

tases. The probability of regional lymph node metastases is 3–5% in patients with a well to moderately differentiated, superficially invasive primary tumour confined to the uterine body.¹ These women have to be identified with a variety of preoperative and intraoperative diagnostic procedures of limited accuracy.

In many centres, especially in Europe, gynaecologists do not perform lymphadenectomy when pelvic lymph nodes are not suspicious. They argue that the benefit of lymphadenectomy is unclear. Indeed, claims of its intrinsic therapeutic value have been challenged.⁵ If lymphadenectomy is performed for diagnostic reasons then histological findings in the nodes should affect a decision on postoperative therapy, usually radiotherapy. Yet many patients with tumour negative nodes are referred for postoperative radiotherapy.³

Doubts about the effects of postoperative radiotherapy in patients with adverse prognostic factors are common.⁶ Dutch investigators have recently described a randomised controlled trial of 714 women with medium risk stage 1 endometrial carcinoma—well differentiated tumours with deep ($\geq 50\%$) myometrial invasion, moderately differentiated carcinoma with any invasion, or poorly differentiated tumours with superficial ($< 50\%$) myometrial invasion.⁷ None of the patients underwent lymphadenectomy. In the irradiated group the five year locoregional recurrence rate was 4% and the five year overall survival rate 81%. In the non-irradiated (control) group these figures were 14% and 85% respectively. Mean follow up was 52 months. Thus these figures show no survival benefit from postoperative radiotherapy. Ten (100/(14–4)) patients would have to be irradiated postoperatively (46 Gy) to prevent one case of locoregional recurrence.

A total of 40 patients from the non-irradiated group developed a locoregional relapse but only four died from it. Because of the limited duration of observation the investigators propose waiting for more mature results from salvage therapy before reaching final conclusions. In general, locoregional recurrences in non-irradiated patients are usually treated with radiotherapy (70 Gy), with an estimated overall cure rate of 67%.⁸

Based on the results from their trial the Dutch investigators have proposed new guidelines for the use of postoperative radiotherapy. They state that, in the absence of survival benefit, postoperative radiotherapy is justified when the absolute risk of locoregional recurrence is $> 10\%$ or $> 15\%$ and the risk of uncontrolled local disease after salvage treatment is high. On the basis of multivariate analysis they have identified two subgroups. In women with either a moderately differentiated, superficially invasive tumour or age < 60 years the risk of locoregional relapse is estimated to be

less than 5%. These women should not need radiotherapy. In the remaining group (age ≥ 60 years and superficially invasive, poorly differentiated tumour or deeply invasive, well to moderately differentiated tumour) the five year locoregional relapse rate is 18% in the non-irradiated women and 5% in the irradiated women. Here, 8 (100/(18–5)) patients need to be treated to prevent one locoregional recurrence without survival benefit.

According to the investigators, the grounds for postoperative pelvic radiotherapy are to prevent uncontrolled local disease and the physical and psychological morbidity of the diagnosis and treatment of a locoregional relapse. One has to ask whether dying from uncontrolled disease outside the pelvis is preferable to dying from disease in the pelvis. Given the 14% locoregional relapse rate in the non-irradiated group and 4% rate in the irradiated group, we estimate that about 30% (4/14) of the locoregional relapses are not prevented by radiation. Complications of radiotherapy do occur in 25% of patients and are severe in 2%. What is the impact of these complications for psychological functioning or more broader quality of life? The great majority of the irradiated patients would never have had a locoregional recurrence.

Adjuvant radiotherapy offers no survival benefit, fails to prevent locoregional recurrence in about 30% of patients, and harms many women who would never develop such a recurrence. It seems justified to abandon postoperative radiotherapy in patients with medium risk stage 1 endometrial carcinoma.

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Societal responsibilities of clinical trial sponsors

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

Education and debate
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BMJ 2001;322:569–70

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

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,¹ 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 603)² 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.³ Statistical stopping guidelines exist for data monitoring committees,^{4,5} 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.⁶

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.² Though such a trial poses an important public health question—does lipid lowering 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.⁷ 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 capitalist 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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