

Stopping trials prematurely: sorting the right decisions from the wrong

→ Anna Wagstaff

Allegations that commercial pressures may be leading to cancer drug trials being halted prematurely hit the news on both sides of the Atlantic last April. Industry leaders are pleading ‘not guilty’. But how can we judge when calling an early halt to a trial is the right thing to do?

Are commercial pressures prompting pharmaceutical companies to stop trials prematurely? A group from the Italian drug regulatory agency, AIFA, and the Mario Negri Institute in Milan, suggest that this may be the case in an article widely reported on both sides of the Atlantic. They draw attention to the sharp increase in the number of cancer trials stopped early on the basis of benefit shown in interim analyses, pointing out that the vast majority were registration trials, aimed at getting marketing approval for a new drug or a new indication.

Their article in the *Annals of Oncology* (2008, 19:1347–1353) surveyed all clinical trials of anti-cancer drugs published from January 1997 to October 2007 that were stopped early ‘for benefit’ (i.e. excluding those stopped due to lack of efficacy or unacceptable toxicity). There were 25 trials in this category.

The survey, say the authors, highlights, “a consistent increase (>50%) in prematurely stopped trials in oncology during the last 3 years in comparison to the whole period analysed.” They point out that, of those stopped prematurely in the last three years, more than 78% were used for registration purposes. “This sug-

gests a commercial component in stopping trials prematurely.”

Senior figures from the industry strongly deny the allegations and are unhappy about the tone of the media coverage prompted by the *Annals* article, which, they feel, fuelled a climate of suspicion and failed to spell out how companies insulate decisions on clinical trials from inappropriate influence.

Stopping a trial early is generally considered undesirable. It is likely to result in losing information of relevance in evaluating efficacy in the longer term, depriving physicians, patients and researchers of important knowledge. The chance to gather statistical data on disease recurrence and progress, drug resistance, metastasis or adverse events may be lost forever.

An early halt has also been shown to lead to a systematic exaggeration of benefit because, in any randomised trial, the smaller the number of outcomes or events, the greater the likelihood that the difference between the arms of the trial at a given moment will represent a ‘random spike’. If the interim analysis shows low benefit, researchers have an incentive to continue the trial as planned to see whether the early results readjust upwards

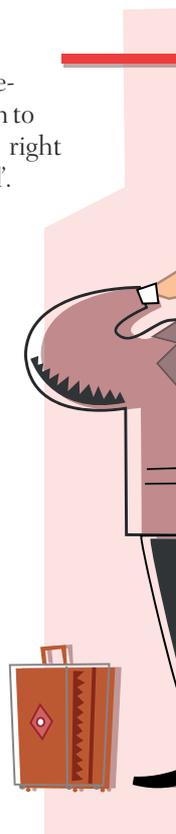
as more results come in. However, if the analysis coincides with a spike that exaggerates the benefit, the question of stopping early may be raised – hence the bias.

The more interim analyses done in a single trial, the greater the likelihood of hitting a random benefit spike, leaving trial sponsors open to accusations of looking for the right moment to ‘quit while they’re ahead’.

