needed to ensure that promises to provide appropriate education, and not just training, are actually kept.

As Hutchinson notes, funding is always contentious and the goal of payment by results for service and education is elusive. Australia will watch with interest.

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1 Hutchinson L. Challenges of training doctors in the new English NHS. *BMJ* 2006;332:1502-4.

2 Downton SB, Stokes M, Rawstron EJ, Pogson PR, Brown MA. Postgraduate medical education: rethinking and integrating a complex landscape. *Med J Aust* 2005;182:177-80.
3 Australian Safety and Quality Council. *National patient safety education framework*. 2005. www.patientsafety.org.au/pdfsdocs/national_patient_safety_education_framework.pdf (accessed 15 May 2006).
4 Productivity Commission. *Australia's health workforce: research report*, 2005. www.pc.gov.au/study/healthworkforce/finalreport/index.html (accessed 15 May 2006).
5 McNair R, Stone N, Sims J, Curtis C. Australian evidence for interprofessional education contributing to effective teamwork preparation and interest in rural practice. *J Interprof Care* 2005;19:579-94.

Research methods
Is restricted randomisation necessary?

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Restrictions during randomisation make it easier for investigators to guess the next allocation. Statistical correction of any imbalance in confounders at the end of the study is equally accurate for most trials and would be safer

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Randomised controlled trials commonly use some form of restriction when allocating participants—for example, blocking, stratification, or minimisation.^{1 2} The main reason is to achieve a better balance of known confounders. For an individual trial simple randomisation may lead to some chance imbalances on some variables. These imbalances are unimportant if the variables have a weak relation with the outcome. However, if by chance the groups differ at baseline on one or more confounding variables, the trial result may be misleading; this effect could be in either direction.

Stratification and minimisation are used to reduce these chance imbalances. Blocking needs to be used in combination with stratification to ensure that roughly equal numbers of participants are randomised to each of the treatments in the individual strata.¹ Otherwise, it is statistically equivalent to using simple randomisation. However, using restricted randomisation can generate its own problems.

Problems with restricted randomisation

Introducing any form of restricted randomisation increases the risk of subversion (conscious or unconscious) and technical error. Most examples of known subversion relate to situations where allocation

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sequences are public knowledge or the concealment of the allocation is inadequate, such as using sealed envelopes that can be tampered with.^{3 4} However, this type of subversion is not specific to restricted randomisation.

With restricted randomisation subversion remains possible even when adequate precautions have been taken to conceal the randomisation sequence.⁵ In an open trial, if we know the block size and we keep a record of previous allocations then we will always be certain about the last allocation in the block. Furthermore, we will also often be able to guess the penultimate allocation correctly. If trialists make predictions only when they are certain of the next treatment, then for a block size of four they will be able to predict 33% of the treatments and for a block size of six they will be able to predict 25%. However, if the trialist simply guesses that the next treatment will be opposite to the previous treatment, then for a block size of four they will be correct 71% of the time and for a block size of six they will be correct 68% of the time.⁶

Predictability can be reduced by using larger block sizes or more than one block size. However, the best way to reduce predictability is to keep the block size hidden and to blind all people in the trial to the treat-

Table 1 Method of randomisation and sample size in trials published in four journals in 2002

Type of randomisation	Journal					Sample size		
	BMJ	JAMA	Lancet	NEJM	Total (%)	Minimum	Maximum	Median
Restricted:								
Minimisation	3	0	12	2	17 (7)	74	20 536	573
Block size small* and fixed	8	8	20	14	50 (22)	16	9 366	301
Block size large† and fixed	3	4	10	1	18 (8)	21	4 136	570
Block size mixed	1	8	5	1	15 (6)	40	42 418	894
Block size random	1	1	2	1	5 (2)	156	7 152	290
Block size unclear	4	4	13	6	27 (12)	40	16 608	920
Simple	6	4	4	7	21 (9)	60	2 475	190
Unclear	9	16	18	36	79 (34)	12	67 800	382
Total	35	45	84	68	232	12	67 800	376

NEJM=New England Journal of Medicine.

*<10.

†≥10.

References w1-w14 are on bmj.com

ment the participants are allocated. When minimisation is used, researchers have advocated adding a random element to the minimisation algorithm to reduce predictability.⁷ The dangers of using restricted allocation were shown in a recent survey of 25 clinicians and research nurses in which four (16%) admitted to keeping a log of previous allocations to help predict future ones.⁸

Restricted allocation increases the complexity of the randomisation process and errors could be introduced into the randomisation. For example, the comparative obstetric mobile epidural trial used minimisation to allocate participants to treatments to improve balance on age and ethnicity.⁹ Unfortunately, the software had an error, which resulted in large imbalances in both of these variables. The trial had to be started again at considerable cost. One of us (DJT) was an external member of the steering group of another MRC funded trial in which a minimisation algorithm with an error was introduced part way through. Fortunately, this error was identified before many participants had been allocated to the treatments. These two examples suggest that even with well funded and conducted trials human error can potentially lead to disaster.

