Viewpoint

The price of autonomy

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Accepted for publication:
27 October 1998

Keywords: clinical trials, harm versus benefit, informed consent, patient autonomy

Summary

The randomized controlled trial produces a clash of ethical principles with the need for informed consent (autonomy) in conflict with the principles of beneficence and justice. Informed consent is one of the major rate-limiting factors of recruitment and this delays the discovery of life-saving treatments indirectly. Whilst supporting the concept of non-exploitation we wish to challenge the prevailing dogma by asking the awkward question 'what is the price of autonomy?'. Using breast cancer as an example we have developed a decision model with explicit assumptions allowing numerical values to be fed into a mathematical equation, which calculates the cost in lives. With conservative assumptions we estimate that the price of autonomy is 2500 lives over a 10-year period in the United Kingdom alone. We issue the challenge to health policy makers and ethicists to survey public opinion to determine the value placed on autonomy in the war against cancer.

Introduction

Over the last 12 months the *British Medical Journal* has hosted a series of articles together with an extremely lively correspondence concerning the thorny issues of informed consent and the ethics of evidence based medicine.[1] The randomized controlled trial remains the gold standard of evidence-based medicine and yet the bug bear of ethicists.[2] Absolutists would argue that consent to randomization can never be truly informed and the subordination of autonomy in the name of the common good can never be ethical; reflecting a fascist tendency amongst the proponents of the randomized controlled trials.[3] At the other extreme are the pragmatists who believe that the only way to derive secure data upon which to base rational clinical decisions is to promote the randomized controlled trial and that a dogmatic insistence of informed consent at a time when patients are frightened and ill subverts the ethical imperative of beneficence and although one may pay lip service to the informed consent procedures, in reality these are nothing but a charade.[4] Thus, like any other tough ethical dilemma, we see a clash of ethical principles with the demands for autonomy in conflict with the demands for justice and beneficence. This debate continues at a rarefied level between professional ethicists, clinical scientists and self-appointed lay leaders. At no time has there been an attempt to elicit the opinions of representative samples of current and potential consumers as to how much autonomy they demand and what rate of progress they will accept.

Principles of consent

Digressing on the principles of consent, we note that during all these discussions, there is one assumption that is taken for granted: that

human beings are usually asked to give their consent for vital decisions that can affect their future welfare. In fact, consent is an exception rather than a rule. First of all, we take no part in deciding whether we are born or not. A mother does not obtain the consent of the unborn foetus when she smokes, takes medicines, or drinks in a smoky bar. As children, we do not consent to our name, the clothes we wear, the house we live in, whether we eat meat (prion-laden or not) and so on. Once we are 'adults', the ability to make our own decisions is bestowed upon us (without consent, of course!) and we are made to believe that it is our right, privilege and indeed, duty to be independent and make our own decisions. We fail to see that when we enter a contract with most service industries we are hardly ever informed of the risks and benefits, leave alone sign an informed consent. When we buy a car, or mobile phone, we are not informed or consented for all the hazards that we face whilst using it. A barber is not legally bound to inform us of the risk of transmission of any type of infection via the instruments and an airline pilot, or the busy air traffic controller at Heathrow, is not legally bound to take informed consent from all the passengers whose life is in their hands. Many of these risks are higher than those faced by a patient on clinical trial, or a patient undergoing cardiac catheterization. Ironically, the commercial industry, whose main concern is to make money from their clients, has no moral, ethical or legal restraints as regards to consent, whilst the noble, trust-based doctor/patient relationship, and progress of clinical science almost stands alone in the legalities of the consent procedure.

In this paper, we wish to explore the consequences of the conventional informed consent procedures for randomized controlled trials and to set a numerical value to such a policy which is the equivalent of the price we are paying for 'autonomy'. It is not the intention to take sides, but simply to pose a very uncomfortable question; although merely by posing the question it may be judged that the authors are not in a state of equipoise, but tilt away from absolutism towards a degree of pragmatism.

Clinical trials for the treatment of breast cancer

Let us anticipate 150 000 deaths from breast cancer in this country over the next 10 years,[5] and then let us make the conservative assumption that we already possess an, as yet unknown, new therapeutic adjuvant that in absolute terms would reduce the risk of death by 6% over this period, in other words, capable of saving 9000 lives.

