

Personal paper

## Are large clinical trials in rapidly lethal diseases usually unethical?

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Medical statisticians have lately been fulminating about the issue of underpowered clinical trials,<sup>1,2</sup> arguing that such trials are not only unscientific but also unethical. The main argument is that patients entering clinical trials are exposed to risk and frequently volunteer for reasons that are in part altruistic. If they enter a study which, because of a lack of power, cannot be expected to yield a reliable result then the trial organisers are guilty of unethically exploiting that altruism.

Several technical statistical arguments have been proposed to counter this view.<sup>3-6</sup> One trial represents only part of the evidence to assess the value of an intervention: even an underpowered trial that gives inconclusive results can contribute to development of a more complete picture. From a Bayesian perspective, therefore, an underpowered trial is not wasted. Moreover, the making of power calculations is a dark art, which makes assumptions that are often unjustified. Only rarely do the actual effect sizes, the placebo effects, the variance of change, and the nature of the population recruited, match the assumptions made before the trial. Choice of the power wanted, whether it is 80%, 90%, or 87.65% is arbitrary and a matter of convention.<sup>1</sup>

How can ethical judgments be made on the basis of a process for which there is little evidence base and experience shows that there are large discrepancies between the expectations of theory and the realities of practice? These uncertainties are such that power calculations are just as likely to lead to an overpowered as to an underpowered trial. If we follow the ethical line of reasoning, an overpowered trial is as reprehensible as an underpowered one because it will lead to unnecessary exposure of patients to a less effective treatment and to adverse effects of treatment. Unfortunately, getting things just right is in practice much more difficult than the writers of statistical textbooks and neat theoretical papers, devoid of prospective real world experimental studies, would care to admit.

Quite apart from the statistical arguments, however, there is one situation in which I believe that large trials are unethical. It is this: in diseases that can be rapidly lethal, say those which kill a high proportion of patients affected in a period ranging from days to perhaps 2–3 years, I submit that large clinical trials are unethical. The pros and cons about such trials do not seem to have been put forward. I believe that, whether I am right or wrong, the issues deserve widespread discussion, one that is at present not taking place.

I have been involved in biomedical research, much of it clinical research, for around 40 years. I am thoroughly

acquainted with the many important ethical and statistical issues that impinge on clinical trials. I am neither a trained ethicist nor a trained statistician, but over the years I have acquired reasonable familiarity with and understanding of most of the key issues. Or at least I thought I had. But 2 years ago everything changed.

After losing to ill health no more than a total of 10 days in 40 years, I became ill with a febrile illness and a mysterious rash, which cleared up after 10 days or so. I began to lose weight. A couple of months later the rash returned, inguinal, cervical, and axillary glands became painlessly enlarged, and I could feel at least two large abdominal masses. Advanced mantle cell lymphoma was diagnosed. I was told that median survival from first symptoms was around 2–3 years. However, in my case, the multiple large tumours, marrow involvement, systemic symptoms, and rapid loss of around 20% of my bodyweight, meant that I could not realistically expect to live much more than 6 months.

And so I entered a universe parallel to the one in which I had lived for 40 years. I became a patient and suddenly saw everything from the other side. I lived in a realm in which much of my time was spent talking to or otherwise communicating with other cancer patients. I scanned every relevant biomedical database I could find seeking information about mantle cell lymphoma. Like any lay person, I surfed the net and found an astonishing array of both sense and nonsense. I developed a whole new attitude to clinical trials and experimental treatments. I was threatened with death but I wanted to live. I looked at effect sizes and power calculations in a wholly new way.

Anyone who organises or undertakes clinical trials understands the relation between effect size, trial size, and statistical power. The larger the effect, the smaller the trial needed to show statistical significance. A very few drug interventions, such as penicillin for pneumococcal pneumonia, are so effective in almost all patients that no placebo-controlled trials are needed to show efficacy. Many drugs show statistically significant benefits with trial sizes of 20 or 30 patients. With such drugs the prescribing physicians can know that most treated patients will show a response that can be reasonably attributed to the drug by both patient and doctor. But as effect sizes become smaller and trial sizes climb over a hundred, it becomes more and more difficult for anyone to know whether what happens to the individual was caused by the drug.

To my dismay I soon learned that in oncology, with few exceptions, effect sizes were very small. To show these effects, trials had to be very large. I also learned from my fellow patients that the real consequences of this situation were rarely spelled out to those volunteering for such trials in terms they could understand. I thought long and hard about this situation and came to the conclusion that, as presently organised, many oncology trials are unethical. Similar considerations apply to any other rapidly lethal disease. My reasons are set out in the rest of this paper.

