



Review

The use of unequal randomisation ratios in clinical trials: A review

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Abstract

Objective: To examine reasons given for the use of unequal randomisation in randomised controlled trials (RCTs).

Main Measures: Setting of the trial; intervention being tested; randomisation ratio; sample size calculation; reason given for randomisation.

Methods: Review of trials using unequal randomisation.

Databases and sources: Cochrane library, Medline, Pub Med and Science Citation Index.

Results: A total of 65 trials were identified; 56 were two-armed trials and nine trials had more than two arms. Of the two-arm trials, 50 trials recruited patients in favour of the experimental group. Various reasons for the use of unequal randomisation were given. Six studies stated that they used unequal randomisation to reduce the cost of the trial, with one screening trial limited by the availability of the intervention. Other reasons for using unequal allocation were: avoiding loss of power from drop-out or cross-over, ethics and the gaining of additional information on the treatment. Thirty seven trials papers (57%) did not state why they had used unequal randomisation and only 14 trials (22%) appeared to have taken the unequal randomisation into account in their sample size calculation.

Conclusion: Although unequal randomisation offers a number of advantages to trials the method is rarely used and is especially under-utilised to reduce trial costs. Unequal randomisation should be considered more in trial design especially where there are large differences between treatment costs.

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Keywords: Unequal randomisation; Randomised controlled trials

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1. Background

In randomised controlled trials (RCTs) the allocation of participants to experimental and control groups is usually balanced leading to approximately equal group sizes. However, whilst balanced group sizes will maximise a study's statistical power, the use of unequal randomisation ratios will only significantly reduce the power of a study if the ratio is 3:1 or more [1]. There are a number of situations, discussed below, where unequal group sizes in a trial may be beneficial. Indeed, it has been argued that the use of unequal randomisation could and should be substantially increased [1].

1.1. Cost

In most RCTs there is probably an unequal distribution of either research or treatment costs between the trial arms. When this is the case, economic efficiency can potentially be improved using unequal randomisation. For a fixed trial budget, using unequal randomisation to favour the least expensive trial arm allows more participants to be recruited thus increasing the power of the trial [2]. Where there is a fixed total sample size available for recruitment, unequal randomisation can confer large financial savings to a trial with limited impact on statistical power [2]. Furthermore, when there is a fixed quantity of treatments available for one trial arm, but more than twice the number of trial participants are available, trial efficiency can be improved using unequal allocation. Allocating more participants to the treatment with no restrictions on availability will increase the statistical power of the trial by utilising all the available participants.

1.2. Learning curves

There are situations where unequal randomisation that favours the experimental group is useful. In evaluations of a new technology that has a 'learning' element, for example a new surgical procedure, more participants might be allocated to the intervention group to reduce the impact of the 'learning curve' on the results of the trial [2]. Allocating more participants to the experimental treatment allows the clinician to climb the learning curve more rapidly and allows for an analysis that compares both treatments when at the top of this curve.

1.3. Ethics

Some have advocated unequal allocation in order to expose fewer participants to the hazards of a treatment in a trial [3]. This view pre-supposes that there is a high degree of certainty regarding the risks and benefits accruing to the treatment under evaluation. Yet, as many RCTs are conducted when there is equipoise, this view cannot generally be used as justification for unequal allocation in trials. However, there may be cases, for example in clinical drug trials, where the beneficial nature of a treatment, known to have unpleasant side-effects, is still being investigated. Here unequal allocation could, potentially, be justified on ethical grounds.

1.4. Other

Unequal allocation can be useful in studies that compare a group with an individual treatment (e.g., group versus individual cognitive behavioural therapy) where it helps to obtain enough participants for the group therapy. Using unequal allocation to increase the number of groups will increase the study's power for a fixed total sample size.

Additionally, a larger number of participants may be allocated to one group when a higher drop-out rate is anticipated, as this will enhance statistical power for a 'per protocol' analysis.

Whilst the literature cites a number of reasons why unequal allocation may be beneficial in RCTs, to date there has been no review undertaken that assesses why this method has been used in practice. We undertook a review of trials that employed unequal randomisation to investigate why it had been used and to discuss these applications further.

