3 Melton LJ, Bickerstaff LK, Hollier LH, Van-Peenen HJ, Lie JT, Pairolero PC, *et al*. Changing incidence of abdominal aortic aneurysms. A population based study. *Am J Epidemiol* 1984;**120**:379-86.
4 Powell JT, Bashir A, Dawson S. Genetic variation on chromosome 16 is associated with abdominal aortic aneurysm. *Clin Sci* 1990;**78**:13-6.
5 Collin J, Murie J, Morris PJ. The Oxford experience of surgery for abdominal aortic aneurysm. A two year prospective analysis. *Surg Gynecol Obstet* 1989;**169**:527.
6 Armour RH. Survivors of ruptured abdominal aortic aneurysm; the iceberg's tip. *BMJ* 1977;ii:1055-7.
7 Ingoldby CJH, Wujanto R, Michell JE. Impact of vascular surgery on community mortality from ruptured aneurysms. *Br J Surg* 1986;**73**:551-3.
8 Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. *Br J Surg* 1986;**73**:101-3.
9 Smith FCT, Grimshaw GM, Shearman CP, Hamer JD. Aortic aneurysm screening in an urban community [abstract] *Br J Surg* 1992;**79**:358.
10 O'Kelly TJ, Heather BP. General practice-based population screening for abdominal aortic aneurysms: a pilot study. *Br J Surg* 1989;**76**:479.
11 Collin J, Walton J, Araujo L, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65-74 years. *Lancet* 1988;ii:613-5.
12 Scott RAP, Ashton H, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysm. *BMJ* 1988;**296**:1709.
13 McGregor JC, Pollock JG, Anton HC. The value of ultrasonography in the diagnosis of abdominal aortic aneurysm. *Scott Med J* 1975;**20**:133-7.
14 Ellis M, Powell JT, Greenhalgh RH. The limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. *Br J Surg* 1991:78-614-6.
15 Turk KAD. The post mortem incidence of abdominal aortic aneurysm. *Proceedings of the Royal Society of Medicine* 1965;**58**:869-70.
16 Office of Population Censuses and Surveys. *England and Wales. Mortality statistics: cause*. London: HMSO, 1986.
17 Collin J, Walton J. Is abdominal aortic aneurysm familial? *BMJ* 1989;**299**:49.
18 Bengtsson H, Norrgard O, Angquist KA, Ekberg O, Oberg L, Bergqvist D. Ultrasonic screening of the abdominal aorta among siblings of patients with abdominal aortic aneurysms. *Br J Surg* 1989;**76**:589-91.
19 Bengtsson H, Ekberg D, Aspelin P, Kallero S, Bergqvist D. Ultrasound screening of the abdominal aorta in patients with intermittent claudication. *Eur J Vasc Surg* 1989;**3**:497-502.
20 Scott RAP, Ashton GLJ. Ultrasound screening of a general practice population for aortic aneurysm. *Br J Surg* 1986;**73**:318-23.
21 Szilagyi DE, Elliot JP, Smith RF. Clinical fate of the patient with asymptomatic abdominal aortic aneurysm and unfit for surgical treatment. *Arch Surg* 1972;**104**:600-6.
22 Bergqvist D, Bengtsson H. Is screening for abdominal aortic aneurysms worthwhile? *Ann Chir Gynaecol* 1992;**81**:203-8.
23 Barodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991;**5**:491-9.
24 Secretary of State for Health. *The health of the nation. A strategy for health in England*. London: HMSO, 1992.
25 Collin J. The value of screening for abdominal aortic aneurysm by ultrasound. In: Greenhalgh RM, Marrick JA, eds. *The cause and management of aneurysms*. London: Saunders, 1990.
26 Blamey RW, Hardcastle JD. The early detection of cancer. In: Russell RCG, ed. *Recent advances in surgery. 12*. Edinburgh: Churchill Livingstone, 1986:29.