Next, let us assume that the breast cancer subcommittee of the UK Coordinating Committee for Cancer Research (UKCCCR) has already endorsed three different clinical trials evaluating three promising new agents; one of which might produce this 6% absolute reduction in mortality (equivalent to a relative risk reduction of about 25% for patients with an average prognosis). Each trial would have to recruit about 2000 patients to ensure adequate statistical power to detect this order of relative risk reduction.[6] Next, in order to be both conservative and even handed in our estimates let us assume that the first trial shows no difference between best standard treatment and the new agent. The second trial shows that the new agent does indeed demonstrate the desired benefit, whilst the third trial shows that the new treatment is in fact worse by the same order of magnitude. This distribution of results does in fact reflect the generality of outcomes for randomized controlled trials.[7] In aggregate, 6000 women will have been recruited to these trials, 120 women will be better off than had they received best standard treatment and 120 women would in fact be worse off than if they had received best standard treatment. However, bearing in mind that patients recruited into randomized controlled trials do better than average, irrespective of the treatments they receive then it would not be too far fetched to say that, rather than being cost neutral, the aggregate of experience within the three trials might demonstrate a modest net benefit.[8]

Next, if we have an efficient clinical trials organization, then on past experience we might expect at best to recruit 1000 patients a year, so whether the trials are running in parallel or in

sequence, the total recruitment time would be 6 years. So far all the assumptions have been based on previous experience using conventional informed consent procedures. Now, for example, let us perturb the model by pre-randomizing the patients within the trial, only soliciting informed consent for those patients randomized to receive the experimental treatment whilst not discussing the issues of random allocation with either group. It then becomes pure speculation as to what extent this will speed up recruitment into the trials. Having informally surveyed opinion amongst a small group of clinical trialists, an estimate that it would double the rate of recruitment would again appear to be conservative. If that is indeed the case then the total sample will be recruited in 3 years rather than 6 years. Assuming that the results of the trials are disseminated rapidly within the country once available we can then calculate the price of autonomy. Remembering that a treatment that produces an absolute reduction in breast cancer mortality of 6% per year would save 900 lives a year and that the treatment would be introduced 3 years earlier, however long it took to demonstrate a result. In this case, the price of autonomy is the cost of 2700 lives lost (see Table 1). For the sake of this argument, the precise numerical values are not that important but by making them explicit it is possible to calculate up and calculate down the unnecessary loss of life which is the price of an absolutist demand for a degree of autonomy which involves a full understanding of the needs for and methods of randomization, the toughest component of the 'informed consent' process.

Table 1 Calculations for the price of autonomy

	Equations/assumption Numerical values as example
Breast cancer	causes D deaths per year 15 000 deaths per year
Better treatment with an absolute risk reduction of 6%	will save $S = D \times 0.06$ lives per year $S = 15\,000 \times 0.06 = 900$ lives/year
Conducting such a trial	will need n patients $n = 2000$ patients
For each successful trial unsuccessful trials	suppose there are k unsuccessful trials $k = 2$
Hence, we will need	total patients $P = n \times (k + 1)$ $P = 2000 \times 3 = 6000$ patients
Let us assume	the present rate of recruitment is p/year $P = 1000$/year
Thus the trial will take	$y = (P/p)$ years and then start saving S lives per year $y = (6000/1000) = 6$ years and then start saving 900 lives per year
Let us assume that	pre-randomization increases rate of recruitment (P) by a factor f (=2) $P = 1000 \times 2 = 2000$ per year
Then the trial will take	y/f years and we will save $Y = y - y/f$ years $Y = (6 - 6/2) = 3$ years
Thus the price of autonomy is	$A = Y \times S$ lives $A = 3 \times 900 = 2700$ lives

A challenge for health expectations

Some critics of randomized controlled trials have argued that it is insufficient to assess interventions purely in terms of evidence of efficacy.[3] Yet how many outcomes of clinical research can one realistically hope for. The objectives of medicine are purely and simply to improve length and quality of life. Any other outcome measures are either surrogate or metaphysical. If the lay public are approached to enquire what is the most important outcome measure in the treatment of breast cancer then the overwhelming majority would vote for an extension of life, however modest, or ideally an opportunity to live out the remainder of a normal expectation of life.[9,10] The pace of progress is, to a large extent, limited by the ethical demand for non-exploitation; and noone would seriously disagree with such a break being applied on progress.

Yet surely the time has arrived for the major stake holders in the game to express an opinion clarifying to what degree they value autonomy, and whether they would favour the scenario described above over current day accepted practice. To seek this opinion in a scientifically valid, evidenced-based manner, it is insufficient to listen to the solitary voices of self-appointed consumer advocates.[11,12] There are accepted methodologies for canvassing public opinion using population polling techniques or focus groups. The challenge to health expectations is to pose these difficult questions in order to determine the views of the health service users.

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