2. Methods

2.1. Search strategy

The Cochrane Library, Medline, Pub Med and the Science Citation Index were searched for all paper abstracts that contained words and phrases related to unequal randomisation. These were: "unequal or unbalanced, randomis(z)ation, allocation or ratio".

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 randomisation. Trials that used a cluster design were excluded from this review.

2.2. Data extraction

Double data extraction was carried out by JD and SH. Data was extracted on: the setting of the trial (primary care, secondary care or university); the intervention being tested; the randomisation ratio; the sample size calculation used and the reason given for unequal randomisation. A sample size calculation was recorded as being outlined when some details of the calculation were provided. We recorded that unequal randomisation 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. Conversely, unequal randomisation was recorded as having not been taken into account if the authors' suggested sample size calculation was for equal group sizes; if we could not follow the sample size calculation from the details supplied we recorded the calculation as being unclear.

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.

3. Results

We identified 65 trials that used unequal randomisation [7–71]. One further paper was identified but was excluded from the study as, although it used unequal randomisation (2:1:2:2:1:1), of the six arms, only three arms were compared in the study and these were balanced. Most included trials (~80%) were identified from personal knowledge and bibliographies rather than from databases. Details of the 65 included trials, in terms of settings, interventions, allocation ratios, sample size calculation, and reasons for use of unequal allocation, are shown in Appendix 1. Table 1 summarises the trial characteristics. Many trials papers ($n=37$; 57%) did not state why they used unequal randomisation in their design; after e-mailing authors 15 replies clarifying the reason for use of unequal randomisation were received.

Of the trials, 56 (86%) were two armed and nine trials had more than two arms. Unequal randomisation favouring the experimental group was used most frequently with the allocation favouring the control group(s) used only seven times (Table 1).

3.1. Reasons for unequal randomisations

The reasons for unequal randomisation given in each study are detailed in the Appendix. Of the seven studies where allocation favoured the control group, four trials used unequal allocation to reduce financial costs as the

Table 1
Summary of investigation

		Number of studies (%)		
Study setting	Primary	9 (14)		
	Secondary	52 (80)		
	Other	4 (6)		
Interventions used	Medication/vaccine	40 (62)		
	Surgery/screening	5 (8)		
	Radio therapy	3 (5)		
	Administration procedure	4 (6)		
	Educational/behavioural	4 (6)		
	Other	9 (14)		
Sample size calculation	Unequal randomisation taken into account	14 (22)		
Reason for unequal randomisation use	Reason provided in paper	28 (43)		
	Reason provided by e-mail	15 (23)		
Reason given	Cost	6 (9)		
	Expected drop-outs	5 (8)		
	Patient acceptability	6 (9)		
	Ethics	3 (5)		
	Other	9 (14)		
	Gaining experience of treatment	14 (22)		
	Not stated	22 (34)		
<hr/>				
Trials	Number of trials (%)	Number favouring the experimental group	Number favouring the control group	Trials with analogous treatments
<hr/>				
Two-armed trials	56 (86)	50	5	1
Trials with >2 arms (various ratios)	9 (14)	6	2	1
Randomisation ratio (two armed)				
2:1	38 (68)	34	3 ^a	1
3:2	9 (16)	8	1	–
3:1	6 (11)	5	1	–
4:1	3 (5)	3	–	–

^a In 2 of these trials unequal randomisation was performed in only some of the centres.

experimental treatment or intervention was more expensive than the control [22,37,38,57]. One further trial was a large screening programme, where the authors state there were a limited number of screenings available: thus they wanted to maximise the power of the study for this finite number of examinations [11]. A second screening trial did not give a clear reason for the use of unequal randomisation that favoured the control group but it is likely to be for similar reasons as the first [21]. The remaining trial that allocated in favour of the control group did so for reasons related to statistical considerations, however, this reasoning did not make the use of unequal randomisation clear [31]. Finally, one of the two trials that compared analogous treatments also used unequal randomisation to reduce cost by minimising the number of participants in the most expensive treatment group [61].