(Accepted 30 July 1992)

AIDS, ethics, and clinical trials

Institute of Medical Ethics Working Party on the Ethical Implications of AIDS

Asking a clinical scientist when he or she last read the Declaration of Helsinki[1] is rather like asking a seasoned airline traveller when he or she last listened to the safety announcement. The declaration sets out ethical principles which no one seriously disputes and on which other authoritative statements[2-6] are essentially commentary. But the Declaration of Helsinki is sometimes more difficult to put into practice than to replicate on paper. Two of its principles, for example, mark out an area of possible moral conflict: "research involving human subjects must conform to generally accepted scientific standards," and "concern for the interests of the subject must always prevail over the interest of science and society." AIDS research highlights this possible conflict but also suggests new ways of resolving it.

"RESEARCH INVOLVING HUMAN SUBJECTS MUST CONFORM TO GENERALLY ACCEPTED SCIENTIFIC STANDARDS"

The scientific gold standard today is the randomised clinical trial. Scientists have found no more effective way to reduce bias, control variables, and establish priorities among the available options. Alternatives which have been suggested—for example, "prospective studies without randomization, but with the evaluation of patients by uninvolved third parties," or "prospective matched-pair analysis in which patients are treated in a manner consistent with their physician's views"[7]—do not remove bias sufficiently.

"CONCERN FOR THE INTERESTS OF THE SUBJECT MUST ALWAYS PREVAIL OVER THE INTEREST OF SCIENCE AND SOCIETY"

Many patients become subjects of research from which they receive no direct benefit. The research may be non-therapeutic or, as a result of randomisation in a therapeutic clinical trial, the patient may be given a treatment which turns out to be ineffective or not given what turns out to be an effective treatment.

A subject's failure to benefit directly need not mean that concern for the interest of science and society has prevailed over concern for that of the subject. Doctors have a duty to avoid harm to their patients and to serve their best interest. But they also have a duty to respect the autonomy of patients as persons, who are the final arbiters of what is in their own best interest. A patient may have an altruistic interest in taking part in non-therapeutic research, or an interest in the possibility, however remote, of direct benefit. Informed consent means that the patient freely accepts the implications of the uncertainty principle which, scientifically as well as ethically, justifies the study.

Is it ethically justifiable to invite patients, for whose condition there is no existing treatment, to be randomised to a new treatment or a placebo? Since a clinical trial implies some chance of the new treatment being effective have these patients, in their own interest, any alternative to accepting? (British doctors, after all, have an alternative. If they judge that it is in their patient's best interest they can obtain the new treatment as an "innovative therapy.")[4]

This argument seems strongest when the new treatment is designed to delay or arrest the progress of a life threatening disease. But such treatment, unfortunately, often carries the highest risks. For the patient the new treatment could result in a shorter or more distressing existence than no treatment. In some clinical trials—for example, a recent cardiac arrhythmia suppression trial[8,9]—non-intervention groups have actually had better survival rates. Asking these patients if they are willing to be randomised to a new treatment or a placebo, then, is not offering them a choice which, in their own interests, they cannot refuse. Here again, informed consent to the implications of the uncertainty principle is the relevant ethical criterion.

