Progress and problems for randomized clinical trials: from streptomycin to the era of megatrials

Lutz Hilbrich1* and Peter Sleight2

1 Medical Science Department, Boehringer Ingelheim Pharma GmbH & Co. KG, 55216 Ingelheim, Germany; and 2 Department of Cardiovascular Medicine, Level 5, John Radcliffe Hospital, Oxford, UK

Received 31 January 2006; revised 29 May 2006; accepted 29 June 2006; online publish-ahead-of-print 26 July 2006

Randomized clinical trials (RCTs) are the definitive contributors to evidence-based medicine. RCTs assessing serious outcomes in cardiovascular disease have grown, with ‘megatrials’ becoming more common with the realization that wrong conclusions resulted from random error in inadequately sized trials. Simple design and a heterogeneous patient population were early features, but multinational trials have increased in scientific, logistical, bureaucratic, regulatory, and legal complexity. These studies now exceed the financial means of academia or medical charities. Governments have left the bill with the pharmaceutical industry, encouraging a symbiosis with academics, who contribute medical and scientific expertise, and access to patients. Industry provides pharmacological, pharmaceutical, technical and regulatory know-how, good clinical practice expertise, and legal assistance during the trial. Study supervision is then in the hands of an independent steering committee and associated subcommittees, until appropriate dissemination of results. Prospectively defined interaction with the sponsor facilitates unbiased design and conduct, but arrangements need careful implementation to avoid conflicts of interest. The patient is protected by a strong data safety monitoring board that is wholly independent. Megatrials are under threat from over-regulation, increasing costs, and difficulties in execution. These issues merit urgent public and political education and debate.

Introduction

Dramatic treatment effects, such as that of penicillin on streptococcal infection, do not need to be tested in trials. Very effective treatments (e.g. streptomycin in tuberculous meningitis) were demonstrated by randomizing small numbers of patients in one of the fore-runners of modern trials.1 The situation is different when treatments have much less dramatic incremental benefit. Conducting randomized clinical trials (RCTs) in large, heterogeneous patient populations overcame the problem of variations in baseline characteristics, concurrent treatment, and concomitant clinical practice. The likelihood of a balanced distribution in the different treatment groups not only for measured baseline variables but also for unmeasured factors was greater. The consequent increase in statistical power allowed identification of moderate, but clinically worthwhile, benefits to the patient. Very large, so-called ‘megatrials’ were also better able to identify serious, although rare, adverse events.

Megatrials have their critics.2,3 Some argue that the necessary reduction of the standard of experimental control (in order to recruit large numbers) introduces a methodological deficiency and believe that bigger patient numbers do not compensate for the diminished control, deficiencies in trial protocol, and the simplicity of the design. Others hold that simplification can be achieved without significantly affecting experimental control or validity of the results.4 The latter view has prevailed; now, many experienced groups are conducting such studies worldwide. Without randomization, we would not have been able to correct the widely believed observational data on hormone replacement therapy, calcium channel blockers, or vitamin supplements.

Despite the undoubted contributions of megatrials, their future is threatened. This review highlights the current difficulties and suggests some remedies in the light of the authors’ joint experience in industry and academia. Some of the points we make are common to all trials, but many are specific to very large studies with increasing collaboration between academics and industry.

Emergence of megatrials

The relatively recent development by the pharmaceutical industry of many new remedies, especially for common conditions such as cardiovascular disease, led to the need for their proper assessment. At first, surrogate endpoints such as blood pressure were used; it was thought that employing unequivocal (i.e. "hard") clinical outcomes would be impossible because of the difficulty of distinguishing between the
International trials

Randomization Issues

Initially, randomization was simple (e.g. by envelope, date, or hospital site), or by other means. All these procedures are currently avoided by minimization algorithms. An even balance is thus achieved between groups for all measured baseline characteristics and important, unrecorded factors.