The remaining studies mostly had more participants in their treatment group(s) than their control group. Five trials used unequal allocation as they were concerned about drop-out or transfer from the treatment group [23,36,43,46,58]. Six trials used unequal randomisation to increase patient acceptability of the trial and therefore recruitment rates [19,29,33,41,49,67] and three trials stated ethical reasons for maximising participants exposure to the treatment [16,27,28]. Individual trials also gave other specific reasons for using unequal randomisation to maximise allocation to the experimental group. These were: the late starting of one arm of the trial [8]; limited variability of the control group [20]; more participants required in the treatment group for the next phase of the study [32]; to give increased power for a secondary analysis [47,64]; increased availability of the intervention service compared to the control service [48,68]; and to ensure maximum use of the available counselling intervention [71].

Only one trial clearly attributed the used of an unbalanced allocation to overcome a learning curve and to gain more experience of a treatment [26]. However, gaining more experience of a treatment, including increased safety and toxicity data, were given as reasons for the use of unequal randomisation in thirteen further trials [9,13,17,18,24,34,40,42,45,51,55,56,66].

3.2. Sample size calculations

Of the 65 trials, 40 (62%) were recorded as having outlined a sample size calculation. Fourteen of these 40 studies appeared to have taken the unequal randomisation into account. The remaining 26 studies that outlined a sample size calculation either did not take unequal randomisation into account ($n=5$) or did not supply enough detail to establish whether unequal randomisation had been accounted for ($n=21$).

4. Discussion

We found few RCTs that employed unequal randomisation. Because unequal randomisation was rarely described in paper abstracts, most papers for this review were identified from extensive combined personal knowledge of clinical trials. This non-systematic approach could be viewed as a possible limitation of this study. Of those trials identified as having unbalanced groups, many gave no apparent reason for using this method. The use of unequal randomisation is an important methodological feature of a trial and studies should give a reason for its use. Trials that did discuss their use of unequal randomisation describe doing so for a variety of reasons.

4.1. Cost

Although the use of unequal allocation can lead to considerable cost savings, economic efficiency was one of the least frequently cited for using unequal allocation. Those studies that did use unequal randomisation to confer savings appeared to do so successfully. For example, in a screening trial where screening cost £70 per person, 195,000 participants were randomised with unbalanced allocation leading to savings of more than £2 million with very little loss in power [11]. Similarly, unequal allocation in a trial of hip protectors [4] reduced the overall cost of the trial by 10% (Torgerson, unpublished observation).

4.2. Maximise available participants

Three studies, in which the availability of one treatment was not restricted [11,48,68], used unequal allocation to *improve* statistical power. For example, had Turnbull et al. [68] used equal allocation rather than unequal allocation they would have recruited over 100 less patients into their intervention group and thus into their trial.

Unequal randomisation can improve power in three armed trials when a dose comparison between two drug arms is being carried out as the differences between drug dosages would be expected to be more muted compared with the placebo comparison. In this review no trial gave this as a reason for using unequal randomisation although one three-armed trial used this design [35].

4.3. Differential loss to follow-up and cross over

Unequal allocation was used because of anticipated differences in drop-out or treatment cross-over rates between groups in five studies [23,36,43,46,58]. The advantage of unequal randomisation in this situation is that it will preserve statistical power for an 'on treatment' or 'per protocol' analysis. However, it is important to note that when large drop-out or cross-over rates are anticipated, unequal randomisation will not reduce the risk of bias through drop-out nor will it prevent 'dilution' effects of participants crossing over into the other treatment arm. Intention to treat analysis, that is analysing all participants in their originally allocated groups, must still be carried out as this gives a conservative but unbiased estimate of treatment effects. The five studies identified here did undertake an intention to treat analysis.

4.4. Treatment experience

Thirteen studies exposed increased numbers of participants to the experimental treatment or procedures to gain more experience in using the treatment. This included the collection of safety and toxicity data including adverse

events. Additionally, further studies that did not state a reason for the use of unequal randomisation were phase I–III-type trials that tested drugs, radiological or surgical treatments and often reported safety and adverse event data. We postulate that these studies used unequal randomisation to increase the amount of information on the new treatment. This application of unequal randomisation has been only briefly discussed in the literature and has been acknowledged as being potentially controversial [6]. Only one study used unequal allocation specifically because of learning curve effects [26]. However, this study did not appear to examine whether there was any interaction between treatment effects and patient recruitment. If learning curve effects are a reason for unequal allocation, it would be logical to look for any effect of learning and, if observed, present an analysis of participants recruited ‘on the top’ of the learning curve.

