

Data will be made available on request.

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