

Unequal group sizes in randomised trials: guarding against guessing

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We cringe at the pervasive notion that a randomised trial needs to yield equal sample sizes in the comparison groups. Unfortunately, that conceptual misunderstanding can lead to bias by investigators who force equality, especially if by non-scientific means. In simple, unrestricted, randomised trials (analogous to repeated coin-tossing), the sizes of groups should indicate random variation. In other words, some discrepancy between the numbers in the comparison groups would be expected. The appeal of equal group sizes in a simple randomised controlled trial is cosmetic, not scientific. Moreover, other randomisation schemes, termed restricted randomisation, force equality by departing from simple randomisation. Forcing equal group sizes, however, potentially harms the unpredictability of treatment assignments, especially when using permuted-block randomisation in non-double-blinded trials. Diminished unpredictability can allow bias to creep into a trial. Overall, investigators underuse simple randomisation and overuse fixed-block randomisation. For non-double-blinded trials larger than 200 participants, investigators should use simple randomisation more often and accept moderate disparities in group sizes. Such unpredictability reflects the essence of randomness. We endorse the generation of mildly unequal group sizes and encourage an appreciation of such inequalities. For non-double-blinded randomised controlled trials with a sample size of less than 200 overall or within any principal stratum or subgroup, urn randomisation enhances unpredictability compared with blocking. A simpler alternative, our mixed randomisation approach, attains unpredictability within the context of the currently understood simple randomisation and permuted-block methods. Simple randomisation contributes the unpredictability whereas permuted-block randomisation contributes the balance, but avoids the perfect balance that can result in selection bias.

A tantalising phone call begins, “I have just read a report of a randomised trial, and I found problems!” All too often, however, the discussion proceeds with: “Look at that difference in sample sizes in the groups—they are not equal. I am suspicious of this trial.” Or in planning a trial, “What can we do to end up with equal sample sizes?” Indeed, large disparities in sample sizes not explained by chance should cause concern,^{1,2} but many researchers look askance at a trial with any disparity. We cringe at this seemingly ubiquitous notion that a randomised trial needs to yield equal sample sizes. Somehow such a notion seems imbedded in many a medical researcher’s psyche.

Such conceptual misunderstanding deters prevention of bias in trials. Exactly equal sample sizes in a randomised controlled trial contribute little to statistical power and potentially harm unpredictability, especially in non-double-blinded trials that use permuted-block randomisation. Unpredictability reflects the essence of randomisation because those involved cannot predict the next treatment assignment. With predictability comes bias.

Greater predictability emanates from randomisation schemes that depart from simple, unrestricted randomisation. Such departures are termed restricted randomisation schemes.^{3,4} They constrain treatment assignment schedules to yield similar or, most frequently, equal group sizes throughout the trial, assuming the most common desired allocation ratio of one-to-one. The restricted randomisation schemes all sacrifice unpredictability, but that increased predictability primarily surfaces in non-double-blinded trials that use permuted-blocks (panel 1).⁵⁻⁷

Trialists rely on the security of unpredictability. In the

past, we suggested cultivation of a tolerance for groups of unequal sample sizes in simple randomised trials.^{8,9} We now suggest cultivation of a tolerance for groups of unequal sizes in restricted randomisation trials as well.

Forcing cosmetic credibility

Studies reported as randomised yield equal sample sizes in the comparison groups more frequently than expected.⁸⁻¹⁰ In simple, unrestricted randomised controlled trials (analogous to repeated coin-tossing), the relative sizes of comparison groups should indicate random variation. In other words, some discrepancy between the numbers in the comparison groups would be expected. However, analyses of reports of trials in general and specialist medical journals showed that researchers too frequently reported equal sample sizes of the comparison groups (defined as exactly equal or as equal as possible in view of an odd number total sample size).^{8,9} In the specialist journals, the disparity of sample sizes in the comparison groups deviated from expected ($p < 0.001$) and produced equal group sizes in 54% of the simple randomised (unrestricted) trials.⁸ This result was higher than that in blocked trials (36%), and blocked trials aspire for equality. Moreover, results of a similar analysis of the dermatology literature showed that an even higher 71% of simple randomised trials reported essentially equal group sizes.¹⁰

Why would investigators seek equal or similar sample sizes in comparison groups? We feel many investigators strive for equal sample sizes as an end in itself. The lure of the so-called cosmetic credibility of equal sizes seems apparent. Sadly, that cosmetic credibility also appeals to readers. Striving for equal sample sizes with simple randomisation, however, reflects a methodological non sequitur.

