reporting on patients from two centres, and the other was a full paper reporting on the patients from only one centre.[8,9] In this second case confirmation was received from the first author.

How can this difficulty be overcome? One possible answer is the development of clinical trial registries in all specialties and the mandatory mention of a trial registration number, which should be a unique number attributed by the registry, on each publication.[10]

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Volunteering for research

SIR,—Your Oct 3 editorial tackles the issue of taking part in clinical trials. It deals essentially with how potential subjects respond once they have been approached, arguing that variations in response, based for example on social factors, might bias the results of the study.

Social factors might bias the results in another way. Protocols for most trials list inclusion and exclusion criteria and the trialist is often required to exclude patients if they are unlikely to comply with the protocol. Initial selection can therefore be determined, at least in part, by a doctor or other researcher using judgment which is subjective, secret, difficult to challenge, and never tested.

Many years ago a researcher involved in a long-term cardiovascular study retired and the responsibility for running the trial was passed to a colleague. The study, which involved face-to-face interviews, took place in an urban city area, and on asking the new trialist how many ethnic minority patients had been enrolled he could recall none. There were no clinical grounds for such a skewed trial population and we were left to worry whether the social factors determining the original trialist's beliefs about likelihood of complying had preselected the volunteers.

Such potential selection bias has clinical and scientific implications which should be considered carefully by those producing protocols as well as by ethical committees when they vet them.

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SIR,—Your editorial on volunteering research emphasises the importance of psychological profile of the subjects participating in clinical trials and draws attention to some concerns about the general applications of the results. With respect to phase-I clinical trials, results are based on an unavoidably small number of non-ill volunteers. Moreover, these subjects have special psychological traits.

In a previous report we showed[1] that a series of university-educated male volunteers participating in phase-I clinical trials presented substantially different personality traits than controls with similar sociocultural characteristics. Volunteers scored higher on extraversion and psychoticism scales, and lower on neuroticism scale of the Eysenck personality questionnaire (EPQ). In a subsequent survey, 67 male students at our school were asked if they would ever participate in a paid prototype phase-I clinical trial and fulfilled the EPQ and Zuckerman's sensation seeking scale form V (SSS) questionnaires. The 43 (64%) who were not willing to participate in a trial were compared with a series of volunteers who participated in phase-I clinical trials (n = 58). Data obtained in this study were consistent with those of the former study: volunteers scored higher on extraversion and psychoticism and lower on the lie scale of the EPQ. In the SSS questionnaire, they also scored higher on all the subscales of the questionnaire (thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility).

These data confirm that the people who volunteer to participate in phase-I clincial studies have a characteristic psychological profile, and therefore should be regarded as a special subsample of the general population. These differences could affect the general applicability of the results obtained when investigating the effect of drugs, especially when subjective and psychological variables are assessed.

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Fibromyalgia: the Copenhagen declaration

SIR,—Now that fibromyalgia has been deemed a condition rather than a syndrome (Sept 12, p 663) there is a danger that clinicians may be tempted to so label any unexplained diffuse-pain state. Despite the best efforts of the American College of Rheumatology,[1] the intuitive leap taken in Copenhagen cannot be justified while the aetiology remains obscure. It may be sobering for the proponents of fibromyalgia to recall that fibrositis, the diagnostic label that fibromyalgia replaced, was declared a "diagnostic scrapheap" nearly forty years ago.[2] Whither fibromyalgia?

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Audit and research

SIR,—Dr Franks (Aug 1, p 308) adds to the debate about the distinction between audit and research by drawing attention to the nature of the question being asked. I describe another distinguishing feature—ethics committee approval.

After a successful bid to audit the bone-densitometry service, by ascertaining patients' and referring doctors' views and by examination of case-notes in South Tees Health District, I wrote to the local ethics committee to seek comments and approval for the study. I was advised that since the proposal was for an audit and not a research project ethics committee approval was not necessary. This response is of concern for two reasons.

Firstly, much of the audit work involves (and should) patient satisfaction surveys, which are not always conducted by people well versed with such methods. In our district, during one of these surveys, a patient was very distressed at being asked an insensitive question (personal communication, Heather Harding, Director of Quality). Secondly, how will the journals view the lack of ethics committee approval in deciding about publishing reports of audits? Some journals (eg, *Health Trends*) require authors to submit a copy of the ethics committee approval letter. What a loss it will be if publication of audit projects was withheld for this reason.

