Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility

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When investigators embark on a clinical trial, they naturally expect that the journey will end with the completion of the scheduled patient follow up and publication of the results. Some trials may sink en route because of organisational or ethical reasons, and such misfortunes must be accepted. Sometimes, however, trials are scuttled by their sponsors. Such premature discontinuation not only is frustrating for investigators but may have important medical implications. In this article we analyse the case of a clinical trial that was recently stopped for financial reasons, discuss the consequences of such discontinuations, and make some proposals to avoid recurrence.

Recent example

Although two trials have shown the efficacy of statins for primary prevention of cardiovascular disease in middle aged people with hypercholesterolaemia,^{1,2} the benefits and costs of such treatments in older men and women are unclear, especially in low cardiovascular risk populations.³⁻⁵ In April 1997, a group of French academics submitted to several pharmaceutical companies the protocol of the first placebo controlled trial of a statin for primary prevention in hypercholesterolaemic men and women aged 70 to 85 in low cardiovascular risk countries. Novartis agreed to fund the study in June 1998, when the company executives were convinced that this study was the best of several possible outcome trials with the new 80 mg, modified release form of fluvastatin. The study included an assessment of cognitive function and cost effectiveness. The follow up of 5400 patients recruited over 18 months was planned to end in the summer of 2004, when 425 main outcome events (death from a cardiovascular origin or non-fatal myocardial infarction or stroke) should have been observed. The study was due to start in November 1998 but was delayed by administrative problems. Recruitment began in Belgium in April 1999, and soon followed in Israel, Spain, Italy, and two big French general practitioner networks with about 1100 doctors. After a slow start, recruitment took off in October 1999 and soared thereafter.

On 21 December 1999, 1208 patients had been randomised, 286 were eligible and waiting for randomisation, and 1211 had been declared ineligible after central biological assessment. At this time, however, Novartis decided to discontinue the study. This decision was communicated orally to the chairman of the steering committee. On 28 January 2000, the steering committee was told that the study had been stopped because it was feared that a similar trial of pravastatin in primary and secondary prevention in the elderly would reach its conclusion before the fluvastatin trial (although it had been launched at the same time) and "the internal and external environment had changed around Lescol."

Summary points

Some trials are discontinued prematurely by their sponsor for strategic reasons

Clinical trials should be discontinued only for reasons pertaining to efficacy, safety, or feasibility

Premature discontinuation of trials for strategic reasons deceives the patients, jeopardises the patient-doctor relationship, and harms the medical community

Giving more power to steering committees that are mostly independent of the sponsor and include patient representatives, may limit the risk of premature discontinuation of trials for strategic reasons

Public financial and scientific participation in some trials and increasing the length of patents may be useful

The company said it was necessary "to reallocate resources from Lescol to the newer growth assets" and cited "the competition entering the elderly segment" (Novartis, personal communication).

Legitimate and other reasons for discontinuing clinical trials

Clinical trials should not be discontinued before the results of the first interim analysis are available unless there are sound and pressing reasons. Many trials are stopped early because of recruitment failure, either because organisation is inadequate, funding does not match the incurring costs, or target patients are so rare that it is impracticable to recruit the required sample. This was obviously not the case in the fluvastatin study because 701 patients had been randomised in the 30 days preceding the discontinuation of the trial and there were several hundred active investigators.

Trials may also be interrupted prematurely because new findings are available regarding efficacy or safety that make them either superfluous or unethical. This was not the case either: no results are available yet for primary prevention with lipid lowering drugs in elderly people and there is no particular concern about the safety of statins in this population. The decision to discontinue the study was therefore made essentially on the grounds of a global marketing strategy; the company believed that a better return on investment would be obtained by diverting the money to other development projects.

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Previous examples of early discontinuation for economic reasons

This is not the first trial to be discontinued for reasons unrelated to efficacy, safety, or feasibility. The early closure of the European pimagedine trial by its pharmaceutical company sponsors for financial reasons was announced in a letter to the *Lancet* in 1997.⁶ An editorial denounced "a curious stopping rule from Hoechst Marion Roussel."⁷ The publicity led to two other cases being brought to the attention of readers: a prospective study of reinfarction after treatment with Cardizem was discontinued after 500 patients had been included out of 7000 planned,⁸ and a study of liposomal doxorubicin in metastatic breast cancer was also stopped early.⁹ In both the pimagedine and the fluvastatin trial the study committees and investigators were notified of the sponsor's decision afterwards. No detail of the way the companies handled the two other cases was given. The pimagedine trial was stopped after Hoechst purchased Marion Merrell Dow; the Cardizem trial was stopped for financial reasons and because generic diltiazem was entering the market; and the liposomal doxorubicin trial was discontinued because it did not meet the direction in which the Liposome Company wished to develop the drug. Other trials have probably been discontinued for such unscientific reasons, but those mentioned above are the only ones that we were able to identify through a Medline search.