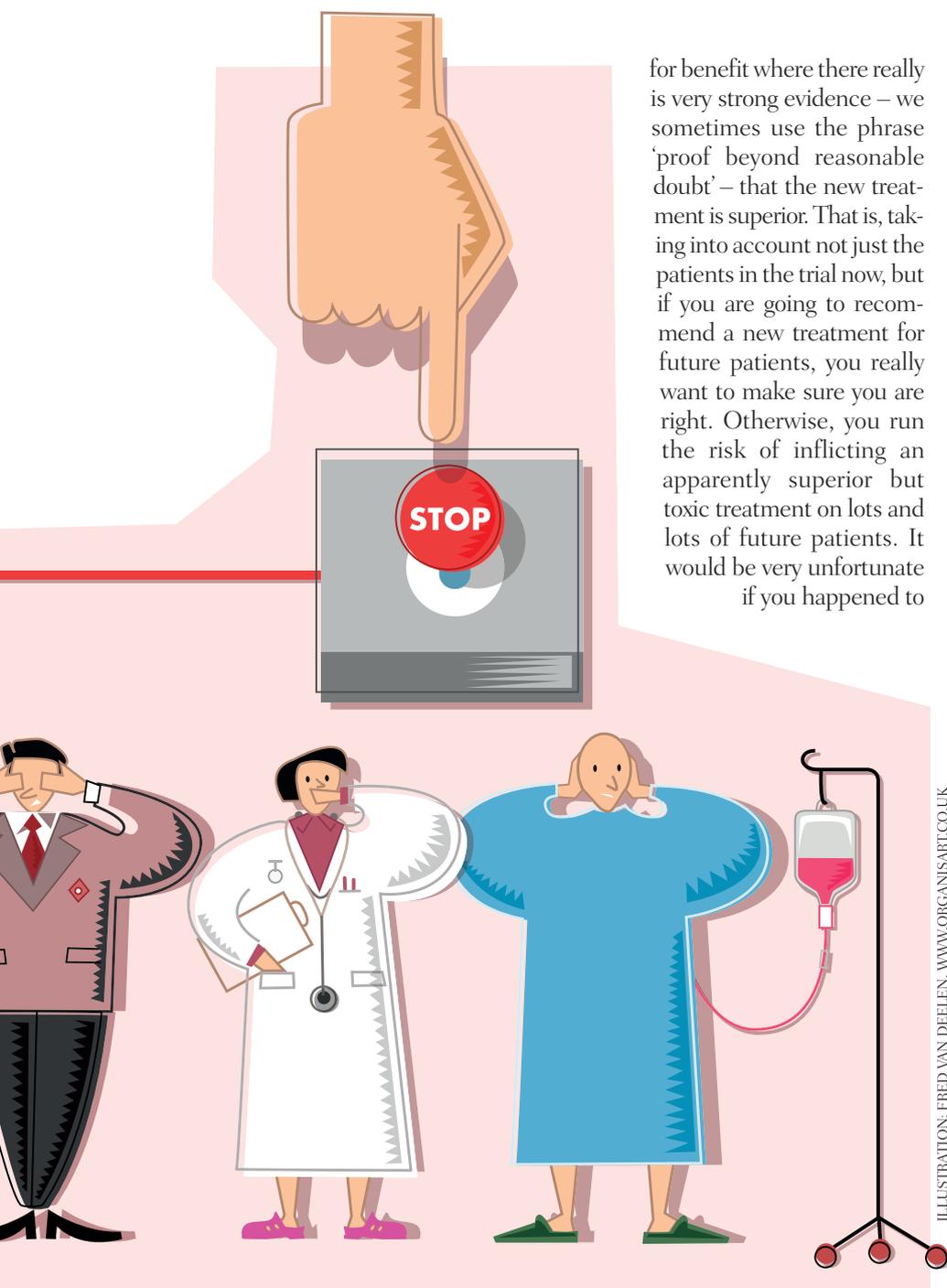
WHY STOP EARLY?

There are of course very good reasons for stopping a trial that shows benefit early – particularly where lives are at stake and there are no therapeutic alternatives. An interim analysis may reveal evidence so strong that it would be unethical to continue to randomise patients to the control arm of the trial and to delay access to the new therapy among the wider patient population.

Stuart Pocock, professor of medical statistics at the London School of Hygiene and Tropical Medicine, has written extensively on this subject. “Good practice should be that you stop



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for benefit where there really is very strong evidence – we sometimes use the phrase ‘proof beyond reasonable doubt’ – that the new treatment is superior. That is, taking into account not just the patients in the trial now, but if you are going to recommend a new treatment for future patients, you really want to make sure you are right. Otherwise, you run the risk of inflicting an apparently superior but toxic treatment on lots and lots of future patients. It would be very unfortunate if you happened to

have stopped on lesser evidence, when in truth the treatment is not superior.”

Establishing sensible statistical stopping boundaries before the trial starts adds objectivity to any subsequent decision to stop early, but the final judgement needs to be based on a wise interpretation of the total evidence available, says Pocock. For example, the leaders of the HERA trial into trastuzumab (Herceptin) as an adjuvant – one of the trials listed in the *Annals* article – justified sacrificing data on side-effects when they stopped the trial early by pointing to the strong data already available from widespread use of the drug in the metastatic setting.