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The first reaction of most people on receiving a diagnosis of a lethal disease is that they want to live. Above all they want to find the best available treatment. Only at a much later stage, when they have in some part come to terms with the fact that they might have to die in the near future—and that there might not be a so-called best treatment, or indeed any even half decent treatment—do they begin to think at all about altruism. Any desire to contribute to the welfare of others usually comes only after hope has come close to being extinguished. The idea that altruism is an important consideration for most patients with cancer is a figment of the ethicist's and statistician's imagination. Of course, many people, when confronted with the certainty of their own death, will say that even if they cannot live they would like to contribute to understanding so that others will have a chance of survival. But the idea that this is a really important issue for most patients is nonsense. What they want is to survive, and to do that they want the best treatment. Altruism, in the sense of volunteering for a clinical trial whose outcome is uncertain, comes a very poor second. I believe that patients who are asked to volunteer for large trials in cancer or other rapidly lethal diseases are being misled. Most such trials cannot be justified on ethical grounds.

First, patients entering large clinical trials have little chance of benefit. If a trial has to be large, say more than 100 patients, it is large only because the expected effect size is very small. That means that most patients entering the trial have little or no chance of receiving benefit. With the toxic nature of many oncology treatment regimens, there may well be a substantial chance of harm. As far as I can learn from my many contacts with fellow patients over the past 2 years, although the risk of harm is usually well described in patient information leaflets, almost nothing adequate is ever said about the assumed effect size and the real chance of benefit. Almost all patients volunteering for most trials in oncology are doomed: at best they can expect little benefit. They are not usually being properly told about this low expectation.

Second, large trials greatly escalate time delays and costs. Anyone undertaking clinical trials in the present environment knows how difficult it is to get a small trial going in a single centre. Both the administrative and ethical issues can be formidable—let alone the clinical and financial ones. But the involvement of more than one centre escalates all the difficulties in a way that has the characteristics of an exponential curve. As a result, large trials in multiple centres almost always take much longer to get going, take longer to complete, and are enormously more expensive than small single centre trials. They have also become major sources of revenue for many institutions. Because large trials have become the norm, all professionals taking part are now reconciled to the idea that such trials will take forever and will cost the earth. As a result, most patients entering most oncology trials will be dead before the results are known. But the institutions in which they are being treated probably benefit greatly financially. Most patient information leaflets do not tell them either fact. This omission is unethical.

Third, the high cost of large trials means that they can be done only on patent-protected new chemical entities. Because large trials cost such very large amounts of money, they are rarely funded by charitable or public money. When they are so funded, there are so many vested and competing interests to be reconciled that delays become extraordinary, which is certainly no help to patients. What the high cost usually means is that only commercial interests can afford to pay for the trial. And

since such companies have to seek a return for investment, trials will be conducted for only a tiny part of the wide range of potential cancer therapies. That part consists of new chemical entities that have a remaining patent life of at the least 10, and preferably 15, years. Cancer patients are, of course, not told that such a small part of potential therapies is open to them. Nor are they told that researchers in most institutions, when considering which trials to take part in, are heavily influenced by the size of the financial contribution from the commercial sponsor. There is distressingly little altruism there.

Fourth, large trials greatly restrict the numbers of treatments that can be tested. For any disease, that the numbers of patients available for clinical trials are restricted is self evident. For all sorts of reasons the realistic universe of patients is much smaller than the actual universe of patients with any particular disease. Thus, a large trial that recruits many patients will considerably reduce the numbers of patients available for other trials. Thus, the number of therapies that can be tested is reduced.

For the past 20 years I have been working in the pharmaceutical industry. Although everyone in the industry will deny it, and I doubt whether there is documentary evidence of this statement anywhere, I know that several of the larger firms use overpowered trials as a way of keeping competitors out of that particular subject. Especially with less common cancers, if a company, by manipulating the power calculations, can recruit for a trial several times more patients than is necessary, then they will gain a clear competitive advantage by making it more difficult for rivals to recruit. This practice is unethical, but it happens, and the statisticians who are enthusiasts for power in clinical trials are often unwitting accomplices of these unethical commercial practices.