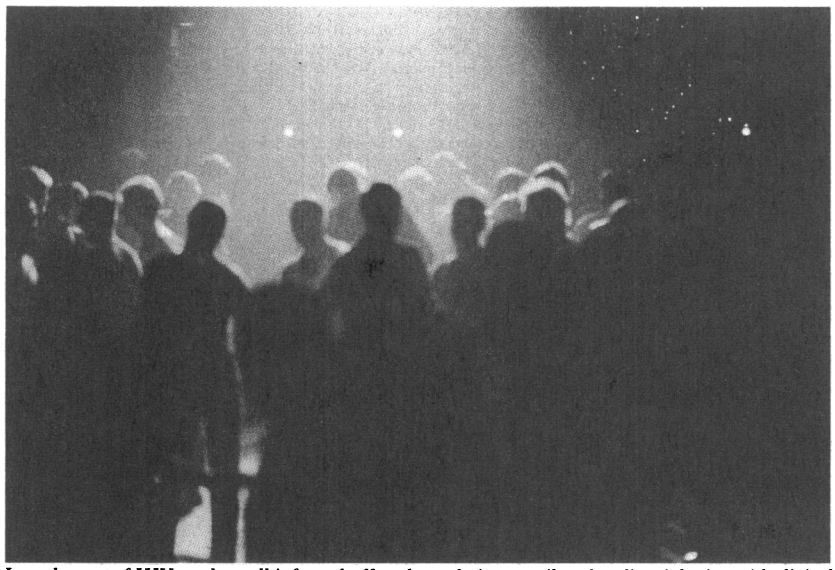
AIDS AND CLINICAL TRIALS IN THE UNITED STATES

For several decades most patients have implicitly accepted the logic of the uncertainty principle and, if asked, have agreed to take part in clinical trials. But in the past few years significant numbers of patients with HIV infection or AIDS have criticised this research method, taken direct action to subvert it, and forced researchers and regulatory authorities to adopt new strategies.[10] Some factors contributing to this are specific to HIV infection and AIDS, to the United States, and to those initially infected there and in Europe. What is being learnt from this experience, however, has wider application.

Institute of Medical Ethics Working Party
Members of the working party are listed at the end of this report.

Correspondence to:
Dr K M Boyd, Institute of Medical Ethics, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW

BMJ 1992;305:699-701



SUNIL GUPTA/NETWORK

Long latency of HIV, and a well informed affected population contributed to dissatisfaction with clinical trials

The specific factors are, firstly, that patients mostly remain well but aware that they have a new and life threatening condition during a long latency period. Secondly, in the United States the only potentially effective treatment known to clinical scientists (zidovudine) was initially available only to patients in placebo controlled clinical trials. For many poorer patients entering these trials was their best and sometimes only hope of effective medical care.[11] Thirdly, those initially infected in the United States and Europe included a large proportion of young and articulate homosexual men, often associated with homosexual organisations politically geared to defend the interests of minorities against establishments.[11]

Many of these patients became exceptionally well informed both about AIDS and about clinical trials. They did not reject the uncertainty principle so much as its interpretation. Were scientists giving patients' interest in treatment the benefit of the doubt over their own interest in reliable data? Against the background of gay politics and American health care inequities organisations like Act Up (the AIDS Coalition to Unleash Power) argued that growing evidence of zidovudine's effectiveness made it unjustifiable to withhold the only effective treatment from any patient who could benefit from it.

Patients themselves also took direct action. According to one American report,[11] "they lie to get into studies (often with the help of their own physicians) and, once enrolled, lie about their medical condition and level of compliance." These patients, the report continued, "attempt to frustrate the use of placebos . . by analysing the drugs they receive, thereby unblinding the study, or by pooling the drugs, which ensures that they will receive some portion of the active substance while playing havoc with the assigned dosage levels."

Widespread recourse to such desperate measures made it clear that the scientific goals of clinical trials could not be achieved if subjects did not share the scientists' interpretation of the uncertainty principle. In response to this the American regulatory authorities shifted from a scientifically very strict clinical trial process to one which allowed large exceptions on social grounds. This included widespread "compassionate release" of "promising" new AIDS drugs before clinical trials of their safety and effectiveness had been completed.[10]

AIDS patients, no less than AIDS researchers, are part of well informed international networks.[12,13] Compassionate release of a new drug in one country can be taken by patients in another as evidence of its effectiveness. This can make it more difficult to recruit patients for clinical trials either of the new drug or of alternative treatments. The "promising" treatment may be better than the alternatives. But without trials on both that cannot be known. As a result even present patients (especially given the long latency period) may be denied the most effective treatment.

Participation, choice, and flexibility

The American experience suggests that allowing either the immediate needs of patients or the long term goals of science to prevail over the other is in the best interest of neither. Both interests are best served, rather, when there is enough mutual agreement about application of the uncertainty principle to persuade patients to be randomised and scientists that the study will yield reliable conclusions. In practice this requires an approach which embodies three features untypical of many clinical trials before the advent of AIDS: participation, choice, and flexibility.

An attempt to embody these features can be seen in the design of the current Medical Research Council alpha trial of didanosine in patients with symptomatic HIV disease who are intolerant of zidovudine.[14] In the test tube didanosine looks like a promising alternative to zidovudine, prolonged use of which 30-40% of symptomatic patients are unable to tolerate, and the efficacy of which probably declines over time.[15] But the risks of didanosine include pancreatitis in 3-29% of patients treated with it,[16] and there is no firm evidence of clinical benefit. One reason for the lack of evidence is that although over 10 000 patients have received didanosine in the United States, they have done so in "compassionate release" ("expanded access" or "compassionate use") programmes (A J Pinching, personal communication).

