Publication of clinical trial results: a clinician's view

Anthony J Pinching DPhil FRCP

J R Soc Med 1995;88(Suppl. 24):12–16 PAPER READ TO RSM MEETING, 13 OCTOBER 1993

Keywords: *clinical trials; publication; AIDS; communication of clinical results*

INTRODUCTION

In looking at the issue of communication of clinical trial results, the symbiotic relationships between medicine, the pharmaceutical industry and the City have become increasingly obvious. However, there are inevitable tensions too, given the parties' very different views on the same subject and their different imperatives. It has, at times, seemed that each member of the triangle may, in disputes over communication, use the third party as a basis for pressing a particular view on publication of results. Thus, we may need to distinguish between the actual views of the parties concerned and perceptions of those views held by others. All too often, the caricature, while containing an element of truth about the motivations behind the players, so distorts the reality that it creates a shadow triangle of false perceptions behind the real one, increasing the complexity of reaching an understanding.

WHO SAYS WHAT TO WHOM AND WHEN?

Perhaps if we also understand better the Why? of each party concerned, it would be easier to achieve a common path. Before dealing with specific issues, we should delineate something of the context in which the debate about clinical trial results occurs. First, there is the need to appreciate the investment of people's dreams and aspirations into such studies and their outcomes. There is a constant, perhaps irresolvable, tension between this and the often more limited reality of what *may* be achievable, let alone what is *actually* achieved. The public, fuelled by the media caricature of science, look for the 'breakthrough', failing to see that most scientific progress is more akin to adding pieces to a multimillion piece jigsaw.

Patients

Patients are obviously those with the most explicit interest in the results of clinical trials, representing the most directly relevant outcome of medical research to their own needs. These are issues that will, or should, directly inform the therapy they receive, helping to make the always provisional decision-making on their treatment more secure.

Louis Freedman Professor of Immunology, Medical College of Saint Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

Activists

In some areas, notably in my own area of HIV/AIDS, there has been another related, but distinct constituency of activists or advocacy groups. These comprise a mix of those affected and those from their peer groups who have set out to compaign on their behalf. This is obviously legitimate, even though their tactics have not always been so. However, there are all too often other agendas being played through this, which are to do with community politics and the making of statements about process and power relationships.

These groups, especially those in the USA, have indeed had a distorting effect on the debate about AIDS therapies, variously pressing for greater speed in conduct of clinical research and in the evaluation and availability of much needed drugs, for changes in the clinical trials process (for example, questioning the use of placebos or randomization), and sometimes targeting a particular drug for wide use in the advance of data or for clinical trial priority, or for its vilification. They have also targeted individuals and organizations for fairly wholesale abuse, questioning their motivations. The pharmaceutical industry, in particular, and statutory bodies such as National Institutes of Health (NIH) and the Medical Research Council (MRC), have been portrayed as pantomime villains, with precious little appreciation of their crucial roles in bringing any drugs forward for clinical use. Individual clinical investigators have been viewed as self-interested agents of a supposedly malign medical profession (a startling distortion), or as agents of the pharmaceutical companies whose drugs they have investigated.

The media

The media have played a further potentially distorting role. Their role in educating and informing the public is all too readily undermined by their parallel role in entertaining. This helps to enhance the cycle of alternately raised and dashed expectations, and may easily modify perceptions of specific agents ('cure of the week') and their role and of the process of clinical scientific enquiry.

Many of the earliest reports about clinical trials or new therapies appear in the financial pages of papers. This raises issues about how or why such reports appear, and who is releasing the information, and for what purpose. My impression is that the appearance of reports in the

financial media is often related to a need for companies to raise awareness of potential new therapies and thus to increase their financial resources, not least with which to proceed with their further investigation in large scale clinical trials. More often, stories in the general media may stem from enthusiasm of individuals, including scientists and clinicians, patients or advocacy groups, to foster a particular 'pet' therapy.

The financial world

The fact that shares go up and down is obviously an essential means whereby share dealing can yield profit for individual or corporate investors, or for pension funds. The judicious timing of sale or purchase is crucial, but is dependent upon the roller-coaster of the shares themselves. Thus, the cycle of hope and disappointment provides a valuable drive to the process, regardless of why the expectations are raised or dashed. In the particular setting of pharmaceutical industry shares, one could be rather cynical about the necessity to drive these up and down by well-timed announcements, when the self-same 'news' has such a potent effect on patients affected by the diseases in question. On the other hand, investigators and potential recipients of effective drugs need a greater awareness of the fact that, without financial resources, none of these agents could be tested, let alone made available.