Although ethics committees may become inundated with protocols in view of the increasing amount of audit, I believe that there ought to be a mechanism to ensure that important issues,

Hereditary tyrosinaemia is a metabolic disorder characterised by cirrhosis and hypophosphataemic rickets. Clinical severity is variable. Death can occur in the first year of life from liver failure or, in the more chronic form, in the first two decades, often from hepatoma. Acute porphyric crises are an important cause of morbidity and mortality.[1,2] The enzyme defect in tyrosinaemia type 1 was defined by the group that included Lindstedt in 1977.[3] They correctly suggested that the primary defect was a deficiency of fumarylacetoacetate hydratase (EC 3.7.1.2.), which catalyses the last step of tyrosine degradation. Treatment with a diet restricted in phenylalanine and tyrosine helps the renal disease but does not prevent progressive liver failure or the development of hepatoma. Until now liver transplantation was the only successful treatment available. The timing of such a procedure is crucial. In the most acute form it is often not possible to do a transplant in time, partly because of the clinical severity and partly because of the limited availability of donor organs of the correct size. In the more chronic forms there is the desire to keep the child going as long as possible and yet carry out the life-saving procedure before hepatoma has developed. Donor organ shortage is again a problem, as is the morbidity and mortality associated with the procedure. However, until Lindstedt's work there seemed to be no alternative to this approach.

Five patients with type 1 tyrosinaemia, including one with the acute neonatal form, have been studied for between 7 and 9 months. NTBC inhibits an enzyme at a stage preceding the fumarylacetoacetate hydratase deficiency and thus prevents the formation of compounds thought to be responsible for the liver and kidney injury and of succinylacetone which inhibits porphobilinogen synthetase. The researchers speculate that this agent prevents the progressive liver damage and the acute porphyric crises. Although follow-up is short, the response in these patients is encouraging. There was an improvement in wellbeing and in standard liver function tests in all cases. There was also a fall in α-fetoprotein concentration in all patients, although in the eldest the value rose again and that patient subsequently received a transplant. In three patients computed tomographic appearances of the liver improved. It was not possible directly to estimate the degree of inhibition of 4-hydroxyphenylpyruvate dioxygenase. However, by indirect measurements it seems that the enzyme was totally or almost totally inhibited. Excretion of succinylacetone fell and activity of porphobilinogen synthetase increased.

Both the quality of life and life expectancy in type 1 tyrosinaemia could be greatly improved if these results are confirmed. Early treatment is most likely to be successful.

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Volunteering for research

Subjects for medical research are almost always selected from a larger pool of potential candidates and various procedures are adopted to ensure that the final sample is representative of the relevant population. An investigation can be worthless if subject selection is confounded with another factor that is known to affect the dependent variable of interest. The use of human subjects in research invokes two conflicting sets of considerations. First, researchers must consider the benefits that might accrue from their work. Occasionally the knowledge gained will benefit the subjects themselves; the beneficiaries are more likely to be the researcher, the wider scientific community, and the community as a whole, in that order. Against these benefits one has to weigh the rights and needs of the subjects. There are very few circumstances in which they should be exposed to dangerous procedures, and we recognise the right of subjects to be adequately informed about the experimental methods and to decline to participate. If sufficient numbers of subjects decline to take part in a study a bias may be introduced into the sample, especially if the reasons for refusal are confounded with the dependent measures. In extreme circumstances such bias may yield seriously misleading results. Refusal rates vary according to the way in which subjects are approached. Postal surveys, for example, often yield participation rates of less than 50%; the individual approach secures much higher recruitment rates.

The reasons why some subjects refuse to participate in research are therefore of more than passing interest. The matter has not been studied much by empirical researchers, perhaps because it is difficult to persuade individuals to answer further questions once they have declined participation. Harth and co-workers[1,2] achieved this goal with parents who either did or did not volunteer their children for a randomised, double-blind placebo-controlled trial of a new oral anti-asthma drug (ketotifen). Volunteering and non-volunteering parents were followed up and asked several questions; they also completed a battery of psychological tests about interpersonal values, self-esteem, and personality. Volunteering parents, by comparison with their non-volunteering counterparts, were significantly less well educated and less likely to be in professional and managerial occupations; they also used more habit-forming substances, enjoyed less social support, and displayed greater health-seeking behaviour. With respect to psychological measures, the volunteering parents put more value on benevolence and less on power and prestige, displayed much lower self-esteem, and showed lower confidence and emotional stability.

