Marketing medicines through randomised controlled trials: the case of interferon

Toine Pieters

Section of Medical History, School of Medicine, Vrije Universiteit Amsterdam, 1081 BT Amsterdam, Netherlands

Toine Pieters, *lecturer*

Correspondence to: Dr T Pieters, Israelslaan 8-iv, 3582, HK Utrecht, Netherlands
tpieters@bio.vu.nl

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Summary points

- Randomised clinical trials are regarded as a most helpful tool to relieve medical practice of subjectivity
- Interferon became a part of everyday clinical practice through randomised clinical trials
- Despite initial disappointment with its clinical efficacy, interferon became legitimised as a part of medical practice
- Randomised clinical trials had the side effect of widening interferon's therapeutic profile and were central to the marketing strategies of pharmaceutical companies
- The use and interpretation of randomised clinical trials differ substantially for experimental drugs in serious illness and for research into less serious diseases

"When it comes to clinical trials, few issues are simple. And many are controversial" wrote the *Science* correspondent Gary Taubes in 1995.[1] Taubes' dictum seems to be at odds with the public model of the randomised clinical trial as a most helpful tool to relieve medical practice of that most feared element known to scientists and regulators: subjectivity. Are most doctors and regulators who firmly believe in the randomised controlled trial as the key to an "evidence based medicine" mistaken? Given an ideal world without social, professional, and economic interests affecting judgments of the efficacy and risks of medical treatments, one might have answered "no." It is impossible, however, to conceive of such a trial taking place in a human vacuum. Conducting randomised controlled trials involves establishing links and commitments between many different individuals and organisations, including clinicians, laboratory researchers, patients and their families, regulators, and drug companies. In being shaped by the specific context of medical practice, clinical trials—even the most sophisticated randomised controlled trials—are not value-free measuring devices that objectively evaluate the efficacy of new treatments. Like any other medical device associated with our daily lives, randomised controlled trials incorporate the beliefs and ideas of the people who developed them and then are moulded by those implementing the methodology.[2] I use here the story of interferon to illustrate the complexities surrounding the application of this supposedly value-free research methodology. Interviews referred to in the article were between myself and the person cited.

Beyond interferon

In the late 1970s, after scientific claims that interferon had an inhibitory effect on tumours, interferon stirred up a global media hype.[3 4] The euphoria surrounding interferon as a "miracle cure" for cancer was short lived and faded when it seemed that interferon's performance in large scale cancer trials had been disappointing and that it often produced side effects in patients.[5] Given the intense disappointment in the early 1980s in the healing power of what later became dubbed "the miracle drug looking for a disease," how did interferon manage to become legitimised as part of medical practice in the 1990s?

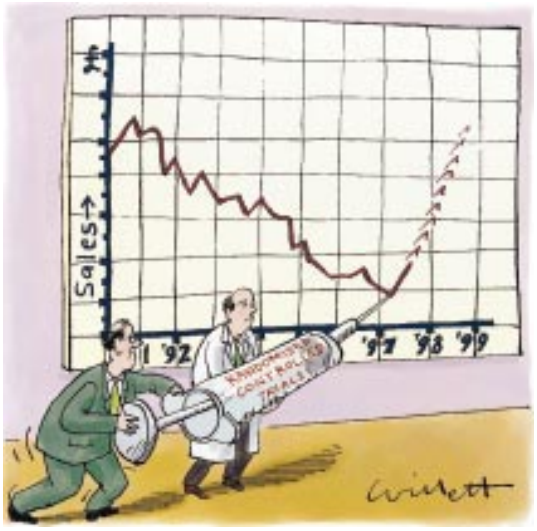
As might be expected, the people working on interferon tried hard to account for the disappointments to safeguard funding. Interferon researchers conveyed the impression that with more questions than answers they were just beginning to explore the potential of the drug. The diversity of interferons with distinct and complementary activities seemed to grow every day, although clinical testing of the first interferon preparations produced with recombinant DNA had yet to start. The consensus view was that, although interferon as a single agent might turn out to be useful in treating viral infection, it might ultimately prove most valuable as part of the increasingly popular "multitreatment" approach in cancer. Interferons could then be used as biological enhancers—helping to increasing the host's own response against the tumour—in combination with the three main cancer treatments: surgery, chemotherapy, and radiation.[6–9]

By creating an image of interferon as a prototype of a promising, new, but still poorly understood area of cancer treatment known as immunotherapy—one that was going to have an important role in future cancer practices—the promoters of interferon established a more permanent base for support. The overall message was, as a science reporter of the *Washington Post* aptly expressed it in his headline, "Beyond interferon."[10] Cancer treatment centres that aspired to maintain an image of being at the cutting edge of the field of clinical oncology could not afford not to study an experimental treatment that was closely linked with the latest developments in tumour biology and molecular biology (interview with E Borden, 12 October 1992, Wisconsin).

In line with government supported research programmes, the pharmaceutical industry focused on interferon as part of a new kind of disease management: immunotherapy within a multitreatment framework. The three "interferon champions" that had most heavily invested in the drug—Burroughs Wellcome and, most notably, Hoffmann-La Roche and Schering-Plough—apparently recognised the strategic and commercial importance of taking advantage of the more general move across medicine towards combination treatment. In 1983 Hoffmann-La Roche and

Schering-Plough allocated 15% of their research budgets—more than $40m each—to interferon (interviews with L Gauci (Hoffmann-La Roche), 18 June 1990 in Basle, and with N Finter, 25 May 1990 in Beckenham, Kent; Powledge[5]).