The high proportion of equal group sizes noted above represent pronounced aberrations from chance occurrences and suggest non-random manipulations of assignments to force equality. Other logical explanations seem plausible, but probably do not account for the degree of aberration

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Panel 1: Unpredictability in allocation sequences

Predictability in clinical trials breeds bias. If trial investigators identify or predict upcoming allocation assignments, they can instill selection bias. In assessment of eligibility, they could exclude a participant destined for, in their opinion, the wrong group. Moreover, various manoeuvres allow them to channel participants with a better prognosis to the experimental group and those with a poorer prognosis to the control group, or vice versa.^{5,6} Irrespective of the reasons for doing so, experimenters bias the comparison. Clinicians might revere predictability in caring for patients, but they must understand that predictability spawns bias in clinical trials.

Trial investigators can guess the next assignments by subverting the allocation concealment mechanism—eg, by holding translucent envelopes to a light bulb.^{5,7} However, proper allocation concealment usually prevents this subversion. Alternatively, with permuted-block randomisation, trial investigators can sometimes predict the next assignments by noting a pattern of past assignments.^{4,5} For example, in a non-double-blinded trial with a block size of four, if a trial investigator notes that the sample size in the two groups equilibrates after every four participants, then many future assignments can be predicted. For example, if the sequence ABA materialises in a block of four, B would necessarily be the next assignment, or if the sequence BB materialises, AA would be the next two assignments.

In non-double-blinded trials, all intervention allocations become known after assignment, even with proper allocation concealment. Thus, if a pattern to the allocation sequence exists, the trial investigator can discern it and predict some future assignments. However, if no pattern exists, or if the pattern is indiscernible, the allocation sequence is unpredictable. Therefore, knowledge of past assignments would not help in prediction of future assignments. Unpredictability is essential in non-double-blinded randomised trials.

Proper allocation concealment before assignment and proper blinding of all involved in the trial after assignment shields knowledge of past assignments and thereby prevents prediction of future assignments. Proper blinding diminishes the need for unpredictability. Even in supposedly blinded trials, however, blinding after assignment is not always successful. If trial investigators perceive quickly developing, clinically obvious side-effects that reveal the intervention assigned, for instance, blinding might not prevent predictions.

witnessed.^{8,10} Such tinkering with assignments creates difficulties by directly instilling selection bias into trials. We hope to remove some of those difficulties by dispelling the mythology behind the drive for exactly equal sizes.

Beyond the issue of non-random manipulations of assignments, however, we will concentrate on the potential bias introduced by balancing group sizes with valid restricted randomisation methods, primarily permuted-block randomisation, that produce equal group sizes throughout the trial. Unfortunately, methods used to ensure equal sample sizes can facilitate correct future predictions of treatment assignments, allowing bias to infiltrate.

Unequal group sizes in restricted trials

The method of restricted randomisation is used to balance sample sizes. That balance usually enhances statistical power and addresses any time trends that might exist in treatment efficacy and outcome measurement during the course of a trial.^{11,12} Moreover, restricted randomisation within strata becomes essential for investigators to attain the benefits of stratification.¹³ Thus, reasonable scientific justification lends support to restriction.

For restriction to be effective, however, it need not yield exactly equal sample sizes. The power of a trial is not sensitive to slight deviations from equality of the sample sizes.³ Thus, restricted approaches that produce similar sizes would yield power, time trend, and stratification benefits much the same as those restricted randomisation approaches that produce equal sizes.