Wise judgement is also needed in balancing the interests of future patients and the patients on the trial. Roger Wilson, a patient advocate who works with the UK national cancer research network (NCRN) expresses the dilemma. “I feel trapped between the two sides, because I really do want to see unequivocal evidence that patients will benefit. At the same time, as a patient, I want to benefit at the earliest possible opportunity should that present itself.”

Wilson regrets the loss of potentially important information about development of resistance that resulted from a recent decision to halt prematurely the ACOSOG trial into imatinib (Gleevec) as an adjuvant in GIST patients. He also believes that stopping early the sunitinib (Sutent) trial for GIST patients who don’t respond to imatinib sacrificed important data on overall survival, making it very difficult for some patients to get the treatment reimbursed.

“In terms of treating patients now – 2006 when they did it – it was

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absolutely the right thing to do. But we are going to have to live with the consequences. All we've got at the moment is about a median of eight months progression-free survival on Sutent for patients who relapsed on imatinib. We haven't got any data to say that patients going onto Sutent live for an extra two to three years. It's just not possible to produce it."

"Patients do benefit in the short term, and that is something we mustn't ignore," says Wilson, adding that crossover trial designs can help resolve the conflict, although they too entail some loss of data. In the end, he says, researchers have to balance the potential short-term benefits to current patients of stopping a trial early, against the long-term disservice to future patients from the loss of data. "You have to operate some sort of balance mechanism, whereby you put the evidence into a pot and come up with a view."

FOR PATIENTS OR PROFIT?

Given the complexity of the issues in deciding to stop early, the seven-page overview of 25 trials in the *Annals* article is not sufficient to show whether the decision was justified on ethical grounds in each case. The authors nonetheless point to a number of factors they say might indicate that commercial concerns played a role – possibly to save the costs of continuing the trial or to steal a march on companies with rival products in the pipeline.

- More than 78% of all trials stopped early for benefit in the last three years were used to support an application for marketing authorisation at the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

- The average time to publication was around two years, suggesting that disseminating information for the benefit of a wider patient population was not the driving force.

- In all, only around 3,300 patients/events out of a planned 8,000 were studied. The authors accept that this could be accounted for by ethical considerations, "However, the relation between sparing patients [from potentially unnecessary randomisation] and saving time and trial costs is also unquestionable, and indicates that there is also a market-driven intent."

Alan Barge, head of Clinical Oncology at AstraZeneca, strongly denies that commercial pressures play any role in his company's decisions about how to take a trial forward, and he says it is also highly unlikely that this happens in other major pharmaceutical firms. "There is not a shred of evidence to show this is the case."

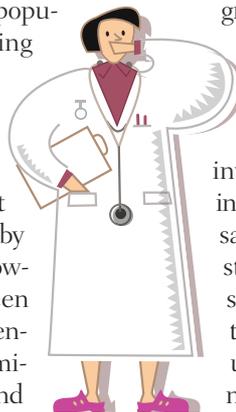
Like most pharmaceutical companies, AstraZeneca uses independent data monitoring committees (DMCs – also known as data safety monitoring committees) to ensure that decisions on stopping early are independent of inappropriate influence – whether from commercial pressures, from enthusiastic principal investigators or from anxious patients. DMC members are appointed according to strict criteria. "They must be completely independent of the study, and independent of any pecuniary interests of AstraZeneca. Second, the DMC must be an independently scientifically

credible group of people. Third, they must be accepted by the principal investigators as an appropriately qualified group to monitor the study. We then make everyone involved aware of the names, including the regulatory agencies."

The DMC then becomes involved in the study design, including defining the efficacy and safety criteria and the statistical stopping boundaries. Once the study has started, no-one outside the DMC has access to unblinded data (without which no comparisons can be made between treatment arms).