4.5. *Unequal allocation in practice*

Practically, carrying out unequal allocation adds little complexity when compared to using balanced allocation. The process of randomisation must simply ensure that, in the case of a 2:1 ratio, double the number of people randomly enter one group compared to the other.

It is important when using unequal allocation to ensure that a correct sample size calculation is performed, and ideally a statistician should be consulted. In a majority of the studies we examined it did not appear that unequal randomisation had been taken into account for the sample size calculation. This is particularly serious where studies have used randomisation ratios of 3:1 or more where the power of the study will have been significantly reduced.

Input from a statistician is also useful in the analysis of data from trials using unequal randomisation. The statistical tests commonly used to analyse data from trials, such as the *t*-test, ANOVA, ANCOVA and regression analysis, make an assumption about the homogeneity of the variance of the residuals across the levels of the independent variables. If the variances are not equal, but groups are equal this does not seriously affect the type 1 error rate. However, where the groups are not equally allocated this does not always hold. Thus the decision to use unequal randomisation must take into account the potential for unequal variance.

4.6. *Reasons for limited use of unequal allocation*

There may be several reasons why trials rarely employ unbalanced allocation. Some might, incorrectly, consider unequal groups sizes as somehow being ‘unscientific’. Indeed, when advocating unequal randomisation, one of the authors (DT) has had such feedback on two different occasions from grant-giving bodies. Also, the need to maximise the power of the study might be the over-riding concern among some trial statisticians and for a given total sample size, balanced allocation, usually, gives the most statistical power. However, for a fixed sample size, unequal randomisation of 2:1 can be used without a serious loss of power [5]. One reason why unequal allocation is not used in factorial trials may be the view that this makes the analysis more complicated. When computations of trials were done ‘by hand’ completely balanced factorial designs were easier to calculate; however, with the use of modern computers this justification no longer holds.

Resistance to unequal randomisation may stem from concern that its use may require the recruitment of an increased number of participants, since recruitment is often a limiting factor in trials. Indeed, where there are a small number patients that can be recruited unequal randomisation may not be advantageous. However, as previously noted, where there is a fixed budget, savings introduced by use of unequal randomisation may allow more sites to be recruited to the trial — thus allowing increased recruitment, which can increase the power of a study [2]. Furthermore, for a fixed sample size potential cost savings from using unequal allocation should be balanced against the loss of power that unequal randomisation will cause.

5. Conclusion

Unequal randomisation is not commonly undertaken. Although by no means suitable for every trial, there are a number of situations where unequal randomisation can be useful, especially by conferring financial savings on trials — yet unequal randomisation is rarely used for this reason and could be implemented more often.

Appendix A

Description of trials

Study	Setting ^a	Description of study	Ratio (treatment: control)	Sample size calculation outlined?	Unequal randomisation taken into account?	Reason
Atkin et al. [11]	PC	Evaluation of flexible sigmoidoscopy in colorectal cancer screening	1:2	Yes	Unclear	Cost (limited treatment availability)
Dowrick et al. [22] ^b	PC	Problem solving treatment and group psychoeducation for depression	~2:1:1	Yes	Yes	Cost
Infant Health and Development Program [37]	SC	Enhancing the outcomes of premature babies	1:2	Yes	Unclear	Cost
ICON group [38]	SC	Treatments for ovarian cancer	1:2	Yes	Yes	Cost
Roberts et al. [57]	U	Effect of direct payment on questionnaire response rates	1:3	No	–	Cost
Sarosdy et al. [61]	SC	Comparison of goserelin and leuprolide in combined androgen blockade therapy	2:1	No	–	Cost
Epstein et al. [23]	SC	D-penicillamine in improving survival in cirrhosis	3:2	No	–	Drop-out expected in treatment group
Hundley et al. [36]	SC	Midwife managed delivery unit	2:1	Yes	Yes	Drop out (due to transfer) expected in treatment group
Knapp et al. [43]	SC	High dose tacrine in patients with Alzheimer's disease	3:1:3:4	Yes	Unclear	Drop-outs expected at high doses
Macvicar et al. [46]	SC	Simulated home delivery in hospital	2:1	Yes	Unclear	Drop out (due to transfer) expected in treatment group
Rodgers et al. [58]	SC	Stroke education program for patients and caregivers	1:1 then 2:1	Yes	No	Drop out/ poor compliance in treatment group
Cunningham et al. [19] ^b	SC	Irinotecan plus supportive care for colorectal cancer patients	2:1	Yes	Unclear	Patient acceptability
Goodwin et al. [29]	SC	Group psychosocial support in breast cancer patients	2:1	Yes	Yes	Patient acceptability
Hoberman et al. [33] ^b	SC	Prevention of otitis media with inactivated influenza vaccine	2:1	Yes	Yes	Patient acceptability
Jonas et al. [41] ^b	SC	Lamivudine in children with chronic hepatitis	2:1	Yes	Yes	Patient acceptability
Nichol et al. [49] ^b	PC	Effectiveness of influenza vaccine in healthy, working adults	2:1	Yes	Unclear	Patient acceptability
Turkington et al. [67]	PC	Cognitive-behavioural therapy in the treatment of schizophrenia	2:1	Yes	Unclear	Patient acceptability
Casley-Smith et al. [16]	PC	Treatment of filarial lymphoedema and elephantiasis with coumarin	3:2	No	–	Ethics
Geraud et al. [27]	SC	Comparison of zolmitriptan and sumatriptan in migraine patients	8:8:1	Yes	Unclear	Ethics
Goodfield et al. [28]	SC	Treatment of dermatophyte onychomycosis with terbinafine	3:1	Yes	Unclear	Ethics