Equal sample sizes, however, can have negative consequences. The predominant restricted randomisation method is random permuted-blocks (blocking). Such an approach effectively attains the goals of equal sample sizes in the comparison groups overall (and, if stratified, within strata). Moreover, the method generates equal sample sizes after every block. With that attribute, however, comes the disadvantage of predictability.^{5,11}

Predictability, particularly, becomes a major weakness in a non-double-blinded trial. We define a double-blinded trial as one in which the treatment is hidden from participants, investigators, and outcome assessors. In virtually all non-double-blinded trials, some investigators become aware of the treatment. Thus, even with adequate allocation concealment, treatment assignments become known after assignment. With that information, trial investigators can unravel the fixed block size (presumably the organisers

initially shielded all block size information from them) and then anticipate when equality of the sample sizes will arise (panel 1). A sequence can be discerned from the pattern of past assignments and then some future assignments could be accurately anticipated. Hence selection bias could seep in, irrespective of the effectiveness of allocation concealment.^{4,5} The same difficulty to a lesser degree might be true in a double-blinded trial in which obvious, perceptible side-effects materialise quickly.

Randomised controlled trials become prone to unravelling of block sizes when the block size remains fixed throughout the trial, especially if the block size is small—eg, six or fewer participants. Hence, if investigators use blocked randomisation, they should randomly vary the block size to lower the chances of an assignment schedule being inferred by those responsible for recruitment and assignment.^{4,5}

Random block sizes, however, are no panacea. Even with random variation of block sizes, blocking still generates equal sample sizes many times throughout a trial. Indeed, based on a modification of a model that measures inherent predictability of intervention assignments with certainty, random block sizes, at best, decrease but do not eliminate the potential for selection bias.¹¹ In other words, random block sizes help to reduce, but in some instances might not eliminate, selection bias. Permuted-block randomisation, even with random block sizes, presents trial recruiters with opportunities to anticipate some assignments.

Alternatives in non-double-blinded trials

For non-double-blinded randomised controlled trials with an overall sample size of more than 200 (an average sample size of 100 in two groups) and within each planned subgroup or stratum, we recommend simple randomisation.¹⁴ It provides perfect unpredictability thereby eliminating that aspect of selection bias due to the generation of the allocation sequence. Moreover, simple randomisation also provides the least probability for chance bias of all the generation procedures,³ and it enables valid use of virtually all standard statistical software. With sample sizes greater than 200, simple randomisation normally yields only mild disparities in sample sizes between groups. The cut-off of 200, however, is merely an overall guideline. Individual investigators might want to judge their particular acceptable levels of disparity.¹⁵ Another caveat centres on potential interim analyses done on sample sizes of less than 200—ie, before investigators reach total sample size. Greater

relative disparities in treatment group sizes could materialise in those instances, although we feel those costs are more than offset by the gains in unpredictability from simple randomisation.

For non-double-blinded randomised controlled trials with a sample size of less than 200 overall or within any principal stratum or subgroup of a stratified trial, we recommend a restricted randomisation procedure. The urn design⁴ functions especially well to promote balance without forcing it.¹⁶ It tends to balance more in the important early stages of a trial and then approach simple randomisation as the trial size increases. This attribute becomes useful with uncertain overall trial sizes, or more likely, uncertain stratum sizes in a stratified trial. It also proves useful in trials that might be ended due to sequential monitoring of treatment effects. Urn designs usually have adequate balancing properties while still being less susceptible to selection bias than permuted-block designs.^{4,14}

With these desirable properties come caveats. Some statisticians recommend use of permutation tests³ with urn randomisation designs. Permutation tests are assumption-free statistical tests of the equality of treatments.^{3,16} Unfortunately, they usually are not available for urn designs in standard statistical software.¹⁶ That adds analytical complexity for researchers and statisticians. However, if no major time trends on the outcome variables exist, use of standard statistical analyses from widely available software on trials that use urn randomisation would normally yield similar results to permutation tests.¹⁶ Moreover, with standard statistical analyses, investigators can easily obtain confidence intervals for common measures of effect.