Adverse consequences of premature discontinuation

Sponsors should not feel exonerated from responsibility towards patients, investigators, and the medical community just because they support trials financially. Most patients give their informed consent because they want to help medical research and future patients with the same condition, especially in countries where most people are covered by a state social security system and cannot expect any financial advantage from participation. The signature on the informed consent form is therefore not only proof that the patient was informed properly of the potential benefits and harms of participation. It is also the image of a moral contract by which

the study (the investigators, the scientists, and the sponsor) agrees to use all possible means to make the patient's participation useful for the community. This commitment includes ensuring the scientific appropriateness of the protocol, quality assurance, and the continuation of the trial to completion unless the results of interim analyses mandate premature discontinuation. In addition, the only justification for the risks and constraints sustained by patients is the potential benefit expected for those in the active treatment group and the benefit for the community. Discontinuation of a trial for unscientific reasons ruins the chances of benefit for both the individuals and the community. Similarly, ethics committees and health authorities approve studies in view of the balance between the usefulness and the risk of the trial. Once the usefulness is lost, the risk becomes unacceptable. Premature discontinuation of a trial for unscientific reasons can also cause actual harm to patients; whatever the official explanation, many of them will have doubts and be anxious about the safety of the drug. This may be particularly the case with elderly patients.

Investigators deserve consideration too, although they are paid for their work. Participation in a given trial may exclude investigators from taking part in other trials and constitutes a scientific investment for which the only return is the study results. Doctors commit themselves when they obtain the patient's informed consent. Premature discontinuation of a trial with no clear scientific cause may result in patients losing confidence in the investigator. The medical community may also be harmed by the premature discontinuation of clinical trials, especially large outcome trials that are the consequence of a subtle interaction of ideas and scientists. It will rarely be possible to relaunch a study that has been discontinued. The fluvastatin trial was planned to answer an important question that will probably never be answered.

Finally, whatever the justification of the decision to discontinue a trial, some respect must be paid to the conventions. Although the sponsor has the final word because it holds the purse strings, any decision regarding the early discontinuation of a trial should be made only after thorough discussion of the causes and consequences with at least the steering committee and the Data Safety Monitoring Board.

Future steps

An unprecedented number of mergers are occurring in the pharmaceutical industry. This will probably result in the advent of a handful of giant companies with huge financial power. This is supposed to facilitate the discovery and development of new drugs, but there will certainly be many internal conflicts for funding of trials between people responsible for different products and even between those who want to develop one product in different ways. These conflicts will be resolved under the increasing pressure of the shareholders.

Because the proof that a drug is efficient in reducing morbidity or mortality gives its owner a big advantage over its competitors, European public funding bodies think that the pharmaceutical industry should pay for outcome trials of drugs that are still protected by a patent. The resolution of many public health

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problems is therefore left to the initiative of drug companies, which engage in a fierce battle to show that their products have an advantage in a new disease or patient population. However, only those who arrive first win the prize, and it may be advantageous to stop a trial that will certainly be overtaken by a concurrent study. Even if there are no concurrent studies, delays in the completion of a trial mean that the sponsor has less time to get a return on its investment before the patent expires. For these reasons, the risk of premature discontinuation of big trials for economic considerations may increase dangerously. We suggest that good clinical practices evolve towards a better protection of patients and investigators. The box gives some suggestions for new rules.

Inclusion of patient representatives on steering committees is important. What happened with the fluvastatin trial probably could not have occurred in a trial on AIDS because of the reaction of patient representatives. The rules would be implemented in the study protocol and the institutional review boards would have to require their presence for giving approval to the study.

The pharmaceutical industry could be reluctant to waive any part of its power in the conduct of studies that it funds entirely. Even if the above rules were adopted, it would be difficult to prevent the constitution of puppet committees, and formal sanctions for not respecting these rules would be difficult to administer. A solution might be for public agencies to participate financially and scientifically in outcome studies that affect public health. Increasing the length of drug patents to take into account the length of outcome studies could also be useful. For the time being, trialists should insist that the sponsor commits to completing the trial before they agree to participate. The usual clause according to which the sponsor "reserves the right to discontinue any study for administrative reasons at any time" should no longer be present in the protocol of a study of morbidity and mortality.

Suggested rules for good clinical practice

- The steering committee (with the Data Safety Monitoring Board if applicable) of multicentre trials should be systematically involved in every important decision concerning conduct of the study, including discontinuation
- Steering committees should include a majority of members independent of the sponsor and act professionally as a representative of the patients, the investigators, and the medical community, while being able to take into account the sponsor's financial constraints
- Patient representatives should be included on the steering committees of large outcome studies

Competing interests: ML has been reimbursed by Novartis for attending a congress; his department benefited from a contract with Novartis for the study data management and analysis. EB has received fees for speaking and reimbursement for attending symposiums from different pharmaceutical companies. PG has been reimbursed by Novartis, Bristol Meyers Squibb, and Parke Davis for attending several conferences and has received fees from Novartis, Parke Davis, and Fournier for speaking in educational programmes. EL has been supported by Novartis for conducting clinical trials of fluvastatin and for lecturing on lipid lowering therapy. GL has received funds for a member of his staff, fees as an investigator in clinical trials, and reimbursement for attending a symposium. PP has been reimbursed for attending a symposium and has received fees for speaking. GS has been reimbursed for attending a symposium. All authors were on the steering committee of the fluvastatin trial.