Eligibility criteria may be set too low or too high, depending on the disease. Many trials only address the disease, whereas others may include any patient with a diagnosis, regardless of severity or treatment status. This may lead to the inclusion of a diverse gene pool, plus the benefit of extensive hospital facilities, but has the potential to bias the results.

Enrollment issues arise when patients are not willing or able to participate. This may be due to the nature of the disease, the procedures involved, or the duration of the trial. "Recruitment" is often a challenge, and may require the use of "minimization" algorithms to balance the groups effectively.

For example, the number of patients needed to be enrolled in a trial depends on the severity of the disease, the expected number of events, the potential differences in dosing due to lower body weight, and the financial burden. Ethical and patient protection issues

Detection and monitoring of fraud

Modern trials often involve the use of sophisticated data analysis techniques to detect any signs of fraud. For example, if the data from a given center is significantly different from the data from other centers, this may suggest the possibility of fraud and the need for closer scrutiny.

In addition, regular monitoring of the data is crucial to ensure that the results are reliable. Data protection issues

Data collection procedures for the proper investigation of such uncommon but destructive practices are crucial. On-site monitoring is commonly used, but adds hugely to costs and rarely detects fraud. In this context, "minimization" algorithms are used to ensure that the groups are balanced.

Increasing measures in Europe and the USA designed to protect patients from clinical practice as "trials. " It is thus no longer possible to search these records for suitable trials, unless they have been given prior permission to do so. This is an over-reaction and goes against the principles of patient autonomy. Patients have not been consulted regarding their inclusion in trials.

China can make its contribution to the trial process as a whole and the burden of stroke will escalate in these countries. The Chinese government has recognized this and is actively promoting the use of large trials in China. This will encourage the development of robust clinical practice guidelines and help to ensure that patients receive the best possible care.

Conclusion

Megatrials have shown that large, complex diseases can be effectively treated with simple and widely practicable procedures. However, the costs and time required to conduct such trials are significant. Therefore, it is essential to carefully consider the benefits and risks of each trial, and to ensure that the results are meaningful and can be applied to a wide range of patients.

The future of trials

The increasing use of technology in trials has made it easier to collect, analyze, and protect data. However, there are still concerns regarding patient protection and the ethical implications of using trial results. It is important to continue to develop new methods to address these issues and to ensure that the results of trials are used to improve patient care.

The International Journal of Cardiology

Acknowledgments

The authors wish to thank all the colleagues and institutions who have contributed to the success of the trials discussed in this review.

References

wishes on these issues. The new regulations have imposed largely unnecessary logistic and financial burdens, which will sound the death knell for academically driven trials.\textsuperscript{21} These well-meaning, but counterproductive, regulations should be revisited as a matter of urgency, with emphasis on public consultation, political education, and lobbying.

Ethical approval for multinational trials still needs streamlining. Currently, multiple photocopied of a central protocol have to be distributed to hundreds of local committees. This is no mean undertaking, but obviously each committee wishes to be seen to be vigilant. There are also problems with an increasing demand from ethical committees for an ‘opt-in’ requirement for patient recruitment, rather than the more laissez-faire ‘opt-out’ approach.\textsuperscript{26} The former recruits less-sick patients, with effects on statistical power and costs.\textsuperscript{22} In practice, even within one country, such as the UK, there is a vast variation in what local ethics committees demand. There are even inexplicable and costly differences between centres in the same local region.\textsuperscript{22}

**Informed consent**

Explicit consent requirements can seriously bias the results in observational studies.\textsuperscript{23} The need for (or indeed legitimacy of) detailed consent to treatment information in very sick or sedated patients is currently the subject of wide debate sponsored by the UK General Medical Council. Professor Harris suggested that it might help to offer a patient the choice between a detailed or a simple, leave it to the doctor, consent procedure.\textsuperscript{24}

**The uncertainty principle**

Ethics of all randomized trials have been questioned, because trial organizers usually begin a study with the belief that the new treatment will be better.\textsuperscript{25} Most maintain that it is equitable to randomize, provided that the randomizing physician has been informed concerning the patient’s baseline characteristics and investigation results, together with information on current guidelines, and then is genuinely uncertain about the best option for a particular patient.

