want to lose the benefits. It seems we are each unwittingly introducing a different bias by what we say.

If randomised clinical trials in cancer are to be successful in recruiting patients, clinicians need more guidance on what is meant by informed consent and how to obtain it. An article by Tobias and Souhami[2] and subsequent correspondence[3] aired some of the issues but did not help with the practicalities. Perhaps the *BMJ* could commission a "How to do it" article—or is it too difficult?

FERGUS MACBETH
Locum oncologist

Christchurch Hospital,
Christchurch,
New Zealand

1 Dehn TCB. Treatment of oesophageal cancer. *BMJ* 1994;309: 126. (9 July.)
2 Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. *BMJ* 1993;307:1199-301.
3 Correspondence. Informed consent in clinical trials. *BMJ* 1993;307:1494-7.

Advertisement for Zantac

EDITOR,—I am concerned by the advertisement for Zantac that has appeared in the *BMJ*.[1] It reads: "It's an effective treatment. Successfully healing both duodenal and gastric ulcers. But, used as prophylaxis, Zantac can actually prevent NSAID-associated duodenal ulcers. In fact it's the only H_2 licensed to do this."

The most likely site of any damage to the gastrointestinal tract associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) is the gastric mucosa and not the duodenum.[2] The *British National Formulary* states, "Therapy [with H_2 antagonists] can promote the healing of NSAID-associated ulcers but there is no proof that the ulcer complications are prevented."[3] Zantac is licensed for prophylaxis against only duodenal ulcers associated with non-steroidal anti-inflammatory drugs. Why Glaxo was granted a licence so inappropriate and open to misinterpretation I can only wonder.

I am concerned that the wording of the advertisement implies that Zantac can be used for prophylaxis against all ulcers induced by non-steroidal anti-inflammatory drugs. If this was not so the advertisement would surely have mentioned only duodenal ulcers. In my opinion this advertisement has been phrased in such a way as to encourage the inappropriate use of a drug outside the terms of its product licence. I have expressed my concerns to the Medicines Control Agency.

FINDLAY M HICKEY
Pharmaceutical prescribing adviser

Grampian Health Board,
Aberdeen AB9 1RE

1 Advertisement for Zantac. *BMJ* 1994;309:between pages 96 and 97 (clinical research edition) (9 July.)
2 How often do NSAID-induced ulcers occur? *MeReC Bulletin* 1992;3:23.
3 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary number 27 (March 1994)*. London: BMA, RPSGB, 1994:33.

Manufacturer's reply

EDITOR,—The advertisement to which Findlay M Hickey objects promotes Zantac for the licensed indications of healing and preventing duodenal ulcers and healing gastric ulcers related to non-steroidal anti-inflammatory drugs (NSAIDs). Hickey's main objection seems to be based on his belief that Zantac should not have been granted a licence for the prevention of duodenal ulcer associated with non-steroidal anti-inflammatory drugs. He apparently believes that the section that he quotes from the *British National Formulary* supports his contention that H_2 antagonists do not have a role in this indication. In fact, the sentence states that there is no evidence that they prevent the complications of peptic ulcers. Indeed, the formulary also states, "Treatment [with ulcer healing drugs] in patients taking NSAIDs may prevent the development of peptic ulcers but has not been shown to prevent complications of bleeding or perforation."[1] Clearly, therefore, Hickey has misunderstood this information.

To extend a product licence it is necessary to satisfy the Medicines Control Agency that there is sufficient evidence of efficacy for a new indication. This has been achieved with regard to the use of Zantac 150 mg twice daily with non-steroidal anti-inflammatory drugs in the prevention of duodenal ulceration but not in the prevention of gastric ulceration; hence the specific indication of duodenal ulcer.

The separate indications of prevention and healing are clearly stated in the text of the advertisement: "Successfully healing both duodenal and gastric ulcers. But, used as prophylaxis, Zantac can actually prevent NSAID-associated duodenal ulcers." In addition, the indications are clearly spelt out in the indications section of the prescribing information in the advertisement and are further qualified in the precautions section. We therefore see no grounds for the allegation that the advertisement implies that Zantac can be used for prophylaxis against all ulcers induced by non-steroidal anti-inflammatory drugs or encourages inappropriate use of the product outside the terms of its licence.