Surprisingly, urn randomisation or other forms of biased-coin designs appear infrequently in reports.⁴ Perhaps another impediment to widespread usage pertains to the conceptual complexities of urn randomisation; it is more difficult to understand than simple or permuted-block randomisation. Whatever the reasons, urn designs languish in obscurity.

Mixed randomisation

Researchers should have an unpredictable approach to use in non-double-blinded trials until they feel comfortable with

urn randomisation or other approaches that enhance unpredictability.¹⁷ We have attempted to identify an approach that builds on the existing knowledge in clinical epidemiology. We propose a restricted randomisation method that should approach the unpredictability of urn randomisation overall while exceeding its unpredictability for small sample sizes, but without its real and perceived complexities. Our proposed approach promotes balance, but not the perfect balance that we feel can lead to predictability and selection bias.

Our solution mixes simple randomisation with permuted-block randomisation. Simple randomisation contributes the unpredictability to the approach whereas permuted-block randomisation contributes the balance. Our mixed approach begins with an uneven block generated by a replacement randomisation procedure (panels 2 and 3).¹⁸⁻²¹ Then, in its simplest form, standard permuted blocks of varying size follow. The replacement randomisation sequence would establish inequality initially and make any anticipation of assignments improbable throughout the remainder of the trial.

Replacement randomisation is basically simple randomisation, with a slight twist.⁴ Since investigators should aim for an uneven block, they would select a prespecified inequality in the sample sizes of the allocated groups. Then they would prepare an allocation sequence by simple randomisation, and check the disparity in sample sizes against their prespecified inequality. If the disparity in sample sizes meets or exceeds their prespecified disparity, then that simple randomisation allocation sequence suffices for the first uneven block. If not, then a whole new simple randomisation list is generated to replace the previous one. They would iterate until a simple randomisation sequence meets or exceeds their prespecified disparity (panel 2). The block size of the first uneven block could be odd or even overall and could be of most any total size, although we conceive of it usually falling in the range of five to 16.

Our basic approach creates an initial imbalance in a trial. Replacement randomisation represents just one approach to creating it. Another choice might be to select from random imbalanced permuted blocks or several variations on that

Panel 2: Mixed randomisation steps

Step 1: Generate one uneven block by replacement randomisation for the first participants

- A Identify block size for the first uneven block. The block size can be odd or even and of any reasonable size, but usually in the range of five to 16.
- B Select a prespecified inequality in the sample sizes of the allocated groups for the first uneven block.
- C Generate a simple randomisation sequence (eg, with a table of random numbers or a computer random number generator).
- D Inspect resultant sequence of assignments for matching or exceeding the desired prespecified inequality from Step B above.
- E If sufficiently unequal distribution of As and Bs, proceed to step 2; if not, go back to Step C above (iterate).

Step 2: Generate random permuted blocks for subsequent participants

- A Select block sizes for the permuted blocks. Longer block sizes, such as ten to 20, are more unpredictable than shorter block sizes, such as two to four. Longer block sizes should be preferred, unless an investigator needs approximate balance in a small trial or a small stratum of a trial. For example, an investigator might select block sizes of eight, ten, 12, and 14 as options.
- B Generate random permuted blocks, randomly varying the block size, as described in many texts.¹⁸⁻²¹
- C Decide if an additional uneven block or simple randomisation block is to be interspersed in the trial. If not, complete the required sample size with random permuted blocks. Otherwise, identify a point at which to interject an uneven block or a simple randomised sequence.
- D If interjecting another uneven block by replacement randomisation, proceed back to step 1. If interjecting a simple random sequence, proceed to step 3.