Anticipatory share dealing in relation to clinical trials is a specific concern. Even without formal early release of data, city analysts are expected to study the likely prospects for companies in regard to the expected performance of their key products. Knowledge that a clinical trial report is imminent may be enough to promote speculation as to the likely result. The fact that a Data and Safety Monitoring Board has reported, for example, to continue a study or to modify recruitment, may be susceptible of some interpretation: reading the runes or interpreting often Delphic statements, gives great scope for the high priests of financial analysis. It was a notable feature of AIDS research that City analysts would seek out experts to anticipate the results of studies at forthcoming conferences. Indeed, some of the AIDS conferences were attended by financial analysts!

The specific issue of share ownership by participants in the whole sequence of drug development, from employees of the companies, clinical investigators, to clinicians, scientific reviewers and health service managers, requires particularly careful thought. The potential for conflict of interest or *de facto* insider dealing is enormous. Surely, share ownership of this sort is unacceptable and must be eschewed.

The pharmaceutical industry

Popular perceptions of the role of the pharmaceutical industry, if taken to the limit, would effectively prevent development of any new agents. The vast majority of effective drugs have been developed by industry, because they are the only organizations with the resources to pursue them. Many agents never reach the market, but for both these and the ones that do, there is a need for vast investment. The cost of drug development, through initial study, safety testing and, most of all, the sequence of clinical trials from phase I and III, is formidable. It evidently needs to be financed by the market price of successful drugs and the judicious use of the financial markets to raise resources. This simple truth often escapes the critics of industry: yet the potential for massaging early data to achieve it and hence to change the gloss put on early results must be an ever-present threat to probity.

Statutory bodies

The statutory bodies involved in medical research have, by comparison with industry, very limited resources to conduct clinical trials. The UK Medical Research Council, for example, repeatedly expresses its horror at the cost of large-scale clinical trials. Yet they, at least, have much less explicit investment in a particular outcome, although politicians may want to present a positive image of their contribution to medical research. Sadly, however, there is little sign that governments appreciate the need to ensure an independent, dispassionate and rigorous assessment of a particular agent, or group of similar agents. This is in order to prevent widespread inappropriate prescription of inadequately tested therapies where, as in the UK, this is funded by the public purse. All too often, therefore, the statutory bodies are obliged to seek substantial funding and participation from companies that have a clear commercial interest in a particular outcome. This may lead to restrictions on what can be tested, and on how the investigation is performed. It can, and has, led to a failure to proceed with an investigation, because of unilateral withdrawl by the industrial partner.

DATA RELEASE

This brief and doubtless partial assessment of the context in which clinical trials are conducted and reported gives an indication of the many competing pressures on the different players. It demonstrates the need for ethical conduct by all parties. While I do not doubt that high ethical standards do indeed inform most of the individual players, their judgements as to what are acceptable standards and acceptable trade-offs are derived from such different domains, it is not hard to understand why disputes and misunderstandings can so readily emerge. The necessity to safeguard the process by which information about studies is released is self-evident, since it is this aspect that is most susceptible to distortion. What is said and on what basis, its

timing and the setting in which it is given, and above all the adequacy of the supporting data to allow others to make their own assessment are critical. Indeed, the purpose and process of releasing information may change what information is presented and how it is perceived. It is generally accepted that the first information about anything, and the interpretation put upon it, is most deeply embedded in people's memories and is hardest to displace. It certainly affects how later information on the same subject is received.

If then, the objective of communicating the results of clinical trials is to allow prompt and well-justified changes in clinical practice, it is necessary to examine how to resolve the tension between releasing the results as soon as they are available and reporting them at a level of detail that can enable clinicians and patients to make up their own minds. Also, we must ask to what extent peer-review is an essential prerequisite for release of information, since this necessarily slows down the process while, hopefully, improving its quality and relevance.

