reduce imbalance between treatment groups, which can arise with simple randomisation, especially if the sample is small.[1]

In a recent study with a target number of 30 patients we wished to balance two treatment groups for age, sex, and baseline systolic blood pressure. Had we used stratified randomisation to balance for these factors, taking account of just two ranges of age and two levels of systolic blood pressure would have required eight strata, which is unrealistic in a study of this size. Instead we used minimisation.[2,3] When treatment was to be allocated, a research nurse telephoned the essential details to the clinical research associate, who used a system of index cards, randomisation tables, and some simple arithmetic[4] to balance the groups for sex, five ranges of age, and four levels of systolic blood pressure, and determined, within a few minutes, which treatment number that patient should receive. Both parties remained blind to the treatment. On analysis the groups were found to be well balanced for age (mean 63·6 *v* 64·3 years), sex (four men and 12 women *v* three men and 12 women), and baseline systolic blood pressure (mean 184·8 *v* 182·5 mm Hg).

Knowing the dates when treatment was allocated, we were able to determine retrospectively how the patients would have been distributed between the groups had we used simple randomisation. Although the groups would have been reasonably balanced for age (mean 62·4 *v* 65·5 years) and sex (three men and 13 women *v* four men and 11 women), they would have differed in terms of baseline systolic blood pressure (mean 187·5 *v* 179·6 mm Hg)—a clinically important difference that would have made the subsequent changes in systolic blood pressure associated with treatment difficult to evaluate.

Here minimisation succeeded in providing well matched groups where simple randomisation would have failed and stratified randomisation would have been impractical. So why is minimisation so seldom used when it can save researchers from the awful realisation, too late, that their results are marred by baseline imbalance because they have trusted to luck—that is, randomisation?

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AUTHOR'S REPLY,—Drs King and Bashir are correct to say that an investigator can abuse the treatment allocation scheme in a clinical trial whether a random or a systematic method is used. This is why a "blind" allocation mechanism is desirable.[1] As I noted in my editorial,[2] systematic allocation—for example, using odd or even birth dates—is not biased if applied properly. It is hard, however, to achieve true blindness of investigators, and knowledge of the system makes abuse simple. Pocock and Keirse give examples of trials in which the use of birth dates gave serious imbalance between groups.[3,4] Drs King and Bashir suggest that randomisation is not always possible but do not indicate the circumstances. By contrast, Pocock suggests that there is "no real justification for such systematic methods since they do contain a potential bias and can be replaced quite simply by randomisation."[3]

I did not refer to minimisation in my editorial in order to keep the message simple.[2] I agree with Dr Cornish and colleagues, however, that minimisation is a valuable technique for achieving balance in small trials; indeed, I recommend it.[5]

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Growth of asthmatic children

SIR,—Drs Ole D Wolthers and Søren Pedersen have reported the results of a double blind trial of the effect of budesonide on the growth of asthmatic children assessed by knemometry.[1] As participants in a multicentre study of a new inhaled steroid of low oral bioavailability, fluticasone propionate, we incorporated a period of knemometric measurements of lower leg growth rate on 13 children receiving a placebo inhaler for four weeks followed by two four week periods of treatment with beclomethasone at 200 mg and then 400 mg per day. The treatments were given in a non-random fashion but all knemometric measurements were taken with no knowledge of previous measurements, as previously described.[2] The mean (SD) lower leg growth rates were 0·38 (0·12) mm/week with no steroid; 0·34 (0·20) mm/week with 200 mg beclomethasone; 0·2 (0·16) mm/week with 400 mg beclomethasone.

The lower leg growth rate before treatment and with beclomethasone 200 mg/day is at the lower end of the range found in non-asthmatic children[2] and lower than that seen in the Danish study. This difference may reflect the increased severity of the asthma in our study compared with Wolthers and Pedersen's study as a recruitment requirement of the trial was asthma of a severity sufficient to need inhaled steroid prophylaxis. The reduction of lower leg growth rate of 0·18 mm/week seen in the children receiving beclomethasone 400 mg/day is significant by ANOVA ($p=0·033$) and of a similar magnitude to the decrease shown by Wolthers and Pedersen (0·17 mm/week) at the same dosage of budesonide. These observations add weight to the suggestion that at least short term growth suppression occurs with doses of budesonide or beclomethasone equal to or more than 400 mg/day. This dose is commonly exceeded in clinical practice and has also been shown to produce measurable adrenal suppression.[3]

Although effective treatment of asthma may be achievable only with inhaled steroids, children should be monitored clinically and auxologically for possible undesirable side effects while receiving these drugs.