Step 3: Generate a simple random sequence for interjection after a set of permuted blocks

- A Identify the size of this simple random sequence. The size can be odd or even and of any reasonable size, but usually in the range of five to 16. We suggest an odd number to ensure some imbalance.
- B Generate a simple random sequence of the chosen size as suggested earlier.^{4,21}
- C Proceed to step 2, B.

Panel 3: Example of mixed randomisation

The randomisation scheme required an overall sample size of 100, based on power calculations. The investigator decided on a first uneven block size of ten and prespecified an inequality of at least four participants between treatment A and treatment B in that first uneven block. The investigator then proceeded to use replacement randomisation by successively selecting a simple random sequence⁴ of ten until that process yielded a sequence of ten assignments with either treatment A or treatment B having at least four extra participants. That sequence was B, A, B, B, B, A, B, B, A, B; actually, three treatment As and seven treatment Bs.²¹ Then the investigator decided to randomly vary the permuted-block sizes between six, eight, ten, and 12, as described in many sources.¹⁸⁻²¹ That could simply be continued over the remainder of the study, but this investigator decided to interject a simple randomised sequence of five assignments after a whole permuted-block passed the 40th participant. The block sizes randomly selected were, in order, 12, eight, and ten. The simple randomised sequence beginning with the 41st participant was B, A, B, A, A. After that simple randomised sequence, the investigator again proceeded with random permuted blocks of six, eight, ten, or 12, with the first randomly selected block size of eight. We depicted the allocation sequence and the total cumulative assignments by treatment for the first 53 assignments:

	Assignment number	Assignment	Cumulative			Assignment number	Assignment	Cumulative	
			A	B				A	B
Replacement randomisation block of 10	1	B	0	1	Random permuted block of 10	31	B	13	18
	2	A	1	1		32	A	14	18
	3	B	1	2		33	B	14	19
	4	B	1	3		34	B	14	20
	5	B	1	4		35	A	15	20
	6	A	2	4		36	B	15	21
	7	B	2	5		37	B	15	22
	8	B	2	6		38	A	16	22
	9	A	3	6		39	A	17	22
	10	B	3	7		40	A	18	22
Random permuted block of 12	11	A	4	7	Simple random sequence of 5	41	B	18	23
	12	A	5	7		42	A	19	23
	13	B	5	8		43	B	19	24
	14	A	6	8		44	A	20	24
	15	A	7	8		45	A	21	24
	16	A	8	8	Random permuted block of 8	46	A	22	24
	17	A	9	8		47	A	23	24
	18	B	9	9		48	B	23	25
	19	B	9	10		49	A	24	25
	20	B	9	11		50	A	25	25
	21	B	9	12		51	B	25	26
	22	B	9	13		52	B	25	27
	23	A	10	13		53	B	25	28
	24	B	10	14		54	-	-	-
	25	A	11	14		55	-	-	-
Random permuted block of 8	26	A	12	14		56	-	-	-
	27	B	12	15		57	-	-	-
	28	B	12	16		58	-	-	-
	29	A	13	16		59	-	-	-
	30	B	13	17		60	-	-	-

Assignment numbers, sequence assignments, and cumulative assignments for the mixed randomisation example, with the successive blocks of assignments alternately bolded.

theme (Douglas G Altman, personal communication). Another excellent easy approach, if investigators can accept variation in the disparity, would involve setting the overall first block size at an odd number, which ensures at least some disparity, and just using simple randomisation (without replacement randomisation).

Identification of an acceptable prespecified inequality for the first block is quite insensitive. Power remains robust up to about a two-to-one ratio for the total sample sizes in the treatment groups.³ Investigators need only create much smaller inequalities than that, particularly in small strata in a stratified trial. Ensuring unpredictability will probably happen as much from small inequalities as large inequalities. Moreover, inequalities can actually slightly increase power in addition to offering enhanced unpredictability. For example, in tests for proportions or life-tables, the maximum power is attained with unequal treatment group sizes.³