When a strictly controlled clinical trial in the United States was invalidated by tactics similar to those described above it became clear that many HIV positive patients did not share their clinicians' uncertainty about potential benefits and risks of didanosine. But the clinicians were sufficiently hopeful about the potential benefits to believe that a clinical trial was merited.

Conducting a trial would be justified, however, only if it was likely to yield reasonably reliable conclusions. This meant recruiting sufficient patients who were willing to abide by the terms of the trial. Participation, choice, and flexibility seemed the best way to achieve this. It was desirable, firstly, for the patient population from which trial subjects would come to be involved in designing the trial and to be represented on the committee overseeing it. This might have been difficult to achieve in the earlier days of clinical trials, but AIDS advocacy groups are only the latest of many disease related patient organisations which have sprung up in the mean time. Participation was desirable, not simply to persuade patients that their interests were being taken seriously but also to establish what these interests were, so that the trial could be designed in a way which took them into account and thus secured maximum recruitment.

Participation confirmed the impression that while many HIV positive patients believed that their best interests would be served by receiving didanosine, some shared the clinicians' uncertainty and wanted more evidence before deciding whether it was best for them. Choice was built into the trial, accordingly, by giving it two arms and by asking patients themselves to decide which they preferred to enter.[13] In arm A patients would be randomised to a high dose, a low dose, or placebo, and in arm B, to either a high or a low dose (the low dose being not so low, however, as to be equivalent to placebo). The clinical scientists

reckoned that if even relatively small numbers of those patients who shared their uncertainty chose A, the trial would yield scientifically reliable and clinically helpful information about the drug's effects. Flexibility was also built in by limiting exclusion and inclusion criteria to the minimum and opening the trial to as many patients as possible—leaving no need for the equivalent to "compassionate release."

Consequences of new approach

This approach has had significant consequences of two different kinds (A J Pinching, personal communication). Firstly, participation in the oversight of a trial can serve both patients' and research interests in quite practical ways. A patient representative can draw attention to the need for investigation and management of possible concomitants of a trial which affect the patient's quality of life—for example, the development of diarrhoea and whether it is linked to either the drug or its packaging.

Secondly, the discouraging immediate consequences of this approach have been followed by more positive long term ones. The immediate consequences were that large numbers of patients were recruited to the study and that some chose to enter the arm including a placebo—but unfortunately not enough to satisfy the scientific requirements. The longer term consequences, however, were that when patients and their representatives became aware of this they increasingly expressed concern about the need for placebo controlled studies—in order to learn more about the effects of the toxic drugs with which so many were being treated.

Thus as a result of researchers encouraging patients to participate and make their own choices patients in due course began to understand and share the researchers' interpretation of the uncertainty principle. But that interpretation now included the researchers' recognition of patients' expectations as a crucial variable in the degree of certainty they could expect from a clinical trial. The implication, therefore, is not that the researchers have regained old ground but that shared understanding can be maintained only by exploring further the new ground on which alpha took a first step.

In AIDS research this may mean devising further trials which give patients the choice of a number of different arms, including placebo options. These might compare, for example, different anti-infective or prophylactic drugs, drugs in different dosages, or different combinations of drugs—the last seeming at present a particularly promising avenue.

This new approach has implications not just for clinical trials involving HIV and AIDS patients but also for medical research generally.[17] Clinical trials were devised at a time when many people regarded science as a mystery, health care as a benefaction, and professional judgment as unquestionable. But times have changed, and patients with HIV or AIDS display, in an accentuated way, the moral claim of growing numbers of people today to be informed about and to participate in choices affecting their lives. The ethical criteria which have been applied to clinical trials with HIV and AIDS patients, in other words, foreshadow those appropriate to medical research trials generally. If the disabling problems which have beset AIDS research in the United States are not to be constantly repeated new ways of implementing this mutually empowering approach must continue to be sought.