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SIR,—We would advise doctors to treat asthma seriously and not to be too worried about growth. Short stature can be disadvantageous but is rarely fatal. The importance of the dose related suppression of short term growth velocity of the lower leg in asthmatic children treated with inhaled budesonide, reported by Drs Ole D Wolthers and Søren Pedersen, is questionable.[1]

Knemometry has been advocated as a powerful means of detecting changes in linear growth velocity of the lower leg over short periods (18 days), but this translates to changes in linear height velocity over longer periods with enormous errors.[2] The reduction in growth velocity in Drs Wolthers and Pedersen's study may have been due to changes in the composition of the soft tissue caused by steroid treatment, which, by the authors' own admission, was not clinically indicated. Estimation of osteocalcin might have clarified the issue.[3]

There is ample evidence of undertreatment of asthma in children, resulting in increased morbidity and absence from school.[4,5] Mortality from asthma in England and Wales continues to increase,[6] and evidence suggests that undertreatment of these patients may be contributory.[7] The authors recommend that knemometry may be helpful in defining a "safe" dose of inhaled budesonide for treatment. We emphasise that a safe dose is one that adequately treats the child's symptoms.

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Hormone replacement therapy in general practice

SIR,—In apparently advocating hormone replacement therapy for virtually all postmenopausal women Dr Jean Ginsburg and colleagues[1] depend on evidence that is largely inapplicable to the central question of the clinical cardiovascular effects of opposed hormone replacement therapy—that is, of regimens that include progestogen. Despite their terminology none of their evidence comes from randomised trials, let alone trials concerned with clinical (as distinct from biochemical) end points.

The estimated 9% of women receiving hormone replacement therapy at the time of our survey[2] is consistent with a considerably higher proportion ever having received it, although this cannot be estimated directly from our data. Our survey does, however, provide an answer to why a large proportion of British women "are missing out on treatment that reduces mortality and morbidity and improves their quality of life," as Dr Ginsburg and colleagues suggest. It is that many general practitioners do not believe that the evidence justifies the uncritical conclusion that all women should be offered hormone replacement therapy regardless of whether they experience menopausal symptoms. Over a third of the doctors we surveyed stated that they would not contemplate routine prescribing even to prevent osteoporosis. Many thought that

long term effects, especially of the extended treatment that they consider would confer maximum prevention of bone loss, are as yet unknown. Dr Ginsburg and colleagues do not even mention the possibility of breast cancer.

We think that Dr Philip C Hannaford and colleagues are unnecessarily pessimistic in their assertion that although trials of hormone replacement therapy are the ideal approach, they are "neither practical nor ethical."[3] The main purpose of our survey was to ask doctors whether they would enter patients into trials, and we found that a large proportion would do so. A pilot trial comparing hormone replacement therapy with no treatment in women who do not need it for menopausal symptoms has received ethical committee approval and is now in progress. Full discussion of risks, benefits, and uncertainties allows each woman to make a fully informed choice about participation. Some believe that any risk of breast cancer, however small, is too great for them to consider hormone replacement therapy, particularly if they do not have any symptoms. Many are not prepared to restart having periods or premenstrual symptoms with opposed treatment. Others think that the potential benefits outweigh these drawbacks. To date, 35 women from a group practice in Harrow have entered the pilot study, providing evidence that such a trial may be practical.

A pilot comparison of opposed and unopposed hormone replacement therapy in women who have had a hysterectomy has now been approved by ethics committees in two areas and is under way in one. As additional reasons for this trial, Dr Hannaford and colleagues do not mention the possibility that progestogens may also confer protection against bone loss or the uncertainty over the effects of progestogen on the risk of breast cancer, points raised during a consensus conference[4] (though we question the logic of some of its conclusions).

Ten or 15 years ago between 1% and 3% of postmenopausal women were using hormone replacement therapy.[5,6] The figure is currently about 8% or 9% and seems certain to continue to rise. If we are not to find ourselves still unsure of the long term consequences a decade from now we must do all we can to complete the necessary trials. A substantial number of general practitioners are prepared to try.

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Surgeons' qualifications

SIR,—It was reported in your "Headlines" on 13 July that "in future a licentiate (LRCS) will be awarded for undergraduate training and membership (MRCS) for basic surgical training, with fellowship (FRCS) being reserved for higher or specialist qualifications."[1]

It is certainly the intention of the Royal College of Surgeons of England to move towards these changes in the titles of our surgical diplomas. It is important, however, to clarify that the recent Medical Qualifications (Amendment) Bill, which now awaits royal assent, relates only to the first of these changes—namely, conversion of the existing MRCS to that of LRCS, so that henceforth the conjoint diploma will become LRCS, LRCP.

The need for a change in the titles of our surgical diplomas stems from the introduction of the intercollegiate specialty examinations which are now held in all the major surgical specialties and which form an integral part of accreditation of specialist training by the Joint Committee for Higher Surgical Training.

