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Societal responsibilities of clinical trial sponsors

Lack of commercial pay off is not a legitimate reason for stopping a trial

A large long term randomised trial is a substantial commitment by its sponsor, its principal scientific investigators, a complex international organisational structure, and the patients who agree to participate. For trials with commercial sponsorship, the company’s business need—to demonstrate their treatment’s advantage—should not conflict with society’s need to enhance knowledge by conducting trials with

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unbiased designs and reporting results without statistical distortion. For both trial sponsors and investigators a tension exists between the “demonstrators” (I want to prove that…) and the “scientists” (I want to find out if…). The goal of regulatory guidelines, and indeed the best intention of sponsors, is to ensure that the scientific search for truth of public health relevance is what actually wins through. Another crucial ethical requirement is that no patient should be knowingly harmed by participating in a trial: hence any trial should stop as soon as the primary answer is clear. A paper in this week’s BMJ (p 605) raises the issue of when else a trial might legitimately be stopped.

Most major trials have an independent data monitoring committee that periodically and confidentially inspects accumulating results for evidence of treatment benefit or harm sufficient to merit stopping early. Statistical stopping guidelines exist for data monitoring committees, and their collective wise judgment requires very strong evidence of a new treatment’s superiority in order to stop early. If a new treatment appears harmful, such evidence “in the wrong direction” usually needs not be so overwhelming to stop the trial.

A trial may also be stopped early on grounds of scientific futility—that is, if the interim confidence interval for the primary treatment difference is much more pessimistic than some minimum required true benefit. Even though there is no clear evidence of inferiority, the trial can validly be stopped because of an inadequate gain in efficacy. Some prefer a conditional power argument whereby if the interim data indicate that statistically significant benefit is unlikely to be achieved on completion of the trial then the trial may stop early. However, this perhaps undesirably shifts the balance of intent back to the “demonstrators” rather than the “scientists.” External evidence, usually arising from other trials, may also justify discontinuing a trial because the questions posed by the trial have now been answered.

Less desirable circumstances are when a trial is proceeding unsatisfactorily. For instance, inadequacies in patient recruitment, compliance with treatment, or quality of trial organisation can be serious enough to affect a trial’s viability. Though errors of judgment and bad planning are regrettable, the ethical stance should be not to prolong research that “is going nowhere.” This may also be important to non-commercial sponsors with limited resources.

A different situation arises when the sponsor’s error of commercial judgment rests in having started the trial at all, as appears to be the case in the FAME trial described this week by Lièvre et al. Though such a trial poses an important public health question—does lipodystrophy with fluvastatin reduce the risk of cardiovascular events in elderly people?—the sponsor thought that the commercial pay off of a positive result became compromised by the fact that a similar trial of another statin would finish earlier. From the sponsor’s perspective this is also a “trial going nowhere” but the difference is that it relates to commercial goals rather than the scientific and public health intent, which were still achievable.

Is such loss of interest by the sponsor another valid circumstance in which to stop a trial early? In general, we think not. It dangerously implies that business needs can override both scientific intent and the ethical obligation to patients already randomised. Are there any mitigating circumstances or compromise positions? For instance, does one need two large trials of essentially the same issue or could the class effect of statins in the elderly be inferred from one definitive trial? Could the FAME trial have been pared down by completing follow up on patients already randomised and combining this evidence with the other trial in a meta-analysis? Could one argue that the scientific question’s originality is compromised by the other trial’s existence? We mention these issues in a spirit of constructive debate, recognising that it is all too easy to criticise commercial sponsors while clinical and scientific collaborators also have their needs and disappointments that are not only about scientific altruism.

Nevertheless, it is commercial sponsors who most seriously have to juggle the need for profit and the research goal of societal benefit. It is great when the two coincide but potentially ghastly when they conflict. Though stopping a trial early for inappropriate commercial reasons is clearly undesirable, it is not the most serious fault relating to company sponsored research. One could argue that it is worse to plan trials in a way that could hide a treatment’s potential inferiority. For instance, it has been argued that the PROVE-IT trial comparing pravastatin with atorvastatin in coronary heart disease has too short a follow up to distinguish between true equivalence of patient benefit and a treatment difference emerging after several years. Also, trials may inadequately document a treatment’s side effects because it is not in the sponsor’s interest. Lastly, many opportunities exist to exaggerate the true benefits of a treatment by statistical manipulation or post hoc prioritisations in trial reports or by overzealous marketing after regulatory approval.

Thus, the issue faced by companies, regulators, the scientific community, and society is to recognise potential conflict between the profit motive in a capitalistic society and public health needs. The profit motive has aided the development of many treatments of much benefit to society. The general moral question is how we ensure that the profit motive is kept in check so that it is not at variance with patients’ best interests, whether by enrolling them in trials going nowhere, as in FAME, or, perhaps more importantly, drawing biased conclusions on benefit and harm from less than ideal clinical trials.

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