(continued on next page)

Appendix A (continued)

Study	Setting ^a	Description of study	Ratio (treatment: control)	Sample size calculation outlined?	Unequal randomisation taken into account?	Reason
Adinolfi et al. [8]	SC	Effects of alpha interferon induction in Hepatitis C	2:2:1	No	–	Other — third arm started after first two arms
Deeks et al. [20] ^b	SC	Discontinuing drug therapy in HIV-infected patients with detectable viremia	2:1	No	–	Other — reduced variability in the control arm
Hadziyannis et al. [31]	SC	Peginterferon- α 2a and ribavirin combination therapy in chronic hepatitis C	1:1:1.5:2	Yes	Yes	Other — statistical need to reduce the exposure of difficult to treat patients to the experimental treatment — not clear
Hadziyannis et al. [32]	SC	Adefovir dipivoxil for the treatment of chronic hepatitis B	2:1	Yes	Unclear	Other — required patients in treatment group for phase II of study
Moss et al. [47] ^b	SC	Prophylactic implantation of a defibrillator	3:2	Yes	Unclear	Other — increased power for a secondary analysis
Straus et al. [64] ^b	SC	Clinical effectiveness of co-trimoxazole for pneumonia in children	2:1	Yes	Yes	Other — increased power for a secondary analysis
Mundinger et al. [48]	PC	Outcomes of patients treated by nurse practitioner	2:1 then 1:1	Yes	No	Other — increased availability of intervention at the start of the trial
Turnbull et al. [68]	SC	Effects of antenatal day care for medical complications of pregnancy	2:1	Yes	Unclear	Other — increased availability of intervention
Zhu et al. [71] ^b	PC	Evidence of real world effectiveness of a telephone quitline for smokers	3:2	No	–	Other — to ensure maximum use of the available intervention
Garry et al. [26]	SC	Laparoscopic versus abdominal hysterectomy	2:1	Yes	No	Gain experience (Learning curve)
Agnelli et al. [9]	SC	Dermatan sulphate for the prevention of deep vein thrombosis in hip fracture	2:1	Yes	Yes	Gain experience of treatment
Barrlett et al. [13] ^b	U	Pirenzepine ophthalmic gel in myopic children	4:1	Yes	Unclear	Gain experience of treatment
Cocconi et al. [17]	SC	Chemotherapy in advanced gastric cancer	3:2	Yes	Unclear	Gain experience of treatment
Critchley et al. [18]	SC	Antihypertensive efficacy of combination therapy with losartan and hydrochlorothiazide	2:1	Yes	Yes	Gain experience of treatment
Errington et al. [24]	SC	High energy neutron treatment for pelvic cancers	3:1 then 1:1	Yes	Unclear	Gain experience of treatment
Home et al. [34] ^b	SC	Insulin vs. human insulin in type 1 diabetes	2:1	No	–	Gain experience of treatment
Johnson et al. [40] ^b	SC	Hepatitis B vaccination in HIV-infected children	2:1	No	–	Gain experience of treatment
Jones et al. [42] ^b	SC	Effects of bicarbonate/lactate-based dialysis solution	2:1	No	–	Gain experience of treatment
MacDermid et al. [45]	SC	Endoscopic versus open carpal tunnel release: a randomised trial	3:1	No	–	Gain experience of treatment
Ondo et al. [51] ^b	SC	Olanzapine for dopaminergic-induced-hallucinations	2:1	No	–	Gain experience of treatment
Pinto et al. [55]	SC	Uterine artery embolization vs. abdominal hysterectomy	2:1	Yes	Unclear	Gain experience of treatment