Our council believes that in future the title of fellow should be reserved for those who pass these examinations, held during higher surgical training, and that the diploma of MRCS would be more appropriate for the recently revised FRCS examination, which is now taken at senior house officer level at the end of basic surgical training. This would then become comparable with the standing of the MRCP examination within medicine, and at the same time the status of the FRCS diploma would be enhanced and brought more into line with comparable diplomas elsewhere in the world.

We believe that most surgeons accept the logic of these proposals. However, we also recognise that traditions die hard and that the Scottish surgical colleges feel that it is premature to change the title of our diplomas at the present time. Clearly it is essential that all colleges in the United Kingdom adopt the same nomenclature; it is for this reason that we are not prepared to force a change but rather to work towards gaining a consensus over this issue within the next few years, during which time the fellows of our respective colleges will be able to express their views.

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1 Surgeons' qualifications. *BMJ* 1991;**303**:76. (13 July.)

Domiciliary thrombolytic treatment

SIR,—Drs J Radford and R G Richards and Dr M S Stead are right to criticise the Royal College of General Practitioners' study of domiciliary thrombolytic treatment.[1,2] Kay's analysis of the relative risks of giving or not giving these drugs to patients who do or do not turn out to have a myocardial infarction finds in favour of taking the chance of giving the drugs, but his information comes from hospital based studies of patients preselected by the referring clinician.[3]

The first step in establishing the risk of thrombolytic treatment at home is to assess the accuracy with which general practitioners suspect myocardial infarction. With hundreds of referrals to hospital every week across the United Kingdom to analyse this would be a quick and easy study to do and would quantify the likely frequency with which thrombolytic treatment might be given inappropriately. The Royal College of General Practitioners wishes to gain this information, but only as a byproduct of the main study – a clear case of the cart preceding the horse.

In clinical practice a diagnosis is reached by refining a list of possibilities, and a general practitioner's list has to be the broadest of all. Myocardial infarction may be suspected more often than a practitioner's referral rate indicates, but will the availability of thrombolytic agents change this?

The medicolegal consequences of inappropriate administration of thrombolytic treatment or subsequent adverse events arising therefrom cannot be ignored. The Scottish Medical and Dental Defence Union's advice to me is to give the drug only when myocardial infarction has been clearly established (including by diagnostic electrocardiographic changes), when immediate admission to a coronary care unit is not feasible, and when adequate resuscitative measures can be used if necessary (W B Mathewson, personal communication). None of these conditions is a requirement for entry to the Royal College of General Practitioners' study.

In the evaluation phase of this new treatment it is essential that general practitioners do not expose themselves, as well as their patients, to avoidable risks. A single case of litigation would do great harm to the prospects of introducing thrombolytic treatment at home, so participants in this trial must temper their enthusiasm for intervention with the need to be rigorous in selecting patients and be fully prepared for the consequences if things go wrong.

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SIR,—Domiciliary thrombolytic treatment and the Royal College of General Practitioners' study seem to be causing much passion and not a little prejudice. Despite my extensive personal correspondence with Dr J Radford, in which I explained that he had misunderstood the purposes of the college's study, he and Dr R G Richards are clearly determined not to allow themselves to be confused by the facts.[1]

The study is purely observational and has two main aims: firstly, to document current management of acute myocardial infarction by general practitioners in the community; and, secondly, to investigate how anistreplase might be introduced into their regimen, to assess its safety in those circumstances, and to determine the practical difficulties that could arise.

Randomisaton of treatment is certainly appropriate for a clinical trial, but this is not a clinical trial; randomisation is inadmissible in a post-marketing study whose object is to assess as closely as possible how a particular agent will be used by doctors in the normal circumstances of their practice. Drs Radford and Richards are correct when they say that the study will not have the power to identify marginal benefits between the use of a thrombolytic agent at home and in hospital if by benefits they are considering only the effect on mortality.

We have already received a precisely documented report of a patient who had unequivocal electrocardiographic evidence of a myocardial infarction at home and was given anistreplase; by the time the patient had arrived at hospital the electrocardiogram had reverted to normal and the patient was well. I am not suggesting for a moment that one case can justifiably be used as an argument for changing clinical practice, but if that case is replicated many times during the course of the study it would be a compelling reason for reducing to the absolute minimum any delay in giving a thrombolytic drug.

We are incorporating in the follow up procedure various methods of assessing the quality of life of subjects, and this may also show advantages that have not, and, indeed, could not, become apparent in the large scale clinical trials, in which, rightly, the one hard measure of outcome was mortality. The "window of opportunity" to influence quality of life of a patient may be much smaller than that to influence mortality. We are collecting multiple data about the timings of the onset of pain, the