**Informing patients of the results of their trial**

At the end of the trial, it seems a matter of common courtesy to communicate the findings to the patients. However, a recent editorial highlights some of the difficulties in framing the information in an acceptable way.\textsuperscript{26} The editorial suggests that there is a need for further debate and discussion.

**Funding of megatrials: conflicts of interest**

To achieve statistical power, patient numbers have expanded, so that it is now relatively common to enrol more than 10,000 patients into a study. Examples of recently reported megatrials are listed in Table 1.\textsuperscript{14,27–37} For studies such as these lasting several years, reliable funding is essential, but government agency-sponsored megatrials are not the norm. Notable recent exceptions to the rule are the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT),\textsuperscript{27} sponsored by the National Heart, Lung, and Blood Institute, and the Heart Protection Study,\textsuperscript{38} jointly supported by the UK MRC and the British Heart Foundation; even in these studies, a major part of the costs was met by industry. Government or national agencies, such as charities, are generally unwilling to fund studies partly conducted in other countries, and obtaining and coordinating matching grants from numerous international bodies is virtually impossible. Even within a single country, it may be quite difficult to obtain adequate funding for important clinical trials. In view of the public-health importance of adequate evaluation of treatment, this official neglect is scandalous.

**Need for independent core funding for established trial organizations**

At the very least, the key personnel (statisticians, programmers, epidemiologists, administrators, team leaders) in one

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Mean duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT\textsuperscript{27}</td>
<td>42 418</td>
<td>Randomized, double-blind (antihypertensives)</td>
<td>6 years</td>
</tr>
<tr>
<td>ASCOT\textsuperscript{28}</td>
<td>19 257</td>
<td>Randomized, open label (lipid-lowering drugs)</td>
<td></td>
</tr>
<tr>
<td>COMMIT/CSS-2\textsuperscript{14}</td>
<td>45 852</td>
<td>Prospective, randomized, open label, blinded endpoint trial</td>
<td>5.5 years (median)</td>
</tr>
<tr>
<td>EUROPA\textsuperscript{29}</td>
<td>13 655</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>4.2 years</td>
</tr>
<tr>
<td>HOPE\textsuperscript{30}</td>
<td>9 541</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>4.5 years</td>
</tr>
<tr>
<td>INVEST\textsuperscript{31}</td>
<td>22 576</td>
<td>Randomized</td>
<td>2.7 years</td>
</tr>
<tr>
<td>LIFE\textsuperscript{32}</td>
<td>9 193</td>
<td>Randomized, double-blind</td>
<td>4.8 years</td>
</tr>
<tr>
<td>NORDIL\textsuperscript{33}</td>
<td>10 881</td>
<td>Randomized, open label, blinded endpoint</td>
<td>5 years</td>
</tr>
<tr>
<td>PEACE\textsuperscript{34}</td>
<td>8 290</td>
<td>Randomized, double-blind</td>
<td>5 years</td>
</tr>
<tr>
<td>SYMPOXY\textsuperscript{35}</td>
<td>9 233</td>
<td>Randomized, double-blind (sibrafiban, aspirin)</td>
<td>90 days</td>
</tr>
<tr>
<td>VALIANT\textsuperscript{36}</td>
<td>14 703</td>
<td>Randomized, double-blind</td>
<td>24.7 months</td>
</tr>
<tr>
<td>VALUE\textsuperscript{37}</td>
<td>15 245</td>
<td>Randomized, double-blind</td>
<td>4.2 years</td>
</tr>
</tbody>
</table>

ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; COMMIT/CSS-2, Clopidogrel and Metoprolol In Myocardial Infarction Trial/Second Chinese Cardiovascular Study; EUROPA, European trial on Reduction Of cardiac events with Perindopril in stable CAD; HOPE, Heart Outcomes Prevention Evaluation; INVEST, International Verapamil SR/Trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; NORDIL, Nordic Diltiazem study; PEACE, Prevention of Events with Angiotensin Converting Enzyme inhibition; SYMPOXY, Sibrafiban vs. aspirin to Yield Maximum Protection from Ischaemic Heart events post-acute coronary syndromes; VALIANT, Valsartan in Acute Myocardial Infarction Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.
or two proven trial organizations in a given country should have independent and long-term funding. This ensures that their expertise is not squandered if funding for the next trial is delayed. This funding should be from government and/or some other independent or charitable foundation.

Megatrials have evolved into a symbiotic relationship between academic groups and the pharmaceutical industry.49 We believe that there is currently no viable alternative. At present, all health services, whether private or public, spend enormous amounts of money on drugs to control risk. Curiously, these services are reluctant to evaluate systematically whether or not this expenditure is worthwhile. The investment of a small percentage of their budget would solve the current problems of public funding of trials.

Problems of industry-funded research

Industry is naturally motivated by profit and not primarily interested in the testing of non-patented treatments. However, many non-patented treatments, from aspirin through magnesium, heparins, vitamins to fish oil, have been successfully tested in factorial trials funded by industry.

The relationship between clinical investigators and the pharmaceutical industry has been described as an ‘uneasy alliance’, with the accusation that academic/industrial trials are ‘tainted by the profit incentive’.40 Experience shows, however, that the collaboration of academicians with commercial enterprises can prove highly effective and beneficial to the patient, provided that both parties carry out their roles with clarity, coherence, and mutual respect.41 To achieve this, development of clearly defined and transparent structures is fundamental, with built-in safeguards from an experienced and tough DSMB, with external audit provided by academic experts and regulatory authorities.

Everyone gains from such structures, as the academic interest generated by the inclusion of another component raises interest and, hence, collaboration and recruitment. The authors propose that the inclusion of representatives from medical societies, such as the European Society of Cardiology, would further help to minimize industry bias. In our experience, it is also helpful to have the co-sponsorship of other well-respected organizations, such as medical charities or government research organizations.

Trial design

Trial design may be sub-optimal in some cases, with a comparison of the newest remedy against an older drug (e.g. newer antihypertensive vs. older drugs, such as beta-blockers or a diuretic), or a newer version of an older drug of the same class (generally produced by another pharmaceutical industry). In these cases, the steering committee has failed to insist on a more relevant comparison, or has failed to convince the sponsor.

Publication issues

Publication of unfavourable results may be impeded by a pharmaceutical company and partially account for the low publication rates of negative trial results.42 Some responsibility also falls on journal editors, who too often refuse to publish negative trials. This should now be remedied by two recent initiatives: the need for the publication of the protocols of all proposed trials including details of the trial sponsor (the International Committee of Medical Journal Editors published a joint editorial in September 200443 to promote registration of the protocol of all clinical trials, and this proposal has now been instigated44); and the offer of the Public Library of Science to publish negative trials in PLoS Clinical Trials.45 The industry sponsor will now have nothing to gain, except a bad reputation, by delaying or suppressing publication of results, because the medical community will automatically assume that the results are unfavourable for the sponsor.

Misrepresentation of data

The results from industry-funded trials have been accompanied by simultaneous or contiguous articles exploring other interpretations of the original data.28,29 Many readers are unaware that these are non-randomized analyses of the original randomized trial.46,47 These analyses may or may not be condoned by the steering committee, which should automatically have access to all study data. A remedy, suggested by one of the present authors, would be to have the data safety monitoring board (DSMB)—who have probably spent more time than anyone else considering the data—sign off the publication, thus indicating that the publication is acceptable.48

However, these criticisms and conflicts of interest may not be confined to industry trials. The US government and trialists’ interpretation of ALLHAT27 has proved controversial, as the primary endpoint of coronary heart disease was identical for chlorthalidone-, lisinopril-, and amlodipine-based treatment, despite lower in-trial blood pressure control with the diuretic.49 In a government-funded study, it was clearly acceptable to favour the cheapest alternative.