Rizzoli et al. [56]	SC	One-weekly alendronate for the treatment of osteoporosis	3:2:2	No	–	Gain experience of treatment
Sundar et al. [66] ^b	SC	Oral miltefosine for Indian visceral leishmaniasis	3:1	Yes	Yes	Gain experience of treatment
Abraham et al. [7]	SC	Liposomal prostaglandin E1 in acute respiratory distress syndrome	2:1	No	–	Not stated
ALLHART Collaborative Research Group [10]	SC	Treatment of hypertensive patients with Doxazosin or chlorthalidone	3:2	Yes	No	Not stated
Bae et al. [12]	SC	Cerebrolysin for Alzheimer's disease	2:1	Yes	Unclear	Not stated
Bianchi Porro et al. [14]	SC	Pantoprazole in the prevention of peptic ulcers	2:1	Yes	Unclear	Not stated
Canal and Imbimbo [15]	SC	Pharmacodynamic activity and cognitive effects of eptastigmine in patients with Alzheimer's disease	4:1	Yes	Unclear	Not stated
de Koning et al. [21]	PC	Large-scale prostate cancer screening trials	2:3	No	–	Not stated (likely to be cost)
Fischl et al. [25]	SC	Zidovudine and Zalcitabine in HIV patients	3:2:2	No	–	Not stated
Griffin et al. [30]	SC	Neutron radiation therapy for head and neck carcinomas	2:1	No	–	Not stated
Hosking et al. [35]	SC	Effects of Alendronate and risedronate on bone mineral density	2:2:1	Yes	No	Not stated
James et al. [39]	U	Effect of sibutramine in weight maintenance	3:1	No	–	Not stated
Krakoff [44]	SC	Nicardipine therapy in ambulatory elderly patients with hypertension	2:1	No	–	Not stated
O' Connor et al. [50]	PC	Sustained-release formulation of ibuprofen in the treatment of arthritis	4:1	No	–	Not stated
Ott et al. [52]	SC	Cyclooxygenase 2 inhibitors in patients undergoing bypass surgery	2:1	Yes	Yes	Not stated
Patat et al. [53]	SC	Trandolapril a new angiotensin converting enzyme	2:1	No	–	Not stated
Piatti et al. [54]	U	Hypocaloric high protein diet spares lean body mass	3:2	No	–	Not stated (small numbers in trials so may have been chance imbalance)
Rudolf et al. [59]	SC	Hydroxyethyl starch for hypervolemic hemodilution	2:1	Yes	Unclear	Not stated
Saag et al. [60]	SC	Amphotericin B with fluconazole in the treatment of meningitis	2:1	Yes	Yes	Not stated
Saunders et al. [62]	SC	Radiotherapy in the treatment of lung cancer	3:2	Yes	Unclear	Not stated
Soto et al. [63]	SC	Topical treatment for leishmaniasis	2:1:1:1	No	–	Not stated
Suckfüll et al. [65]	SC	Fibrinogen and LDL apheresis for the treatment of sudden hearing loss	2:1	Yes	Yes	Not stated
UK Prospective Diabetes Study Group [69]	SC	Cost effectiveness of transplantation types for lymphoma	2:1	No	–	Not stated
van Agthovan et al. [70]	SC	Cost-effectiveness analysis of improved blood pressure control in hypertensive patients	2:1	No	–	Not stated

^a Primary care (PC), Secondary care (SC), University (U).

^b Reason for unequal randomisation not stated in paper but given on e-mail.

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