Although pharmaceutical companies are not required to substantiate the validity of indications in product licences, references to published studies appear in the advertisement for Zantac and we would be happy to provide them to Hickey or any other appropriately qualified person on request.

DARRALL L HIGSON
Associate medical director

Glaxo Laboratories,
Uxbridge,
Middlesex UB11 1BT

1 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary number 27 (March 1994)*. London: BMA, RPSGB, 1994:33.

Experimental and observational methods of evaluation

EDITOR,—Trevor A Sheldon's editorial perpetuates the false dichotomy between experimental and observational research.[1] Once again an advocate of randomised controlled trials seeks to discredit evaluative research that uses observational data as if the two methods were alternatives rather than complementary approaches. Extremist supporters of either camp offer unacceptably simple accounts.

Of course in some people's ideal world every intervention in the biological and social spheres would be evaluated with a randomised controlled trial. But the world is not such a utopia. As a consequence there are important roles for observational methods used with the care and rigour that, hopefully, trialists bring to their studies. What are those roles?

Firstly, some interventions, such as defibrillation for ventricular fibrillation, have an impact so large that observational data are sufficient to show it.

Secondly, infrequent adverse outcomes would be detected only by randomised controlled trials so large that they are rarely conducted. Observational methods such as postmarketing surveillance of medicines are the only alternative.

Thirdly, observational data provide a realistic means of assessing the long term outcome of interventions beyond the timescale of many trials. An example is long term experience with different hip joint prostheses.

Fourthly, whatever those who question the value of health care interventions might think, many clinicians often will not share their concern and will be opposed to a randomised controlled trial; observational approaches can then be used to show clinical uncertainty and pave the way for such a trial.

Fifthly, despite the claims of some enthusiasts for randomised controlled trials, some important aspects of health care cannot be subjected to a randomised trial for practical and ethical reasons. Examples include the effect of volume on outcome, the regionalisation of services, a control of infection policy in a hospital, and admission to an intensive care unit. To argue that these topics could theoretically be evaluated by a randomised controlled trial is of little practical help in advancing our knowledge.

Why advocates of trials feel the need to criticise the use of non-experimental methods is unclear. After all, randomised controlled trials have their limitations. Evaluation would benefit if everyone recognised and appreciated the vital and complementary roles that experimental and observational methods have.

NICK BLACK
Reader in public health medicine

Department of Public Health and Policy,
Health Services Research Unit,
London School of Hygiene and Tropical Medicine,
London WC1E 7HT

1 Sheldon TA. Please bypass the PORT. *BMJ* 1994;309:142-3. (16 July.)

Inventing a new diagnostic test

EDITOR,—I was most interested in the article by Tom O'Dowd and Nick Bourne about their experience in technology transfer from university to industry.[1] They failed to mention how they handle the problems of indemnity against product liability and proof of intellectual property rights and how they and their industrial partners share this. It would be most helpful if they could give us the benefit of their experience on these issues.

PETER SÖNKSEN
Professor

Division of Medicine,
St Thomas's Hospital,
London SE1 7EG

1 O'Dowd TC, Bourne N. Inventing a new diagnostic test for vaginal infection. *BMJ* 1994;309:40-2. (2 July.)

Authors' reply

EDITOR,—We agree with Peter Sönksen that universities need to make sure that they have their act together in the complex world of exploiting medical research. He asks two important questions, on product liability and on proof of intellectual rights.

Under the terms of our arrangement, our licensee was required to indemnify us against product liability claims against third parties. It is advisable actually to see a copy of the licensee's insurance cover to assess its extent. Such indemnities can prove extremely expensive in litigious territories like North America.

We were licensing an idea, which was worked up to the stage of prototype kit. We did not actually license a product, but an idea on which the company itself would base a future product. It is important that the company makes its own assessment of the technology to ensure its "fitness for purpose." As a further precaution the licensee should make a "no warranty" statement in the licence agreement. Our experience indicates that commercial partners see such precautions as good business and indeed sound investment.

As to proof of intellectual rights, a licenser of a