Harmful consequences of recent regulatory changes

Enrolment difficulties

One easy way of reducing the size and cost of a trial is to recruit subjects with a known disease or who are older and more likely to experience events. The approach was used by the Heart Protection Study,38 but is now frequently barred on the basis of patient privacy. The patients themselves have not been consulted regarding the protection of their privacy. Not only clinical trials but also valuable epidemiology are threatened by this new regulatory attitude.

Sponsorship and contract issues

Now, in the EEC, a trial is required to have a ‘sponsor’.50 This does not pose a problem for industry but is a major hurdle for universities or health authorities who are not geared for such a role.

Critical role of the DSMB

Credibility is an essential requirement of any clinical research. The adherence to good clinical practice guidelines, such as those issued by the UK MRC51 and International Conference on Harmonisation,20 safeguards the study population. Little has been published about the
practical experiences of DSMBs, which is a pity, as these accumulated examples could be informative. A UK government-funded study group, Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES), has recently published sensible guidelines for DSMBs. We believe that the role and composition of the DSMB is absolutely crucial to the proper conduct of clinical trials.

The members should be seen to be truly independent of industry pressures. DSMBs should be composed of respected figures, unafraid of unpopular action to terminate a trial if there is evidence of harm in any group. They should include a statistician and physicians knowledgeable about the clinical issues and be able to assess an ongoing trial in the light of other emerging data. They should resist rigid statistical stopping rules and should have the ability to judge whether or not a trial should continue, even if a stopping boundary is reached, if they judge that the result at that point would be insufficient to sway clinical opinion. They should keep minutes of meetings and reasons for decisions and consider disseminating these when the trial results have been published. An important function is to ensure that the conduct of the trial, data collection, and trial procedures are efficient; it is unethical to allow a trial to continue if it is clear that the poor execution will jeopardize a meaningful analysis.

Another issue which we have found to be increasingly frequent is that the regulatory authorities in a given country may demand detailed information about specific results, as a consequence of their receiving possibly unbalanced data on some serious adverse event, such as renal failure. Serious adverse events have by law to be reported promptly by industry to the regulatory authorities, but the authorities remain ignorant of the real hazard/benefit equation! In our experience, this may jeopardize a trial, as the hazards are publicized although the benefits remain unknown. The DSMB needs to be firm in resisting requests for the release of further data. At the same time, DSMB members need to be tactful and mindful of the perceived (although usually misguided) anxieties of government agencies. The stature and perceived independence of the members help greatly in this confrontation.

Advantages of industry-sponsored collaboration

Industry provides in-depth knowledge of the products to be tested, as well as financial, organizational, logistic, regulatory, good clinical practice and legal support. A survey of clinical trials published in five leading medical journals reveals that the percentage of industry-sponsored clinical trials increased from 26% of the total between 1981 and 1984 to 62% during the period 1997–2000.

Steering committee as the final arbiter

To avoid any industry bias, it is imperative that the design, implementation, data analysis, interpretation of results, and publication of a megatrial’s findings be guided exclusively by an independent steering committee. This decision-making body is assisted by its subcommittees, such as the Substudy and Publication Committees, as well as being supported by the DSMB and the Adjudication Committee (Table 2). In the case of cardiovascular trials, there is a stronger tradition of independent input by a steering committee than for trials investigating most other diseases.

The function of the steering committee is to make all major decisions on scientific, medical, statistical, ethical, and practical issues, taking into account the recommendations of the associated committees and subcommittees and observing the requirements of the regulatory authorities. The steering committee should include internationally recognized medical/scientific experts. Ideally, there should representatives from the different geographical regions/countries. If included, representatives of the sponsoring pharmaceutical company may serve purely in an advisory capacity with no vote (although few committees actually vote in a formal way).