These findings have important implications for the interpretation of scientific results and for the ethical conduct of scientific investigations. In particular, they give credence to the hypothesis that people who agree

to participate in research, although less preoccupied by personal gain, may also be those who are least able to understand what the research is about, and who are less confident in their ability to challenge authority.[3] This observation should be a cause for concern to anyone who seeks good practice in research, but is especially worrying when those making a decision about participation in research are doing so on behalf of a minor. Ideally, a decision about whether or not to volunteer for research should reflect the values of the individual concerned and nothing else. If this goal is to be achieved in practice, researchers must be prepared to give potential subjects even greater opportunity to express dissent from participation than in the past. For example, it may be possible to eliminate sampling bias due to assertiveness, intelligence, and education by taking greater care when obtaining informed consent. Thus, information should be presented in a way that is easily comprehended by people of moderate intelligence and low confidence. Further studies are needed to determine the extent to which the effects discovered by Harth and co-workers are influenced by the way in which informed consent is obtained. Meanwhile, these workers have done a great service in pioneering an area of empirical investigation that may ultimately have a profound, if uncomfortable, impact on medical research in general.

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Post-term induction: don't kill the messenger

Induction of labour has had a bad press for over two decades since the excesses of the 1960s prompted media attention and consumer resistance. Obstetric units often cite low rates of induction with pride as an index of their moderate non-interventionist approach. The consensus is that induction of labour may "expose the parturient and her baby to a cascade of related events each contributing its own hazard, the culmination of which is less favourable than would be obtained if nature were allowed to follow its course".[1] However, in view of the results of a randomised prospective trial, induction may now be ripe for rehabilitation.

Never has a clinical impression proved more misleading than in the context of post-term induction of labour. Although attempts to bring forward labour in women who remain pregnant at 42 weeks' gestation are unquestionably associated with high rates of operative intervention, the underlying reasons for the intervention may be unrelated to the induction process itself. To explain this paradox one has to focus on the characteristics of women with prolonged pregnancy. First, prolonged pregnancy is more common in primigravidae,[2] who as a group have more difficult labours than parous women. Second, even among primigravidae who go into labour spontaneously, the incidence of caesarean section at term increases progressively with gestation so that the rate at 41 weeks is double that at 37.[3] For whatever reason, failure to go into labour by 42 weeks may indicate impending trouble, irrespective of the mode of onset of labour.

Meta-analysis of randomised studies in which wholesale induction at 42 weeks was compared with selective conservative management does not confirm an increase in caesarean section in women randomised to active intervention.[4] In fact, the most recent published trial showed a higher rate of caesarean section in the group managed conservatively.[5] By preventing a 43rd or 44th week of pregnancy, routine induction also effectively removes the small but finite risk of antepartum stillbirth that might otherwise have occurred at these gestations. Moreover, it seems that this small risk cannot be prevented totally by careful antenatal supervision.[5] In the randomised studies undertaken so far the small numbers of antepartum deaths have nearly all been associated with expectant management. Earlier in pregnancy, induced labour may lead to higher rates of operative intervention than in labours of spontaneous onset, but for the 5–10% of women who reach 42 weeks, induction may do more good than harm.

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Colons and keyholes

Laparoscopic cholecystectomy has swept the board. Launched by Wall Street with barely a glance at clinical trials or orthodox medical conventions, it stands out as the first big patient and technology led revolution in health care. Appendicectomy and highly selective vagotomy seem imminent conquests; laparoscopic hernia repair may yet need to prove itself in respect of recurrence. Now colorectal surgery comes in for laparoscopic attention. In this issue (p 831) Monson and colleagues from St Mary's Hospital, London, predict that laparoscopic assisted colorectal surgery will have a considerable impact.

Archimedes said "Give me a place to stand and I will move the world". So it is with the craft of surgery, in which access and exposure have always been prerequisites of high quality work. The gallbladder is a simple end-organ which is awkwardly placed for open