Barge says that this insulates the trial from commercial pressure. "Knowing as I do the degree to which DMCs jealously guard their independence, and also the view that regulatory agencies take of clinical trials stopping early, I cannot envisage a situation where my commercial colleagues would try to put me or, more importantly, the independent physicians conducting the study and the DMC under pressure to stop a trial early, or in any way influence their view about the medical rationale or ethics for continuing."

Barge argues that the pharmaceutical industry is second only to the nuclear industry in its level of regulation. "If a company were to decide to stop a trial based on commercial considerations or otherwise conduct a trial in a way that would not be considered appropriate, those actions are discoverable when the dossier is filed with the regulatory agency. Any company that were to do that runs the risk of being found out, which would fundamentally damage their credibility."



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Academic trials, he adds, are subject to far less scrutiny.

Diane Young, head of global medical affairs at Novartis Oncology, says she and her colleagues were disappointed by the press coverage, given the weaknesses of the *Annals* article. “In order to do the type of analysis they are trying to do, they would have to look at all the protocols for each study, and understand the statistical model, and why an interim analysis was built in... You can’t just look at it on a surface level and say they did or did not do the right thing.”

She accepts that pharmaceutical companies could improve the way they report decision-making processes when they publish trial results. “Maybe there is an educational opportunity here, that people need to understand that there are significant safeguards built into the design of these trials. We do it in collaboration with a lot of independent people as well as the regulators.”

One of the 25 trials listed in the *Annals* article was the letrozole (Femara) trial, stopped after one-third of the planned events. Young points out that, although this was a registration trial for a Novartis therapy, it was initiated, designed and conducted entirely by an independent trials group, led by the Clinical Trials Group of the National Cancer Institute of Canada and including the North American Breast Intergroup and the Breast International Group.

The trial was studying the therapy in an adjuvant setting in a population of women who had already received five years of tamoxifen, so that ‘events’ regarding the primary outcome measure of disease-free survival, took a long time to

accrue. Carrying that trial to its planned conclusion, Young argues, would have delayed access to a beneficial treatment for years. She also denies that the decision to stop early saved money; the women are still being followed up, even though the trial has stopped.

The ACOSOG trial, she adds, was also entirely in the hands of a cooperative group of investigators, who have their own procedures. “We got the phone call the day before they were going to announce they were going to stop the study”.

Both Barge and Young

believe that the increasing number of trials being stopped early may simply reflect the surge in the number of cancer trials being carried out in recent years. They also suggest it could be linked to the move towards novel targeted therapies. “Because we are using targeted agents we are often able to pick populations where there aren’t other therapies available. In these populations, if you have solid data at the interim analysis that the drug is beneficial to patients, because you have patients on the trial and out in the world too who don’t have any alternative, it is important to make that information available,” says Young.

Interim analyses also have a much more important role to play in developing drugs aimed at specific targets, says Barge. “In the past you might have been taking forward a cytotoxic drug that was slightly different to a previous version of

the same drug, where you already had phase II data showing that it shrank tumours. The same is true of hormonal agents developed in the ’70s and ’80s. Proof of concept was already established. There was no need to look for early evidence of efficacy in a large trial. The issue was all about safety.”

By contrast, when developing a drug based on a new concept, and trying to find the appropriate dose and patient population, the rationale for interim analyses is much greater. However, it is not an easy option, says Barge, because the

mere fact of conducting an interim analysis incurs a penalty—you have in effect to show a higher level of significance in your final results than would otherwise have been the case.

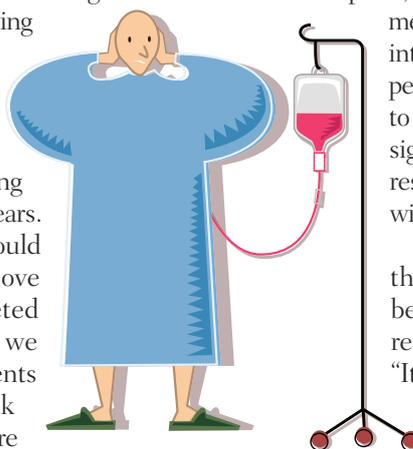
Young takes issue with the assumption that because a trial ends early, research comes to a halt.

