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Cluster randomised trials: time for improvement

The implications of adopting a cluster design are still largely being ignored

Cluster randomised trials, where groups of patients rather than individuals are randomised, are increasingly being used in health services research. Randomisation by individual is inappropriate for evaluating some interventions, such as organisational changes, where it may not be feasible to randomise at the patient level. In such cases cluster randomisation at the level of the health professional or organisation is necessary. Such randomisation can also minimise the potential for contamination between treatments when trial patients are managed within the same setting.

The main consequence of adopting a cluster design is that the outcome for each patient can no longer be assumed to be independent of that for any other patient (which is the case in an individually randomised trial). Patients within any one cluster are more likely to have similar outcomes. For example, the management of patients within a single general practice is more likely to be consistent than management across several practices.

This lack of independence has implications for the design and analysis of these trials.[1] The statistical power of a cluster randomised trial is greatly reduced in comparison with a similar sized individually randomised trial. Therefore standard sample size estimates have to be inflated to take account of the cluster design.

The impact on sample size can be substantial and depends on the size of the clustering effect and the number of clusters available. The clustering effect would be high if, for example, management of patients within individual hospitals was very consistent but there was wide variation across hospitals. Consider a trial of an educational intervention to implement a clinical guideline. A patient randomised trial would require 194 patients to detect a change from 40% to 60% in the proportion of patients who are managed appropriately (with 80% power and 5% significance). However, this design would be inappropriate because of the potential for contamination. For a cluster randomised trial with a moderate clustering effect and 10 available patients per cluster the equivalent sample size adjusting for clustering is 38 clusters or 380 patients—that is, almost double.[1]

The analysis of cluster randomised trials must also take into account the clustered nature of the data. Standard statistical techniques are no longer appropriate, unless an aggregated analysis is performed at the level of the cluster,[2] as they require data to be independent. If the clustering effect is ignored P values will be artificially extreme, and confidence intervals will be over-narrow, increasing the chances of spuriously significant findings and misleading conclusions.

Although an aggregated analysis can be performed at the cluster level using standard statistical tests, this approach is statistically inefficient. Furthermore, it does not allow variation at the patient level to be explored—for example, it cannot take account of patient characteristics such as disease severity. More advanced techniques have now been developed to analyse patient level data arising from a clustered design, which allow the hierarchical nature of the data to be modelled appropriately.[3] They essentially allow variation to be modelled at each level of the data—for example, at both the practice and the patient level.

Despite the increased use of cluster randomised trials, the implications of adopting such a design continue to be largely ignored. For example, a review by Devine et al which examined studies of physicians' patient care practices observed that 70% of studies identified had not appropriately accounted for the clustered nature of their study data.[4]

Many trials do not take cluster randomisation into account when calculating the required sample size, resulting in studies which are underpowered. This may, in part, be explained by the lack of published information on the likely size of the clustering effect, known as the intracluster correlation coefficient.[5] Reliable estimates of this coefficient are required to ensure robust sample size calculations, yet publication of intracluster correlation coefficients in trial reports is rare.

We need a standardised approach to the reporting of all aspects of cluster randomised trials, including intracluster correlation coefficients. The CONSORT statement for standards of reporting of patient randomised trials[6] has improved the reporting of such trials, and a similar approach for the reporting of cluster randomised trials would be beneficial. A letter to the *BMJ* highlighted the need for such an approach,[7] and a proposed amendment to the CONSORT statement is being formulated. We believe that this will aid the appraisal of published trial reports and the planning of future research. It deserves the full support of the medical research community.

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Being a modern pharmaceutical company

Involves making information available on clinical trial programmes

What does it mean to be a modern pharmaceutical company? Rapid changes in society and advances in science and medicine mean that the pharmaceutical industry has several important roles today that would not have been apparent as recently as 10-15 years ago. To provide medicines of value the modern pharmaceutical company has to meet the needs of patients for better medicines while taking full account of the realities of healthcare economics. It has to harness scientific advances, particularly in genetics and information technology, and work in partnership with researchers, healthcare providers, and governments. One substantial outcome of these partnerships is a better understanding of the need for openness and transparency in clinical trials.

For healthcare providers the cost of health care is a paramount issue, and the industry knows that new medicines have to deliver real benefits over existing ones. Delivering better medicines—demonstrated by the right clinical studies, with the right comparators and demonstration of appropriate dosages and use—is exciting but is accompanied by dilemmas which have to be faced and resolved. Society expects the industry to behave responsibly and to disclose information whenever possible.

Decision makers clearly want more access to information on clinical trials. Our industry is based on a rigorous process of conducting, analysing, and reporting clinical trials—a task we undertake as part of the regulatory approval system. By law we are required to include all trials involving a product in the regulatory submission for that product. The problem for decision makers and prescribers is that much of this information is not in the public domain. We have traditionally relied on a long established process of submitting trials to peer reviewed journals as a way of presenting data to the medical and healthcare communities. That process of peer review is important and should continue, but we can certainly improve on the timeliness and tracking of information and help avoid bias in reporting clinical trial data. The internet offers great scope for disclosing information: it is searchable, quick to access, and has global reach.

GlaxoWellcome has introduced a policy of registering information on its future clinical trials programmes. The objective of this policy is to help those undertaking systematic reviews of clinical data and to help reduce the impact of publication bias.[1 2] We have committed to register clinical trial protocols so that they are accessible to healthcare professionals and researchers outside the company. Our policy applies to all studies undertaken by GlaxoWellcome worldwide. In future, protocols for completed phase II and III studies will be registered around the time of regulatory approval and the register will then be updated at least annually with protocols for our largescale phase IIIb and IV studies. The first trial details are available on a password protected area of the new GlaxoWellcome external research and development website (science.glaxowellcome.com).

We have also committed to publishing all clinical trials, as far as this is possible, and will assign a unique identifier to each trial which may be included in all subsequent publications. This will help those undertaking systematic reviews to identify duplicate publications and thus avoid any impact this might have on the estimation of efficacy via meta-analysis.[3]

Pharmaceutical companies cannot, however, solve the problem of publication bias alone. All those undertaking research need to make similar commitments—indeed the recent guidelines from Britain's Medical Research Council on the performance of clinical trials highlight the need to publish the results of all studies.[4] The editors of medical journals also have an important role, and progress in electronic publishing would increase the speed of publication and reduce the potential for lack of space to influence the inclusion of a study.

Disclosure of clinical trials may have additional benefits. The reorganised NHS research and development programme has concentrated research funding in Britain on areas important to the NHS itself. A comprehensive register of clinical trials will improve communication about what research is taking place, so that duplication can be avoided and resources used more effectively.

GlaxoWellcome has taken the lead in disclosure of information, and I hope that the rest of the pharmaceutical industry will join this initiative. As a knowledge based industry we understand well the value of information, and we want to create a climate of openness where the evidence for prescribing our products is clear.

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