Censuses and Surveys' omnibus survey shows that only 2·1% of families with children contain children from both a previous and the current partner.[3] This proportion is low because, although many people change partners, they tend to do so after they have had most of their children. An unknown proportion of families with lone mothers contain two or more children of different fathers; if this proportion were half it would represent an extra 4% of all families with children. This would make the cost of the two screening methods similar.

The main reason, however, for preferring couple screening is not economic but medical.[4] In sequential screening 97% of women who are positive on screening will have a partner who is negative, some of whom will carry a mutation for cystic fibrosis that cannot be detected. These women may resent the anxiety generated by being identified as a carrier, with the resultant increased risk of an affected pregnancy but no diagnostic test available to resolve the uncertainty. This problem is avoided in couple screening, as carriers with non-carrier partners are regarded as being negative on screening.

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Couple screening would be easier for many centres

EDITOR,—H S Cuckle and colleagues provide further economic evidence supporting antenatal screening for cystic fibrosis.[1] The couple model is estimated to cost more than the sequential model, largely because of retesting in subsequent pregnancies if the woman's partner has changed. However, the estimate takes into account neither the cost nor the complexity of counselling and other contact with the patients in the sequential model. The cost of counselling would be modest, but locating each woman who was a carrier, explaining the need for and obtaining a sample from her partner, and subsequently explaining the results of the test would add complexity in decentralised health care settings. Furthermore, counselling 3% of couples, only one member of whom is a carrier, can raise anxiety with no prospect of definitive resolution by prenatal diagnosis. Some investigators report anxiety to be a continuing problem in the sequential model.

Besides avoiding these problems, the couple model requires that both the pregnant woman and the father agree to screening and submit samples at the outset. This simplifies the overall process, minimises further contact, and adds assurance that the decision to be screened is neither casual nor due to coercion. Genetic counselling is required for only the 0·1% of all couples (carrier woman with carrier partner) to whom definitive prenatal diagnosis can be offered.

Between June 1994 and December 1995 our group carried out a pilot study to evaluate antenatal screening for cystic fibrosis.[2] Enrolled couples lived in a sparsely populated region (Maine) and received antenatal care from 68 physicians at 38 health care sites. Before initiating the pilot study we determined that these sites could, without difficulty, provide initial printed information and material for collecting samples, obtain informed consent, and answer general questions. The staff could not, however, offer the more sophisticated counselling necessary for people found to be carriers. The sequential model would require that the physician's office recontact each carrier woman, obtain her partner's sample for analysis, explain the need for counselling, and arrange it. This was viewed as burdensome. Particularly in the case of couples in which the woman was a carrier but her partner was not, geographic barriers and work schedules could restrict access to timely genetic counselling. These considerations led us to select the couple model for the pilot study.

The staff at the sites where antenatal care was given and a random subset of patients were surveyed at the end of the study to identify problems. Both patients and staff reported a high level of satisfaction. The couple model could thus more realistically be implemented in our setting.

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Authors should have used marginal analysis

EDITOR,—The paper by H S Cuckle and colleagues should aid purchasing decisions regarding screening for cystic fibrosis on the basis of only a single genetic marker.[1] The evaluation is, however, seriously flawed with respect to screening for multimutations because the authors have fallen into the classic error of using average rather than marginal analysis.[2]

In table 1 the authors show that screening for a single mutation, with uptake of 75% and a detection rate of 80%, detects 384 affected pregnancies for a total cost of £17 758 000, giving a cost effectiveness ratio of roughly £46 000 per pregnancy detected. The authors go on to show, however, that if a multimutation test is used then this results in an average cost effectiveness ratio of about £70 000. The authors should have used marginal analysis,[2] which is done as follows.

The single mutation test detects 80% (that is, 384) of affected pregnancies. If it is assumed that the multimutation test increases the detection rate by 10% to 90%, this would result in 432 affected pregnancies being detected (that is, $(384/0{\cdot}8)\times 0{\cdot}9$). What the authors have done is to take the total cost of screening with the multimutation test and divide it by the total number of affected pregnancies, which produces an average cost effectiveness ratio of £70 000, thus implying a total cost of £30 240 000 (that is, 432×£70 000—although there seems to be an error in the authors' calculations as substituting £33 for £16 in the figure leads to a total cost of £33 697 556).

What the authors should have done is take the incremental cost of multimutation screening, which is £15 939 566 (that is, £33 697 566–£17 758 000) and divide this by the extra 48 affected pregnancies detected (that is, 432–384), which results in a marginal cost effectiveness ratio of £332 074. This marginal ratio is nearly five times greater than the average ratio and is more likely to influence purchasers to buy the single mutation test rather than the more expensive multimutation test.