“It simply isn’t possible to answer every question and do it well in one study. But it’s

important to have a programme of research that answers the questions.”

Barge agrees. He has spent years trying to figure out why dramatic phase II responses to AstraZeneca’s non-small-cell lung cancer (NSCLC) drug gefitinib (Iressa) were not replicated in the phase III trial. “It’s a rather simplistic view to say you will never know those things if you stop clinical trials early. You set out on a series of clinical trials to answer different questions.”

He points out that clinical trials are



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designed to much more robust standards than used to be the case. “The initial approval for taxotere in NSCLC was based on only around 100 patients. In one of our drugs recently, we have done a direct head to head comparison with taxotere, and we studied 1,400 patients, just to demonstrate that our drug, which is a well-tolerated oral drug, is as good as taxotere.”

AN IMPORTANT ISSUE

Pocock, who has been following the issue for many years, says: “Practice is better than it was in terms of sensible choices as to when to stop trials, but there is still a problem and we need to improve. Certain trials do stop too soon – it’s a question of educating investigators and sponsors.”

Pocock feels that the *Annals* survey “went slightly beyond what we can conclude” in singling out commercial interests. “I think it’s probably a mix of industry motivation of getting to profit fast, over-enthusiasm of investigators and over-enthusiasm of DMCs to stop trials too quickly.”

He suggests that pseudo-ethical arguments can often lead to decisions to call a premature halt. “Many will stop because they think it is ethical to stop, but their judgement may not be the wisest one on that particular issue. If you have some evidence, and you are passionate about your treatment anyway, whether as an investigator or as a sponsor, you may feel, ‘Ooh it’s heading in that direction, I always knew it would, therefore I should stop early.’”



“One can speculate, but it is dangerous ground to think you can tell what the specific motives are in a particular circumstance.”

However, the underlying concern raised by the *Annals* article – that a trend towards stopping trials early is resulting in unclear and poorly defined risk/benefits – stands regardless of the motivation. It is a concern that urgently needs to be addressed, as physicians struggle to use appropriately a stream of new therapies about which too little is known.

Francesco Trotta, lead author of the *Annals* article, says he and his co-authors would like to see action on three fronts. They want DMCs used in all clinical trials (there were no DMCs in almost a quarter of the trials in the *Annals* survey) and greater transparency over who sits on them. Names should be made publicly available either in the clinical trial registers (when the trial is ongoing) or in the published articles (when the trial terminates).

They want trial patients to be made fully aware when they sign consent forms that the primary purpose of research is to reach robust conclusions. “Before the trial starts, investigators should inform patients that interim results should be considered as partial, and that only completing the trial allows the achievement of the study objectives.” Wilson, with his experience as a patient advocate, points out that consent forms usually do make this point. “The trouble is that people who have never been exposed to the clinical trials environment

TRIALS STOPPED EARLY

The *Annals* article listed 25 trials into anti-cancer therapies that were halted early between 1997 and 2007. Among them were registration trials for:

- sunitinib (Sutent) in (i) metastatic renal cell carcinoma, and (ii) advanced gastrointestinal stromal tumour (GIST)
- sorafenib (Nexavar) in advanced clear-cell renal cell carcinoma
- bevacizumab (Avastin) in (i) a combination regimen for non-small-cell lung cancer; (ii) various combinations for metastatic colorectal cancer; and (iii) metastatic renal cell cancer
- lapatinib (Tykerb) + capecitabine for HER2+ metastatic breast cancer
- trastuzumab (Herceptin) for early HER2+ breast cancer
- letrozole (Femara) for receptor-positive early breast cancer
- irinotecan (Camptosar) + cisplatin for metastatic small-cell lung cancer

don’t ever actually get that message.”

Above all, they want to explore ways of improving the methodology governing the early truncation of trials to ensure that trials only stop early when this is demonstrably appropriate, and that they are followed up with confirmatory trials wherever possible.

This is one of the big challenges of current drug development. Finding solutions will require constructive dialogue involving not just academic researchers and statisticians, but the regulators, patient advocates... and the industry – commercial interests and all.