Any scientifically or medically qualified person who develops a lethal cancer rapidly learns many things. Two of them were especially surprising to me. First, as in my own case, the usual effects of standard treatments are all-too-often both toxic and of minimum therapeutic value. Occasionally patients do very well, but the outlook for most is gloomy. Moreover, the evidence base is near useless as a guide to what is likely to happen in one's own case, partly because the exclusion and inclusion criteria for trials are often so narrowly drawn that most individuals are unlikely to fit them. Another contributing factor is that effect sizes are so small that the numbers needed-to-treat to get one durable response may well be over 30 and often even higher. So, for the individual, treatment is indeed a lottery. In view of the frequently severe adverse events, usually much more predictable and reliable in their occurrence than is a therapeutic response, a decision on the patient's part not to be treated is not irrational. I learned that few patients are made aware of this fact: that is unethical.

The second surprising thing that I learned is that, for most cancers, there are many potential treatments, many of which are not toxic. Contrary to general orthodox medical opinion, most such potential treatments are neither fringe nor irrational. They are based on solid biochemical in-vitro work, on reliable work in animals, and occasionally on a few well documented case histories. But they have not been adequately tested in well designed trials, and most of them never will be. The reason for that has nothing to do with their scientific rationale or the strength of the evidence: it is simply that they are unpatentable or difficult to patent. Without patent protection, in the present climate, such potential remedies will never be tested.

Take the example of my own illness, mantle cell lymphoma. This disease is quite well understood. Most, and perhaps all malignant mantle cells have a striking rise of cyclin D1, a factor that drives cell division.<sup>8-10</sup> This increase is usually due to a translocation of the IgG promotor to the cyclin D1 gene. Cyclin D1 values can be suppressed by several well known agents, including the antifungal drug clotrimazole, the polyunsaturated fatty acid eicosapentaenoate, and the antidiabetic thiazolidinediones.<sup>11-13</sup> The publications in which the effects are described are in leading cancer journals and come from institutions such as Harvard, which are hardly on the fringe. No trials have been done on any of these agents. There are also rational but more complex cases to be made for the possibility of treating mantle cell lymphoma with cyclo-oxygenase inhibitors, or thalidomide, or certain groups of nutrients; but that any of these will be properly tested in this disease is unlikely.<sup>14</sup> I was fortunate to be able to discuss these unproven approaches with sympathetic haematologists and to devise a regimen, which so far seems to have been helpful. But most patients are not in that position.

This is a depressing example of the law of unintended consequences. 50 years ago, good scientific evidence of a potential therapeutic effect would quickly have generated a small clinical trial in one or two centres with perhaps 30 or 40 patients. Such a trial would have cost almost nothing. It would certainly have missed small or marginal effects, but it would not have missed the sort of large effect that most patients want.

Unfortunately, now, such an approach has become impossible. Ethics committees, clinical trial regulations, and research costing by administrators would put the cost of even a small pilot study up to £100 000 (about US\$160 000) or more. Without patent protection, that anyone would fund such a pilot study is very unlikely. And so, as is easily demonstrable by reviewing publications, scores of compounds that might have a therapeutic effect will never be tested. The escalation of costs has therefore drastically reduced the range of compounds from which new treatments can be drawn. If a compound is not protected by patent it will not be developed, which would not matter if current research in oncology were producing large benefits in common cancers.

But despite huge expenditure, success has largely eluded us. The few outstanding successes in rare cancers cannot hide the overall failure. This situation has to mean that there is a real possibility that standard approaches are wrong, and that we have no firm rational basis for predicting the directions from which success might come. Our best hope of changing our practice is to test as many different approaches and compounds as possible, looking for substantial effects. But the demand for large trials that are adequately powered to detect small effects and that are undertaken in many centres, and a substantial bureaucracy, has effectively killed this possibility.

I submit that there is a strong basis for the claim that large trials are indeed unethical in patients with diseases that have a high probability of killing the patient within 2–3 years. Patients with lethal diseases want to get better, not to have their lives extended by a few weeks or months at great cost in toxicity and time in treatment. The only reasonable approach, if this goal is to be achieved, is to scan a wide range of diverse therapies. Certainly, the mainstream ideas that we have been having for the past 50 years have not done a great deal for us. The only way in which our approach might change is that we largely abandon large-scale trials looking for small effects and instead do large numbers of small trials, often in single centres, looking for large effects. I suspect that patient participation in the trial process would become much more enthusiastic. Most people are more interested in the remote chance of a cure, than in the certainty of toxicity and the near certainty of no useful response.

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