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Review article

Clinical Trials – Past, Present and Future

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The modern concept of testing new treatments in randomised control trials began in 1948 when the Medical Research Council in the UK reported the results of a trial of streptomycin for pulmonary tuberculosis which had been organised by Drs D'Arcy and Daniels. However, even before this trial started in 1946, another randomised trial had begun to assess the effect of immunisation for whooping cough. In both studies, subjects were randomly allocated to the two arms of the trial and every attempt was made to 'blind' both the subject and the Physician so that assessment could be entirely objective. Even in the early years, there was considerable debate about the use of a placebo. The concept of randomisation was not new and was described in 1662 by van Helmont who advocated allocation to treatment groups by tossing a coin but it appears not to have been adopted into clinical practice. The idea lay largely dormant until R.A. Fisher began a series of experiments on agricultural crops in 1926 using methods of randomisation. The introduction of such methods back into clinical medicine was due to Bradford Hill who initially advocated in 1937 that treatments should be allocated to alternative patients but then in 1946 recommended randomised allocation to allow random error to be calculated and to avoid bias in selection.

Gastroenterology was perhaps the specialty that adopted these new approaches with the most rigour. Thus, in the 1950s a series of trials came from the Central Middlesex Hospital (led by Avery Jones) to test various treatments for peptic ulcer such as bed rest, diet and antacids. At the same time, Sidney Truelove and L.J. Witts were testing cortisone for the treatment of active ulcerative colitis. This seminal trial was followed by many others exploring the role of other steroid compounds, sulphasalazine, and topical therapy to name a few. Virtually all the trials in the 1950s and 1960s were designed by physicians, run by physicians and analysed by physicians. Nevertheless, the trials of the 60s were performed to the Ethical Standards laid down by the Declaration of Helsinki in 1964. Things began to change in the 1970s because new compounds were being developed by pharmaceutical companies and they wished to organise the pivotal trials. A number of events followed this process. There was a recognition within the scientific community that the number of patients entered into a trial had to be sufficient to satisfy power calculations which immediately increased the numbers needed for recruitment, especially if a new drug was being compared to standard treatment. Thus single centre studies became progressively more difficult. Secondly, competition between pharmaceutical companies became fierce with the advent of 'me-too-drugs (e.g. H_2-antagonists and b-blockers in the 1970s). This resulted in multi-centre trials in order to get quick results. At the same time, drug regulatory authorities became concerned about the design and process of trials, the statistical analysis and the ethical aspects. As a result, guidelines for trials were drawn up by, amongst others, the International Conference on Harmonisation and these were published as 'Good Clinical Practice' (GCP). These have been updated from time to time, the latest being in 1996. Then, Editors of journals became concerned that reports of clinical trials were not always fully transparent and full details of, for example, randomisation procedures were not always given (CONSORT statement). They were concerned that bias might occur as a result of an inadequately reported trial which could therefore be open to a range of interpretation. A checklist was published in order to assist Authors in writing up the data to ensure an acceptable report. This, like GCP, should help to raise standards and has indeed been helpful. However, one suspects that there is also a legal motive to protect the journal against potential litigation and it did not address the difficulty of publishing negative

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data however stringent a trial had been with regard to GCP and the CONSORT statement. When meta-analyses are performed, it is the failure of negative trials to be fully reported that can lead to a major bias. Thus, the standards of trials, both in their execution and in their reporting, should now be of high quality. Is that true? It is hard to answer the question with facts but it is almost certainly so. The CONSORT Group have preliminary evidence that reporting has improved and the very large trials concerning the management of acute coronary syndromes (e.g. ISIS and GISSI studies) have been superb models. Within Gastroenterology, trials on the management of bleeding ulcers from Hong Kong and the Crohn's disease trials from France by GETAID are also excellent examples, but there are many more that could be quoted.

However, all is not well and there are real problems which have largely resulted from these formalised attempts to proscribe design and methodology. Some of these problems are readily perceived by anyone who participates in any of the current trials.