The first results from a clinical trial will generally be known when the primary analyses presented to the Data and Safety Monitoring Committee lead them to stop the study and to enable all trial participants access to the preferred treatment arm. With well-informed patients, this will be tantamount to public release of data. Thus, it is argued, there should be a public statement, usually a press release, to coincide with this decision. Yet, by definition, the full results will not have been analysed, and more complete data analysis will yet have to be performed. Trial design should be such that these later analyses, and data completion and 'cleaning' will not change the substance of the message, though they may significantly affect emphasis and the assessment of potential trade-offs between efficacy and toxicity.

The next key stage in the process of data release will be the scientific meeting, at which investigators will present an oral report of the main findings, again often based on the initial, not the final, analysis. In high-profile areas such as AIDS, these meetings are very public, with media, activists and financial analysts present. Should the oral presentation be accompanied by a press release, or even by a detailed text with 'executive summary' of the available data? This stage will involve more detailed presentation of data, yet generally without any substantive peer-review or independent oversight. The quality of such presentations and data summaries varies enormously, with room for plenty of gloss.

Or should there be an embargo on any public presentation pending the release of the definitive peer-reviewed scientific publication, with the inevitable longer delay for the substantive report? While this view will be attractive to the purists and could well be in the long-term interests of all concerned, realism dictates that studies of high public interest are unlikely to be able to achieve the 'radio silence' required. Information is likely to seep out in a partial and uncontrolled manner and is, thus, even more likely to distort the message. Patients and their advocates will reasonably demand that the information should not be withheld in such a way as to disadvantage those patients whose current treatment will be affected.

How then can we proceed, balancing these competing demands from the many different perspectives? Some form of compromise will evidently be needed. We have not yet achieved it, though recent approaches have offered some partial solutions that, with refinement, could provide a framework for an acceptable means. This can be illustrated with some of the emerging problems and solutions with respect to studies in HIV disease, primarily as they relate to the use of zidovudine (AZT).

The first phase II trial on the use of zidovudine in AIDS patients in the USA was announced at a press conference. Very limited information was available to the public, especially those outside the USA: essentially only the 'bottom line', i.e. that the drug worked and had reduced early mortality sufficiently to justify halting the study. Information about these conclusions was not even shared at the time with co-investigators on other planned or ongoing studies on the same drug in similar settings, apparently for fear of revealing 'price-sensitive' information. Insufficient data were available for clinicians to discuss the study and its implications with patients in an informed way. Company-organized meetings were held some months later to present more detail, but it was many months more before the publication appeared with sufficient detail to allow a dispassionate assessment of its relevance to clinical practice. In the meantime, the drug had been widely licensed. It is arguable that the heavily affirmative tone of the early reports, combined with the evident need for some positive therapeutic news for people affected, was responsible for the initial demands from the community for wider access to the drug, and inevitably, for the later disenchantment and unduly negative tone subsequently taken by the same groups, as the pendulum of enthusiasm swung viciously back.

Despite this experience, when the large USA study (ACTG 019) on the use of zidovudine in asymptomatic HIV infection (CD4 counts below 500) was reported 2 years later, much the same sequence occurred. The news was broken at a press conference, giving a very affirmative line about the value of the agent in this setting. There was little caution expressed about the limitations of the study, and, again, the view was heavily projected that the drug worked. The company, trialists, NIH and health officials took up strong advocacy positions. Guidelines were soon produced in the USA which recommended treating people with

asymptomatic HIV infection and CD4 counts below 500 with zidovudine. Clinicians and patients were again obliged to discuss the results without sight of any detail, although some data were presented to USA clinicians. Attempts by UK investigators and the MRC to obtain more information were declined, except for a strictly confidential briefing of the committees responsible for the similar Anglo-French Concorde study. Later, USA colleagues were surprised to find that these confidences had indeed been fully respected and clearly felt that the briefing had constituted a much wider dissemination of the results to UK clinicians than was in fact the case. Again, it was many months before the substantive publication appeared, and when it did, many of the reservations that had been felt in the UK and Europe from the early and fragmentary reports were felt to have justified.

Yet clinical practice had already been changed by the perceptions and recommendations, and in response to the great needs and expectations of patients. Furthermore, the prevailing view about the conclusions of 019, even though it was based on few events in a short follow-up period, were considered sufficient to oblige the Coordinating Committee for Concorde to allow patients to withdraw from allocated treatment to take open treatment with zidovudine if their CD4 count fell below 500. Ironically, the very constituencies that had created this perspective (USA investigators and the company) were the most vocal critics of the 'dilution' effect this was purported to have had on the Concorde trial when it was concluded!