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Commentary: Early discontinuation violates Helsinki principles

K Boyd

Medicine and the market seem uneasy bedfellows. But in the words of Tom Lehrer ("The Old Drug Peddler") doing well by doing good sometimes characterises doctors as well as drug companies, and moral high ground can be slippery. Medical science, one of its spokespersons wrote recently, is just as self serving as any other branch of human inquiry.¹ Quite so, pharmaceutical company directors might reply. The cost of discontinuing the fluvastatin study may be that medical science is left with unanswered questions about such treatments in elderly people. But what of the opportunity cost of continuing it? Other drugs, beneficial to patients as well as profitable, might not be developed. As a response to critics of "me too" drug development, discontinuation of the fluvastatin study

because of "the competition entering the elderly segment" could even seem altruistic.

How do you weigh the answers the study might have produced against possible alternative benefits? Can such an economic and clinical utilitarian calculus be constructed, let alone completed? Even if it could be, what further imponderables would have to be factored in? Is such action in the company's own interests? Might it lead investigators to refuse the cooperation the company needs for clinical trials to proceed? Or do investigators need drug companies as much as drug companies need investigators? If the answer to that last question is yes, an ethically satisfactory response to economic discontinuation may be difficult to construct on utilitarian grounds alone.

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Ethical issues

But deontological principles and procedural ethics also demand consideration. The relevant principles include beneficence, consent, and non-maleficence. Here investigators have firmer moral ground to stand on, articulated by the recently revised Declaration of Helsinki²: considerations related to the well being of human subjects should take precedence over the interests of science and society; subjects must be volunteers and informed participants in the research project; and research involving humans should be conducted only if the importance of the objective outweighs the inherent risks and burdens to the subject. As Lièvre and colleagues observe, once the usefulness is lost, the risk becomes unacceptable. With the usefulness gone, so too are the grounds on which both patient consent and ethical approval were given; and to the moral insult, injury may be added. The latest revision of Helsinki warns that some research populations are vulnerable and need special protection and states that the needs of the economically and medically disadvantaged must be recognised. Lièvre and colleagues suggest that there may be a particular risk of harm in the case of elderly patients like those in the fluvastatin study.

Legal claims on behalf of such patients may be precluded by the usual clause reserving the right of the sponsor to discontinue the study for administrative

reasons at any time. But the moral claim that Helsinki principles are violated by unilateral economic discontinuation of clinical trials is difficult to dispute. In terms of procedural ethics, the new rules outlined by Lièvre and colleagues suggest a reasonable remedy, and their reference to the example of AIDS trials is pertinent.³ Discontinuing a clinical trial for economic reasons may not always be wrong, but that needs to be determined by transparently equitable decision making procedures involving representatives of patients and investigators. The legitimate commercial concerns of pharmaceutical companies may make such procedures difficult to negotiate. But Lièvre and colleagues' interim negotiating position—that, before agreeing to participate, trialists should require sponsors to commit to complete trials—deserves support. If drug companies need investigators as much as investigators need drug companies, it might be the first Lysistrata-like step towards a happier marriage between medicine and the market.

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We invited three pharmaceutical companies—Novartis, GlaxoWellcome, and SmithKline Beecham—to comment on this article; all declined.

Asylum seekers and refugees in Britain

The health of survivors of torture and organised violence

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This is the last in a series of three articles

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This final article in the series describes how torture and organised violence may affect the health of survivors. A definition of torture, often used for asylum purposes, is shown in the box. It should be noted, however, that not all those who employ torture are acting in an official capacity.

Organised violence is defined as violence which has a political motive. Survivors of torture or organised violence have often been ill treated by government agents such as the army, police, or security forces or other groups perpetrating organised violence, including rebel groups. States have a duty to prevent, investigate, and

United Nations' definition of torture¹

Any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person for such purposes as:

obtaining from him or a third person information or a confession,

punishing him for an act that he or a third person has committed or is suspected of having committed,

or intimidating or coercing him or a third person,

or for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of a public official acting in an official capacity.

Summary points

Torture and organised violence are still prevalent in many countries and have previously been experienced by some refugees in the United Kingdom

The problems of survivors of torture and organised violence are not fully appreciated within the health services

Survivors of torture may not volunteer their history due to feelings of guilt, shame, or mistrust; consideration must be given to building a relationship of trust

Much can be done by health workers to alleviate the physical and psychological difficulties that face survivors

prosecute cases of torture, but if those who are supposed to do this are themselves the torturers, then there is no official protection. Systematic torture is designed to break the spirit of an individual,² but in many countries the intention is also to intimidate a minority or dissident group or even an entire population.