After the first uneven block, investigators should proceed as in normal permuted-block randomisation (panels 2 and 3). We suggest that they randomly vary the block size and use as long a block size as practicable for greater unpredictability.⁴ For added unpredictability, investigators could also intersperse additional uneven blocks generated with replacement randomisation throughout the trial. For example, another uneven block could be interjected after a permuted-block surpasses the next 50 participants (using the whole block, which means that the next uneven block would likely begin beyond 50). Alternatively, for these interspersed blocks, investigators could just use simple randomisation. That would be slightly easier, likely provide additional unpredictability, and also provide a richer set of potential allocation sequences. Other potential options for these interspersed uneven blocks exist—eg, imbalanced permuted blocks—but they extend beyond the range of this essay.

For analysis, we suggest use of standard statistical analyses with readily available statistical software—ie, the simpler approach. Slightly greater credibility for hypothesis testing might be gained with design-based permutation tests,¹¹ but we favour the estimates with confidence intervals that standard statistical analyses produce.¹⁴ We also agree with the acceptability of ignoring blocking in the analysis.¹⁸ This straightforward approach usually produces slightly conservative results in trials that use blocking, if a time trend on the outcome exists, but otherwise produces similar results to an analysis that incorporates blocking.¹¹

Those issues, however, pale in comparison to the potential effects of selection bias that could arise in the absence of unpredictability. Once selection bias infiltrates a trial, it becomes imbedded and usually prevails undetected, except in limited situations where investigators might use an innovative detection approach.²² Moreover, empirical evidence points toward substantial selection biases.^{5,6,23} However, the discussions of standard statistical analyses versus permutation tests, or unblocked analyses versus blocked analyses from trials with permuted-block randomisation focus on seemingly smaller increments of *p* values or power. Irrespective of the analysis method chosen, the interpretation from a trial in many instances would be the same. More importantly, unlike selection bias, investigators have a straightforward remedy. If a journal editor or statistical reviewer insists on a different approach, investigators can usually retreat to a blocked analysis or a permutation test. In sum, investigators should use their energy to focus on prevention of biases in the design and implementation of their trial, with an unpredictable allocation sequence being an integral part of that effort.

Full disclosure in the protocol?

Provision of explicit details of the randomisation scheme in the protocol might facilitate deciphering of the allocation sequence, thus undermining the process. We recommend that researchers not fully describe their generation scheme in their research protocol and investigators manual. They would have to describe any stratification plans, but those implementing the trial should be kept ignorant of the full details of the method to generate the allocation sequence.

Some funding authorities require more documentation to ensure that researchers know proper randomisation methods. Appropriate rationale and references might suffice. If the funding agency requires more specifics, a researcher should provide a separate generation of the allocation sequence plan to the funders that will not be shared with those enrolling participants. However, in the final trial report, researchers should fully document the randomisation approach.^{13,24}

Conclusion

Investigators underuse simple randomisation and overuse fixed-blocked randomisation. They do so because they inadequately appreciate the importance of unpredictability and overvalue equal treatment group sizes. Simple randomisation is totally unpredictable, implements easily, and enables use of standard statistical analysis software. For non-double-blinded trials larger than 200 participants, investigators should use it more and tolerate, if not celebrate, the disparity in group sizes. Such unpredictability reflects the essence of randomness.

For non-double-blinded randomised controlled trials smaller than about 200 participants overall or within any principal stratum or subgroup, the urn design enhances unpredictability compared with blocking. Our mixed randomisation method, however, attains unpredictability within the context of the currently understood simple and

permuted-block randomisation methods. We urge researchers to use our method, at least in non-double-blinded trials.

Why add complexity to implementation of trials? The answer resides in the overriding importance of protecting the integrity of randomisation. Proper randomisation minimises bias, more than any other methodological aspect of a trial: “When the randomization leaks, the trial’s guarantee of lack of bias runs down the drain.”²⁵ Those involved in trials go to great pains to decipher randomisation schemes.^{5,6,23} Accordingly, researchers who design trials must take equally great pains to thwart those efforts.

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