In the succeeding years, it was generally felt by patients and clinicians, at least in Europe, that the continuation of Concorde was an essential, indeed the only, means of determining the long-term role of zidovudine in this setting of symptomless infection. As each Data and Safety Monitoring Committee (DSMC) review recommended 'carry on', so expectations of a valuable additional perspective mounted, though what that would be could only be (and was) guessed at.

After the Committee finally recommended cessation of the study, there was a 2 week period of silence, and members of these committees studiously refrained from explicit or implicit comment. Through prior arrangement, a brief but informative letter was prepared for and published in the *Lancet*, and its publication coincided with briefing for investigators, community groups and the press. International colleagues and organizations were given access to the same information. A similar process had previously been used for publication of preliminary data on the ALPHA trial on didanosine in advanced HIV disease by the same organizations, with a good measure of success.

However, it soon became apparent that the burden of these early Concorde results, indicating a lack of general benefit of zidovudine in asymptomatic HIV infection and hence a change from the prevailing view, was too much to be borne by such an inevitably brief publication. None the less, many felt it to have been more appropriate to present substantive data, albeit preliminary, in an international medical journal than at a press conference. The subsequent delay in publication of the main report inevitably compounded the problem, though this delay was also in large part a consequence of the conclusion, which was evidently and understandably less than welcome in some quarters.

The next forum at which more substantive data were seen, therefore, was not in a publication but at the Berlin AIDS conference. There, the high level of interest and the variety of settings in which they could be presented, meant that the study was very fully explored and discussed. It certainly contributed substantially to the dominant air of gloom and disappointment that followed that meeting. By the time the publication appeared many months later, again in the *Lancet*, most of the debate had occurred and most clinicians had discussed its impact with patients and resolved a way forward (though, as ever, there were many such ways).

No-one could claim that this sequence was an ideal solution, though it was probably greatly preferable to the earlier experiences with the Phase II study and ACTG 019. We need to determine what mix of such measures could be used to limit the real difficulties and uncertainties that resulted from the elongated timescale and the 'slow burn' of the supply of data.

An intruiging footnote to these events regards the changes in the company's share price between the DSMC decision and the announcement of the results. The publication of this graph in the Editor's choice column of the *British Medical Journal* caused much speculation about how this happened. Was this a pessimistic but uninformed piece of anticipatory share dealing or did people involved in the trial's analysis and oversight sell their shares and encourage others to do so? There has been no evidence to support this latter accusation: indeed, at this meeting the Editor of the *British Medical Journal* has shown that it seemed to be part of a general fall in pharmaceutical share prices, probably consequent upon concerns about the impact of USA health reform proposals on the industry in general. However, the speculation about what had been going on added to the prevailing cynicism about the motivations of the players in this process.

Early results from high profile and critical studies should be presented to the international scientific and medical community within a few weeks of the decision to stop a study, through a widely available scientific publication, such as a letter to the *Lancet*. There must be sufficient detail to allow clinicians and patients and others to make up their own minds about how this should inform therapeutic

decision-making, pending the definitive report based on the fuller validated data set following peer review. Formulation of treatment guidelines and policy decisions, including licensure, should if possible be deferred until after such publications, to avoid prejudging the conclusions. Dissemination of results to the press and the financial world should be in parallel with the initial scientific reports and must not be regarded as a sufficient means for public dissemination of such crucial information. Limited distribution of executive summaries, etc., to people attending meetings or to physicians in certain countries seem to me to be an inequitable and unsatisfactory compromise.

Dialogue between all the different players in this difficult process will certainly foster a better understanding of their differing perspectives and imperatives, and should avoid some of the worst examples of inappropriate publication. Finally, the errors that have been committed were probably not generally motivated by malign intent: rather they resulted from a limited perspective on a complex and emotive problem, and indeed by a well-meaning wish to herald good news.

DECLARATION OF INTERESTS

The author is a member of the MRC's AIDS Therapeutic Trials Committee and was Principal Investigator for the ALPHA study on didanosine. He had no involvement in the oversight, analysis or publication of Concorde. This article expresses his personal views and not those of the MRC or its committees. The author has received funding for conduct of small clinical and scientific studies and for attendance at scientific meetings from the Wellcome Foundation, but considers that at no time has this constrained his personal or scientific views.