Members of the Institute of Medical Ethics Working Party on the Ethical Implications of AIDS: The Right Hon Sir Patrick Nairne (chairman); Professor Brenda Almond (director, Social Values Research Centre, University of Hull); Miss Marija Danilunas (solicitor, Gray's Inn); Miss Ursula Gallagher (nursing adviser, Charing Cross Hospital, and research fellow, Institute of Medical Ethics); Dr Raanan Gillon (general practitioner and editor, *Journal of Medical Ethics*); Mr Jonathan Grimshaw (director, The Landmark); Mr Kenneth Howse (philosopher and honorary research fellow, Institute of Medical Ethics); Dame Rosalinde Hurley (professor of microbiology, Royal Postgraduate Medical School); Mr Michael Marland (headmaster, North Westminster Community School); Professor Anthony Pinching (professor of immunology, St Bartholomew's Hospital Medical College); Mrs Renee Short (member, Medical Research Council); Mr Richard Wells (oncology nursing adviser, Royal Marsden Hospital); Mrs Patricia Wilkie research fellow, St George's Hospital Medical School); Mr David Zideman (consultant anaesthetist, Hammersmith Hospital); Dr Kenneth M Boyd (secretary).

1 World Medical Association. *Declaration of Helsinki: recommendations guiding medical doctors in biomedical research involving human subjects*. In: Mason JK, McCall Smith RA. *Law and medical ethics*. 3rd ed. London: Butterworths, 1991:446-9.
2 Royal College of Physicians of London. *Research involving patients*. London: RCP, 1990.
3 Royal College of Physicians of London. *Research on healthy volunteers*. London: RCP, 1990.
4 Royal College of Physicians of London. *Guidelines on the practice of ethics committees in medical research involving human subjects*. London: RCP, 1990.
5 Department of Health. *Local research ethics committees*. London: DoH, 1991.
6 Scottish Office, Home and Health Department. *Local research ethics committees*. Edinburgh: SHHD, 1992.
7 Hellman S, Hellman DS. Of mice but not men. Problems of randomized clinical trial. *N Engl J Med* 1991;**324**:1585-9.
8 Passamani E. Clinical trials—are they ethical? *N Engl J Med* 1991;**324**: 1589-92.
9 Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406-12.
10 Merigan TC. You can teach an old dog new tricks. How AIDS trials are pioneering new strategies. *N Engl J Med* 1990;**323**:1341-3.
11 Arras JD. Noncompliance in AIDS research. *Hastings Cent Rep* 1990;**20**: 24-32.
12 American Foundation for AIDS Research. *AIDS/HIV treatment directory*. New York: AFAR, 1991-2.
13 National AIDS Manual. *UK directory of HIV treatments and trials*. London: NAM Publications, 1992.
14 Noticeboard. Clinical trials of dideoxyinosine in HIV disease. *Lancet* 1990; **335**:596.
15 Marx JL. New AIDS drug passes first clinical test. *Science* 1989;**245**:353.
16 Valentine C, Deenmamode J, Sherwood R. Didanosine and amylase monitoring. *Lancet* 1992;**339**:999.
17 Brown P. How AIDS made the patients act up. *New Scientist* 1992;**134**:1824.

(Accepted 22 July 1992)

ANY QUESTIONS

Are there any gastrointestinal pathogens that water sterilising tablets, used correctly, do not protect against?

Commonly used water sterilising tablets depend for their action on the liberation of chlorine or iodine. Chlorine tablets are bactericidal (except with regard to *Mycobacterium tuberculosis*) and fungicidal, but they have limited or no effect on protozoa and viruses. Even when used correctly they will not destroy giardia and amoeba, perhaps the commonest troublemakers. Iodine tablets containing tetraglycine hydroperiodide will kill the vast majority of bacteria and also fungi, viruses, cysts, and protozoa. Iodine will kill amoeba and giardia. Iodine tablets are not easy to keep: unless the container is airtight the volatile halogen evaporates and attacks metal in the neighbourhood. Neither chlorine nor iodine will work if there is a lot of protein in the water.[1] It is therefore imperative to filter the water before sterilisation.[2]—BENT JUEL-JENSEN, *emeritus consultant physician in communicable diseases, Oxford*

1 Goodman LS, Gillman A, Gillman AG. *The pharmacological basis of therapeutics*. London: Pergamon, 1985:964-5.
2 Expedition Advisory Centre. *Expedition medicine*. London: Royal Geographical Society, 1989:35-7.