Purchasers might still have considered the multimutation test on the basis of evidence contained in the present paper, as £70 000 is still less than the 25 year discounted (at 6%) excess NHS cost of treating a person with cystic fibrosis (assumed to be £8000 a year[1]), which is £104 026. If purchasers realised that they would actually be paying £332 074 per extra affected pregnancy detected, however, they would be less likely to fund the extra costs of multimutation testing.

Inappropriate use of average rather than marginal analysis is all too common in published economic evaluations, particularly screening studies.[2]

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2 Torgerson DJ, Spencer A. Marginal costs and benefits. *BMJ* 1996;312:35-6. (6 January.)

Study might be better described as a cost description of screening

EDITOR,—H S Cuckle and colleagues' paper on the cost effectiveness of antenatal screening for cystic fibrosis raises several important questions.[1] Firstly, their choice of cost effectiveness analysis rather than cost-benefit analysis makes an implicit assumption that the goal of a screening programme is to reduce births of affected infants and thus reduce health expenditure. This can be achieved only by introducing screening into a situation where there is high uptake (that is, antenatal clinics) and maximisation of the rate of subsequent termination of affected pregnancies. This is not the only model of screening. Indeed, it is one that explicitly limits reproductive choice in those women and couples who would not consider termination but might consider preimplantation diagnosis or artificial insemination by donor.

We know that a proportion of women in Britain would not consider termination of an affected pregnancy.[2] In their cost effectiveness analysis Lieu *et al* found that the proportion of women accepting termination of an affected pregnancy had a large effect on costs, particularly when it fell below 50%.[3] In Cuckle and colleagues' example the cost per affected birth avoided would increase to £92 000 if therapeutic abortion was accepted in only half of the cases.

Lieu *et al* also showed that increasing costs of lifetime medical care for a patient with cystic fibrosis had a large effect on the cost effectiveness of a screening programme. Unfortunately, Cuckle and colleagues quote a single annual figure for medical care derived from a single unit treating adult patients. This does not account for the fact that care may be cheaper for children, who tend to be in better health than adults with cystic fibrosis, nor does it use discounting over the current median life expectancy of 28 years.[4] Indeed, their study might be better described as a cost description of screening for cystic fibrosis, since effectiveness is not considered in great depth and factors known to affect cost effectiveness have been omitted from the sensitivity analysis.

This study makes other important assumptions, not the least of which is that a disease for which the life expectancy for the current birth cohort is probably at least 40 years should be prevented. The study shows what a programme that maximises termination of affected pregnancies might cost the NHS, but not that it is cost effective. It does not address the moral and ethical issues that such

screening would raise, or the costs of providing a service for women who would not consider termination of pregnancy. We may be able to screen, and might potentially be able to do it cost effectively, but should we do it and, if so, how?

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Authors' reply

EDITOR,—Counselling is an important component of screening, but unless an appropriate level is adopted the cost will be unsupportable. Therefore in our analysis we used two levels: a low cost option (basic information in a leaflet, which was reinforced by a midwife or general practitioner) for all people who might be screened, and expensive genetic counselling (by a nurse specialist) for carrier couples. Unlike David J H Brock, Joan Morris, and Richard A Doherty and colleagues, we are not convinced that the expensive option is needed for carrier women whose partners have yet to be tested. Carrier couples have a 1 in 4 chance of having an affected pregnancy, and the next step is to consider having an invasive diagnostic procedure with the possibility of subsequently terminating the pregnancy. In contrast, carrier women have only a 1 in 199 chance of having an affected pregnancy, and the next step is simply to test their partner. Since this step is implicit in the woman's agreement to be screened we costed only repeating the original information to the partner—the approach taken in the Yorkshire pilot study of over 6000 women.[1]

Done this way, sequential screening will be more cost effective than couple screening even if, as Morris claims, only 4% of women change partners between pregnancies. Other options short of full genetic counselling are possible, but more research would be needed to determine their cost effectiveness. Our preferred strategy is disclosure couple screening, which costs no more than sequential screening but retains some of the advantages of full couple screening.[2]

The marginal (or incremental) costs of detecting mutations additional to ΔF508 were included in our results. These are much higher than the average costs of the single mutation test, provided that under 10% more carriers are detected, and so a full analysis was not included. The incremental cost quoted by David J Torgerson is incorrect: 90% detection of carriers and 75% uptake of screening yields 486 affected pregnancies in 1 000 000 women (400×75%×90%×90%×2), not 432, and would cost £158 000, not £332 000. Torgerson's suggestion that screening should be restricted to women already undergoing invasive prenatal diagnosis would be relatively cheap but is unattractive to health planners as it would have little impact on birth prevalence.