Simple randomisation: the solution?

Simple randomisation is safer than restricted randomisation as it is completely unpredictable (assuming steps have been taken to prevent foreknowledge of the sequence) and is less prone to technical error. The main reason for restricted randomisation is for stratification on important covariates. However, we do not need to stratify the randomisation because we can do this statistically at the end of the trial.¹⁰ Grizzle noted that for sample sizes above 50, stratification followed by an adjusted analysis does not add much to the statistical efficiency (the statistical power to detect a treatment effect) of the study,¹¹ even if we stratify on strong prognostic factors. Similarly, Rosenberger and Lachin state that for sample sizes of 100 or more there is less than 0.01 probability that an unstratified randomisation will reduce the relative statistical efficiency of 0.9 or less.¹²

Others recommend simple randomisation for sample sizes above 200.¹³ Even if simple randomisation results in quite large imbalances, with large sample sizes an adjusted analysis with simple randomisation will be virtually as efficient as stratified randomisation plus an adjusted analysis. Given the dangers of introducing selection bias when restricted randomisation is used, it seems better to sacrifice a small amount of precision rather than risk introducing bias.

Small trials

Although restricted randomisation may improve precision and reduce chance bias in small trials, it also presents problems. As the number of stratifying variables increases so does the number of randomisation sequences required to implement the procedure. This can lead to more strata than participants in the trial or increase the chance that various cells produced by the stratification will include no participants. Therefore small trials should stratify on only one or two variables. If a larger number of stratifying variables is required it might be better to use minimisation, which does not have this problem.

Current practice

We recently reviewed trials published in 2002 in four general medical journals and examined the adequacy of allocation concealment.¹⁴ We examined the trials in this database to assess what kind of randomisation they reported. Of the 232 trials we identified in that review, only 21 (9%) used simple randomisation (table 1). Interestingly, although three out of the four journals endorsed the CONSORT statement, which asks authors to clarify how randomisation was undertaken, we could not decide how randomisation was done for 79 (34%) of the trials. Furthermore, two trials that claimed to have used stratified randomisation, implying some form of restriction, seemed actually to have used simple randomisation.^{15 16} Thus Durelli and colleagues reported that: "Randomisation was done centrally by the coordinating centre. Randomisation followed computer generated random sequences of

Table 2 Characteristics of 14 open trials with small block sizes

Study	Intervention	Sample size (block size)	Allocation concealment	Stratifying variables
DAVID trial ^{w1}	Implantable defibrillator	506 (2,4)	Central allocation	Site + 2 clinical variables
Demetri et al ^{w2}	Imatinib for gastrointestinal tumours	147 (4)	Central allocation	None
Gerritsen et al ^{w3}	Splitting v surgery for carpal tunnel syndrome	176 (4)	Sealed opaque envelopes opened by a third party	Site
Ghofrani et al ^{w4}	Sildenafil for lung fibrosis	16 (4)	Not clear	None
Green et al ^{w5}	Physiotherapy for stroke patients	170 (4)	Numbered, sealed, opaque envelopes	None
Joly et al ^{w6}	Corticosteroids for bullous pemphigoid	341 (4)	Central allocation	Site and disease severity
John et al ^{w7}	Fruit consumption on blood pressure	729 (4)	Not clear	Smoking status
Kinley et al ^{w8}	Preoperative assessment by nurses or junior doctors	1907 (4)	Sealed opaque envelopes	Site
Macfarlane et al ^{w9}	Patient information leaflet to reduce antibiotic use	212 (4)	Sealed envelopes	Site
Morice et al ^{w10}	Stents for coronary revascularisation	238 (4)	Sealed envelopes	Site
Smidt et al ^{w11}	Corticosteroids or physiotherapy for lateral epicondylitis	185 (3 (3 armed trial))	Sealed opaque envelopes	Site and duration of disease
Sundar et al ^{w12}	Miltefosine for visceral leishmaniasis	400 (4, allocation ratio 3:1)	Not clear	None
Walsh et al ^{w13}	Voriconazole or liposomal amphotericin for neutropenia	849 (2)	Not clear	Site, risk of fungal infection, and use of medication
Yuyama et al ^{w14}	Bone marrow transplantation for limb ischaemia	44 (4)	Central allocation	None