Table 2 Committees/subcommittees reporting to a megatrial steering committee

<table>
<thead>
<tr>
<th>Committee/subcommittee</th>
<th>Responsibilities</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publications</td>
<td>Coordinating publications arising from the trial</td>
<td>Academic and pharmaceutical company representatives</td>
</tr>
<tr>
<td></td>
<td>Ensuring timely and accurate publication of the results</td>
<td></td>
</tr>
<tr>
<td>Substudies</td>
<td>Identifying additional substudies in a subset of the patients and analysis of the data prior to the closing of the database</td>
<td>Academic and pharmaceutical company representatives</td>
</tr>
<tr>
<td>Drug Safety Monitoring Board</td>
<td>Evaluating outcome and safety data in the light of emerging data from other trials Identifying problems in trial conduct, enrolment, sample size, patient compliance, and data collection Establishing guidelines to protect the safety of the participating patients</td>
<td>Experts in the trial’s therapeutic field, biostatistics, ethics, and clinical trials; strictly independent of steering committee and sponsoring company</td>
</tr>
<tr>
<td>Adjudication and assessment</td>
<td>Confirming primary and predefined secondary outcomes while the data are still blinded</td>
<td>Academic representatives only</td>
</tr>
</tbody>
</table>
Role of the pharmaceutical company

The development of the protocol is a joint venture, but it has to be acknowledged that, if the industry partner does not agree with the protocol, the trial would not be funded. Both the steering committee and the industrial sponsor ensure that the regulatory requirements are met. The steering committee is ultimately responsible for approving the protocol. At the planning stage, the sponsor makes key contributions to what can be very time-consuming activities. Compilation of regulatory documentation, provision of medications, shelf-life testing, blinding, labelling, packaging, and distribution of the drugs to the study centres can be performed by the pharmaceutical company without influencing the study design and its results. This expertise, country-by-country, considerably lightens the burden of the steering committee.

The credibility of the results is greater when the steering committee and industrial organization are competent to collect and collate the data, or do so via an independent statistical organization. There is a perception that, in those cases where the company has access to the data at any time, it might make decisions that protect its financial interests; so, until completion of the study, industry access to the data should be restricted. In those cases where industry insists on collecting the data, there should be firewalls between the marketing department and statistical analysts/data managers. Industry can assist in the statistical handling of the blinded data in accordance with the procedures outlined in the protocol. Exclusive control of the study data by the pharmaceutical company is avoided by the steering committee using their own statisticians to rerun the analyses. It goes without saying that the academic investigators should be seen to have no financial interest in the results of the trial, particularly stock ownership or options.

Conclusions

Close collaboration between academic bodies and industry has been very successful in the development of new cardiovascular drugs and/or exploration of new indications. There remains a need for further large-scale RCTs in cardiovascular medicine but, importantly, there is a great need for similar studies in other medical specialties.

Recommendations for the relationship between the sponsors and the investigators in the design and conduct of clinical trials in stroke have been recently published. The establishment of subcommittees with experts in all key aspects of the conduct of clinical trials provides multiple levels of supervision and guidance to ensure robust data quality, reliable results, credibility, and transparency.

Both industry and academics need urgently to address the recent legislation that currently threatens the viability of future trials. Most importantly, we need to examine issues of recruitment, informed consent, and the balance of public health vs. over-regulation based on ill-perceived protection of patients. Above all, we need, as a matter of extreme urgency, to involve both the general public and political leaders concerning these current dangers to unbiased research. Fortunately, in a recent issue of the British Medical Journal, there now seems to be a genuine willingness to address these issues constructively, albeit with obvious delays and harm to large-trial recruitment during the period of debate.

Conflict of interest: none declared.

References

24. Davies J. Doctors should be allowed to offer patients a simplified form of consent, expert says. BMJ 2005;331:925.
49. Tavazzi L. Evidence-based therapeutic strategies. There is the need to bridge the gap between simplified megatrials and individual prescrip- tions. Circulation 2001; 103:767–772.