1. Clinical trials have become extremely expensive and there is a considerable trend to devise complex studies so that several questions can be addressed simultaneously. This leads to unwieldy and complex Clinical Record Forms (CRF) which inevitably results in incomplete or wrongly entered data. Careful monitoring can overcome some of this but many trials have an undue proportion of discarded data because of 'protocol violations' which will include missing data.
2. The concept that data entered on CRFs should be checked against the originals in the hospital notes is good in terms of quality control. However, what has happened to the principle that hospital records are a confidential document between the patient and his/her Physician? I find it extraordinary that we now allow an independent Monitor to have free access to these Records.
3. In order to recruit large numbers quickly, most recent trials in Gastroenterology enrol very many centres who recruit only a few patients thus risking a very high degree of heterogeneity. Of course, it can be argued that if the numbers of patients recruited is large, randomisation will take care of the heterogeneity. Nevertheless, more patients from fewer centres still remains an ideal.
4. Pharmaceutical companies are naturally and sensibly very concerned about safety. This is manifested by large numbers of exclusion criteria. That, of course, makes rapid recruitment more difficult (leading to the inclusion of yet more Centres) but also leads to 'sanitisation' of the Trial such that the patients entered into the study barely resemble those that will eventually be treated in clinical practice. Many recent trials in patients with Crohn's disease have disallowed concomitant therapy with immunosuppressants such as azathioprine but relapses even while taking immunosuppressives are frequent and further therapeutic intervention is needed. It has been encouraging that the Infliximab trials have allowed concomitant medication as that truly reflects 'chronic active' or 'refractory' disease.
5. Endpoints of Trials can also be divorced from clinical practice. Until the National Cooperative Crohn's disease Study in the 1970s, no satisfactory trial in Crohn's disease had been performed largely because it was difficult to assess activity of such a heterogeneous disease. That all changed with the development of the Crohn's Disease Activity Index (CDAI) which allowed disease activity to be assessed by different physicians in different clinics with a reasonable degree of objectivity. It is far from perfect but has become the standard. However, how many gastroenterologists have an idea of what constitutes a fall in 70 or 100 points on the CDAI? Is that a clinically significant reduction in disease activity? Nevertheless, these are common endpoints in trials and even the National Institute for Clinical Excellence (NICE) in the UK has approved Infliximab usage for chronic active Crohn's disease on the basis of the CDAI or the simpler Harvey-Bradshaw index which was derived from the CDAI.
6. One of the most serious issues in Trials sponsored and run by Pharmaceutical companies concerns availability of data to the Investigators and publication agreements. According to GCP, all protocols should include a statement concerning subsequent publication. However, it is not always easy for the Investigators to obtain the raw data which then makes publication difficult. There is inevitably going to be occasional tension between academic freedom and commercial interests when the results of a study are not in line with expectation but scientific integrity should override all other considerations.

THE FUTURE

Despite their shortcomings, some of which have been alluded to, assessment of new treatments has become

more scientifically rigorous. However, the problems that have arisen are real and have occurred in many specialities. It is not easy to see how they can be overcome although common sense is clearly going to be crucial. Unfortunately, this may be difficult. GCP has recently become a European Directive and should become law in each of the Member States by 1st May 2003. Although the Directive recognises that it may need to adapt to scientific and technical progress, the exact means of doing so and the rapidity by which it can be done are by no means clear. Sadly, the introduction of 'guidelines' intended to be helpful and to raise standards has ultimately lead to ossification and rigidity.

Inspection of centres will also become more common. We have become used to the potential for inspections from the FDA to visit a centre that has taken part in a pharmaceutically sponsored trial. By all accounts, it is a harrowing experience as CRFs are gone through in detail, they are checked against the hospital records, and laboratory procedures closely scrutinised. The new Directive also demands that Member States of the E.U. appoint inspectors who will visit trial sites, manufacturing sites where the trial medication is made, laboratories where analyses are performed, and the Sponsors' premises. This will apply regardless of whether the sponsor is a pharmaceutical company or a Physician. Thus a site is potentially liable to be inspected by both the FDA and the E.U. Inspectorate.

We are heading for an over-regulated, rigid and cumbersome system generated partly by a genuine desire to improve standards but partly from a belief that no one is to be trusted where financial gain is at stake which includes sponsors and triallists. Urgent thought is needed to devise other systems. We may need to explore setting up University Departments devoted to running large trials – sponsors would fund the University but the trial would be conducted independently of the sponsor and the data would be held and analysed by the University. The Oxford Clinical Trials Service Unit originally established by Professor Sir Richard Doll and now run by Professor Sir Richard Peto is an excellent example of what can be achieved for the benefit of medicine as well as the sponsor.

SUGGESTED READING

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