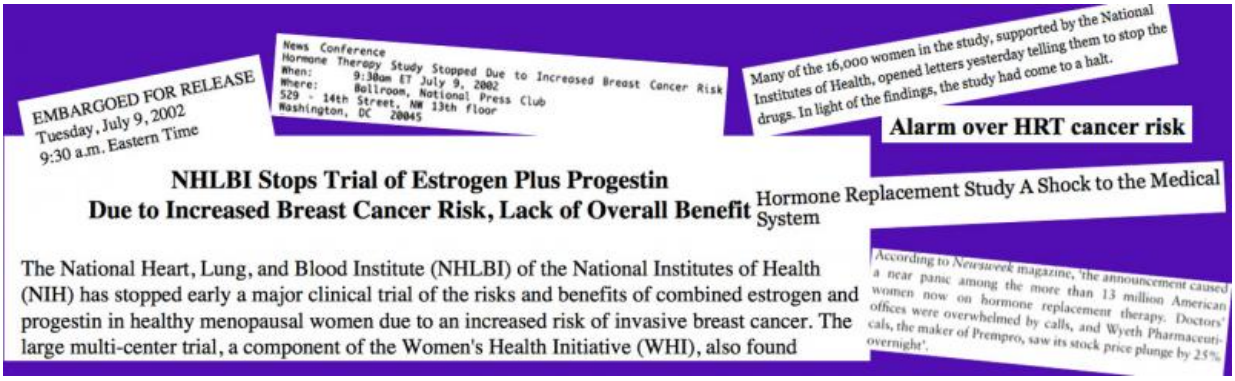
The mess that trials stopped early can leave behind

September 30 2015, by Hilda Bastian



The drama of NIH's 2002 announcement that the estrogen plus progestin trial had been stopped early.

Many trials end with a whimper. But some end with a bang.

Press release, press conference, lots of fanfare – and backlash. The drama of another clinical trial being stopped early burst into public view this month. This time it was an NIH blood pressure trial called SPRINT.

Testing treatment aimed at a lower-than-usual blood pressure target against standard management was supposed to go on for another year. They've ended that after monitoring of interim results found a big difference in favor of aiming for lower-than-usual blood pressure. More on that later. But first let's look at some examples that show why

stopping any trial early is so controversial.

To start: a tale of 2 trials of a drug for secondary progressive multiple sclerosis (SPMS) (interferon beta-1b). One started in Europe in 1994; the other got underway in the US and Canada in 1995. The European trial stopped 2 years early after interim results "gave clear evidence of efficacy. Treatment with interferon beta-1b delays sustained neurological deterioration" – the first treatment found to do that for SPMS.

So what then for the North American trial, still in its early stages? The knowledge base providing the ethical justification for their trial had shifted – and they had hundreds of people on placebos. The trial had a data monitoring committee (DMC). The DMC has the role of protecting participants against harm and making judgments about the data during a trial. (A DMC is also called a data monitoring and safety board (DMSB) or data monitoring and ethics committee (DMEC).)

The DMC looked at their data, and decided to keep going. They stopped early, too, in November 1999 – not because of benefit. Unfortunately, there was no benefit on delaying disability. They stopped early for futility – the belief that the outcome wasn't going to change if they continued.

Where did that leave people with SPMS? Despite 2 trials, the picture was murky. It took another big trial that didn't stop early to be sure. According to a systematic review in 2011, a systematic review, the evidence that interferon beta-1b doesn't work is "conclusive" (PDF). (The drug is not approved for the indication of SPMS by the FDA.)

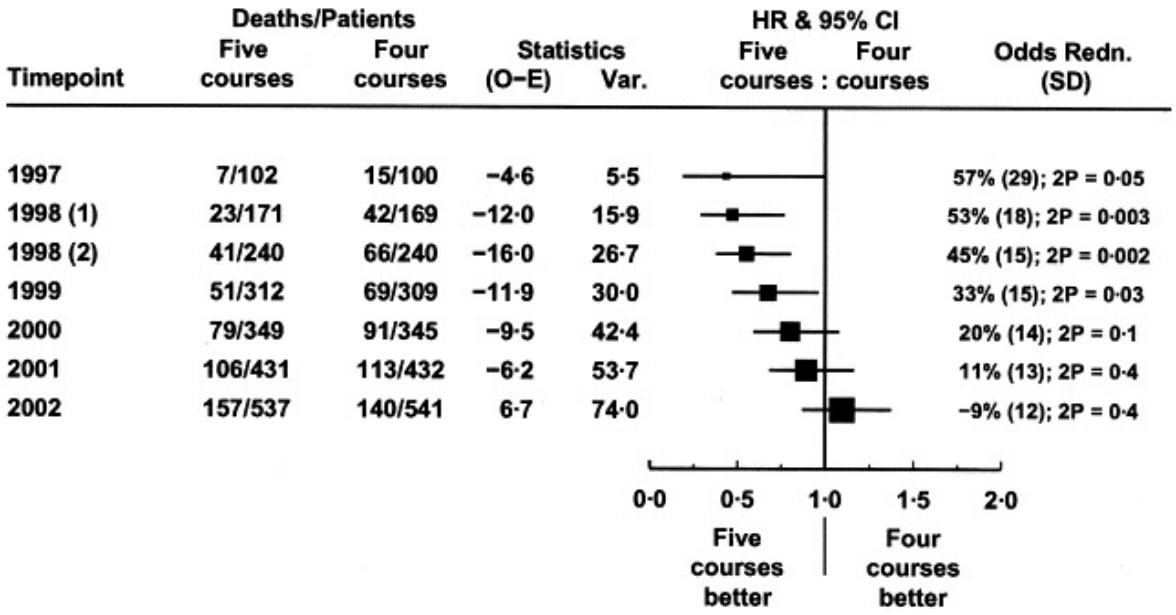
That time, the reason the first trial came to an exaggerated impression seemed to be the number of patients who might not have fully progressed to SPMS.

Our next story is an example a few years later. This time the disease is a form of leukemia (AML), and the trial is testing 5 courses of treatment against 4 courses, to see if the burdens of extra toxicity and intensive treatment lengthen life.

The study's statistician, Keith Wheatley, and chair of the DMEC, David Clayton, tell the story of what happened. It was an MRC trial in the UK, and the data in leukemia trials for those was monitored annually. The first set of data showed major benefit to 5 courses: there were only 7 deaths compared with 15 in the group having less treatment.

The DMEC "deliberated at length", and decided not to recommend stopping the trial but to check the data again in 6 rather than 12 months. When it came, the benefit in favor of 5 courses had grown stronger: "Again, the DMEC deliberated long and hard and again concluded that recruitment should continue".

When the trial finished as planned, there was no mortality benefit from the extra course of treatment. The figure below shows what happened as the trial moved to its final tally: 157 deaths in the group having extra treatment compared with only 140 in the other group.



"A remarkable fluke": Early apparent benefit on mortality of an extra course of leukemia treatment disappearing as the trial progressed. Credit: Wheatley and Clayton, 2003

They now conclude it was "a remarkable fluke". Why didn't they recommend stopping for benefit at the time? The DMEC had no stopping rule – a guideline agreed at the outset about the results that would trigger a recommendation to stop the trial. They had come to the decision that it was clinically implausible for an extra course of treatment to have such a dramatic effect:

Quite extreme chance effects can and do happen more often than many clinicians appreciate. At any one time, there are hundreds, if not thousands, of trials ongoing, often with analyses at several time points and with a number of subgroup analyses. Thus it is inevitable, with all these

multiple comparisons being undertaken, that highly significant results (p