Sarah Walters seems to confuse cost effectiveness and cost benefit analysis—for example, lifetime medical costs do not affect the cost effectiveness of detecting an affected fetus. As we stated in our discussion, we chose cost effectiveness because the valuation of life is difficult and involves ethical issues, which fall outside the realm of economics. Others can build on our results to develop a more comprehensive decision analytical model incorporating the valuation of all outcomes and costs including treatment.

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Clinical trials and rare diseases

Statistical results should be expressed in different ways, depending on circumstances

EDITOR,—Since the *BMJ* requested that, when possible, the statistical analysis of results should give confidence intervals, the relevance of many studies has become clearer. In recommending a bayesian approach to clinical trials in rare diseases Richard J Lilford and colleagues point out that power calculations are based on the probability of the proposed hypothesis being true, even though the frequentist test giving the P value (the possibility that the null hypothesis is true) is almost always used to justify the results.[1] Perhaps the *BMJ* should encourage authors to present results as the likelihood of the hypothesis being true, whenever this is appropriate.

In some situations the appropriate test is to consider the possibility that the conclusion is wrong (here, a low P value indicates significance), while in others it is to consider the probability that the conclusion is right (here, the higher the P value the greater the significance). On the one hand, when a new discovery is made it is appropriate to consider the possibility that the effect has arisen by chance and to test a null hypothesis. On the other hand, when two treatments are known to be effective the relevant statement is the probability that one is superior to the other by a certain amount. Should we not express our findings in this way?

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1 Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995;311:1621-5. (16 December.)

Trials of adequate size are possible with the right organisation

EDITOR,—Richard J Lilford and colleagues have opened the debate on the difficult problem of clinical trials in rare diseases with insight and clarity.[1] We are concerned, however, that some of the messages conveyed in their article may be open to misinterpretation.

Firstly, readers should not accept that a trial that is not powerful enough to provide a definitive answer is as good (that is, clinically useful) as one that is appropriately sized. There is a hierarchy of evidence, with some forms of evidence carrying more weight than others. A trial that can produce reliable evidence must be better than one that cannot, although we agree that some evidence from a small trial is usually preferable to non-randomised evidence, even if this is based on large numbers.

Secondly, different parties may interpret the word "rare" in different ways. The authors quote the example of a trial of fetal surgery, which, if it was to be capable of producing a definitive answer, would need to recruit from a population of 12 million pregnant women. They imply that this would be impossible, which we do not accept. A trial of this size has not yet been done in this field, but that is not to say that it is impossible. Examples of trials in rare diseases show that widespread international collaboration is possible. A trial of the management of posthaemorrhagic ventricular dilatation in neonates is currently recruiting from 137 centres in 26 countries. This condition is very rare, and, although recruitment will take several years, the size of the trial has been calculated so that it will be capable of providing a definitive answer to the question being posed. If the main barriers to conducting large collaborative trials in rare diseases are organisational should we not be investing our scarce resources in overcoming these barriers to collaboration rather than relying on evidence from trials of inadequate size that may provide misleading evidence?

We agree with the authors that "any randomised evidence is better than none." We are concerned, however, that this approach may encourage researchers and funding bodies to support inadequately sized trials when trials that may provide definitive answers are possible with the right organisation and commitment from participating centres.

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GMSC's advice on intrapartum care is unhelpful

EDITOR,—The General Medical Services Committee recently issued guidance stating, "We think that practitioners who are going to provide intrapartum care should be the relatively few GPs [general practitioners] who are highly skilled and practised in this area . . . these GPs are referred to as GP obstetricians. Only they should undertake home deliveries and deliveries in GP units."[1,2]

We believe that this advice is unhelpful as it is likely to reduce the number of general practitioners prepared to attend women in labour. Few would be prepared to have their professional skills judged against some hypothetical standard of "general practitioner obstetrician," would describe themselves as "highly skilled and practised in this area," or would ever exercise obstetric skills at home. It might be argued that this advice seeks only to regulate the current position, but such general practitioners have never argued that they are doing anything more than exercising the skills that all general practitioners should have. The advice is counter to that in *Changing Childbirth* and that of the Royal Colleges of Midwives and General Practitioners,[3,4] which says that those general practitioners keen to provide care to women in