Summary points

Most randomised trials use some form of restriction when allocating participants

Restricted randomisation increases the chance of selection bias and technical error

Simpler randomisation is safer

Differences in baseline characteristics arising during simple randomisation are generally unimportant

For sample sizes over 100 stratification can be done statistically at the end of the trial without loss of power

digits that were different for each centre and for each sex, to achieve centre and sex stratification. Blocking was not used.”¹⁵ While Hulscher and colleagues stated: “Randomisation was stratified according to the hospital and tumour site (esophagus or cardia). No blocking was used within each of the four strata.”¹⁶

As we stated earlier, blocking should be used in combination with stratification to achieve covariate balance between groups. These two examples highlight the confusion among some researchers about exactly how the randomisation sequence was generated. It also shows the importance of giving a full description of the methods used to generate the randomisation sequence, as encouraged by the CONSORT statement.¹⁷

A large number of trials in our review reported using some form of restricted randomisation (table 1). Despite the dangers of using small, fixed block sizes 50 trials reported using these methods, with 46 reporting a block size ≤ 6 and 35 reporting a block size ≤ 4 .

Restricted randomisation is most beneficial for relatively small sample sizes. Therefore, we would expect to see a relation between the type of restricted randomisation used and the sample size, with larger trials using simple randomisation or large block sizes more frequently than small trials. However, table 1 shows no relation between sample size and use of restricted randomisation. Indeed, the average sample size for the most restricted randomisation schedules seemed to be as large, if not larger, than the average sample size of the trials that reported using simple randomisation.

Investigators are more likely to be able to predict upcoming treatment allocations in open trials that use small block sizes. Trials are considered open if the investigators and participants are aware of the allocated treatment. Table 2 shows the characteristics of the 14 trials that fall into this category. Many of the trials reported that opaque envelopes were used to conceal allocation. However, as noted above, this method may not be secure. We examined the baseline tables of the trials and did not find any clear evidence of differences between groups, although subversion would have to have been quite substantial for this to be observable.⁵ Interestingly, one trial reported using a block size of four (and opaque envelopes) and stratified the randomisation by site.¹⁸ This resulted in numerical imbalances of 11 at two of the three sites, which should not have occurred using a block size of 4. Altman noted a similar occurrence in a blocked randomised trial.¹⁹

Only 32% (74) of trials in our review had a sample size smaller than 200, with 11% (25) smaller than 100 and 6% (n=13) smaller than 50. This suggests, in terms of statistical power, that most of the trials identified in our review could have used simple randomisation with covariate adjustment rather than restricted randomisation.

Discussion

Fewer than 10% of our sample of randomised trials published in major medical journals reported using simple randomisation. Although some form of restricted randomisation seems to be accepted practice, simple randomisation may be best. Simple randomisation will lead to more trials looking cosmetically unbalanced at baseline, but these differences are generally of no consequence. It is important for statisticians and non-statisticians to realise that trials that are numerically imbalanced will not be either unscientific or lose much statistical power. Loss of power occurs only when the imbalance is much greater than 2:1.

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- Altman DG, Bland JM. Statistics notes: How to randomise. *BMJ* 1999;319:703-4.
- Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005;330:843.
- Schulz KF. Subverting randomisation in controlled trials. *JAMA* 1995;274:1456-8.
- Kennedy A, Grant A. Subversion of allocation in a randomised controlled trial. *Control Clin Trials* 1997;18:S77-8.
- Berger V. *Selection bias and covariate imbalances in randomized clinical trials*. Chichester: Wiley, 2005.
- Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials* 1988;9:327-44.
- Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. *Stats Med* 1999;18:1903-4.
- Brown S, Thorpe H, Hawkins K, Brown J. Minimization-reducing predictability for multi-centre trials whilst retaining balance within centre. *Stat Med* 2005;24:3715-27.
- Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001;358:19-23.
- Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical-trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585-612.
- Grizzle JE. A note on stratifying versus complete random assignment in clinical-trials. *Control Clin Trials* 1982;3:365-8.
- Rosenberger W, Lachin J. *Randomization in clinical trials: theory and practice*. New York: Wiley, 2002.
- Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet* 2002;359:515-9.
- Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. *BMJ* 2005;330:1057-8.
- Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* 2002;359:1453-60.
- Hulscher JBF, van Sandick JW, de Boer AGEM, Wijnhoven BPL, Tijssen JCP, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662-9.
- Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
- Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, et al. Effectiveness of appropriately trained nurses in preoperative assessment: randomised controlled equivalence/non-inferiority trial. *BMJ* 2002;325:1323.
- Altman DG. Randomisation in the SYMPHONY trial. *Lancet* 2000;356:1521.

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