However, the regulators found the multitreatment approach difficult to assess as their evaluative practice and standards were still governed by a single agent, therapeutic philosophy. For interferon—a pharmacologically active compound—to be considered legally as a new therapeutic drug, it had to be officially evaluated as a single agent. This implied that before licensing procedures could be taken into consideration, the companies had to look for a disease, rare though it might be, that justified a need for interferon (interviews with J Petriccianni, 6 November 1992, Cambridge, MA, and with L Gauci, 18 June 1990). As most trials showed that interferon alone compared unfavourably with drugs already available, the interferon industry faced the seemingly Herculean task of establishing an unambiguous justification for clinical use.



Promoting use of interferon

In search of suitable diseases as candidates for interferon as a treatment, the drug companies actively supported randomised controlled trials to evaluate the effects of the drug on as wide a variety of diseases as possible. They offered clinical investigators worldwide—free of charge—large quantities of their interferon products to perform randomised controlled trials. Interferons were tested against hepatitis B, lymphomas, colds, breast cancer, prostatic cancer, multiple sclerosis, herpes keratitis, malaria, AIDS, and many other diseases related to cancer and viruses. The drug companies mounted one of the most intensive clinical trial programmes ever set up to evaluate a new pharmaceutical agent.[11–14]

Once the indication for hairy cell leukaemia was officially established in 1986, the marketing branches of the drug companies worked hard to create a need for interferon (interview with T Pike (Roche), 22 June 1990, Basle). The drug industry was well aware that it was highly dependent on the cooperation of clinicians both to define additional clinical situations in which the interferons might be applied and to help market the multitreatment concept. Highlighting success instead of failure in research publications sponsored by industry—without denying current limitations—came to form the implicit justification for the further growth of the clinical trial "enterprise."[15–18] The impression conveyed was that participating clinicians would stand out as pioneers of a new era of treatment (in 1983 the drug company Schering made available a series of three films (*Interferon in Prospect*) to clinical investigators worldwide).

Optimising response rates seemed to be the explicit aim of virtually any clinical research project dealing with interferon.[19–21] Clinical researchers who participated in testing interferons claimed response rates of 10-50% except for hairy cell leukaemia (response rate higher than 80%). The problem and advantage of using percentages was that success seemed to be a highly ambiguous term. Overall response rates ("efficacy") resulting from clinical studies under controlled circumstances might look promising, even when it remained unclear what this actually meant for individual chances of success and how well a treatment might perform in everyday clinical practice ("effectiveness"). Regardless of interpretation, however, response rates remained low in most diseases, suggesting that it could help only some of the patients some of the time.

Under normal disease conditions this kind of negative scientific assessment would dissuade doctors from applying a therapeutic drug. But in circumstances where there is no hope for a cure, the rules of the game are different for both doctors and patients. In diseases in which successful treatment is rare, seeking treatment through medical intervention is a gamble which can have few winners. Gambling is an alluring analogy for all parties as it turns poor clinical results into acceptable chances, allotting responsibility for failure to bad luck rather than medical or other capacities.

With the relentless support of the drug industry and patients in desperate need of a cure, and through scientific drive and professional ambition, clinicians continued to tinker with the design of trials. They tried different combinations and different routes and durations of administration.[20–22] In doing so, they ultimately tinkered towards success in terms of establishing new therapeutic drug practices for interferon and actively working on the treatment's effectiveness. Although superior treatments for the treatment of hairy cell leukaemia became available—and have largely replaced the use of interferon for this condition—interferon as an adjunct to other treatments became part of the routine treatments of a growing number of diseases.

In positioning interferon as a "helpful neighbour," compatible with and supportive of existing treatment practices, the pharmaceutical companies succeeded in having interferon relatively quickly absorbed into the medical infrastructure, requiring increasingly large amounts of money for its use. As a consequence, opposition to interferon currently revolves less around questions of need than around questions of cost or economic feasibility, which increasingly dominate the political agenda of "marketplace" medicine.

Organising marketing strategies around randomised controlled trials

The story of how interferon managed to become part of the "doctor's bag" clearly shows how the conduct, organisation, and evaluation of randomised controlled trials, and what they are capable of, is dependent on the specific context of use. The interferon case provides a warning example to those who uncritically promote randomised controlled trials as the badge of rational medicine. In achieving a key position in the distribution of research resources and materials needed to set up such trials, the pharmaceutical industry increasingly dictated development and clinical use of interferon. It was the industry itself that profited most from the very dialectical nature of the "enterprise" of the randomised controlled trial. I have shown that the randomised controlled trials proved effective not only in evaluating the safety and benefit of interferon as a therapeutic drug but also in the marketing of the commercially interesting multitreatment concept that turned the interferons from unwanted drugs into top selling pharmaceuticals.

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"A calculated risk": the Salk polio vaccine field trials of 1954

Marcia Meldrum

National Institutes of Health, Bethesda, MD 20892
Marcia Meldrum
DeWitt Stetten memorial fellow in the history of the biomedical sciences

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Summary points

The 1954 polio vaccine field trials used a singular statistical design

Over 600 000 schoolchildren were injected with vaccine or placebo and over a million others participated as "observed" controls

This dual protocol illustrates both the power and the limitations of randomised clinical trials to legitimate therapeutic claims

The polio vaccine field trials of 1954, sponsored by the National Foundation for Infantile Paralysis (March of Dimes), are among the largest and most publicised clinical trials ever undertaken. Across the United States, 623 972 schoolchildren were injected with vaccine or placebo, and more than a million others participated as "observed" controls. The results, announced in 1955, showed good statistical evidence that Jonas Salk's killed virus preparation was 80-90% effective in preventing paralytic poliomyelitis.[1]

The statistical design used in this great experiment was singular, prompting criticism at the time and since. Eighty four test areas in 11 states used the textbook model: in a randomised, blinded design all participating children in the first three grades of school (ages 6-9) received injections of either vaccine or placebo and were observed for evidence of the disease. But 127 test areas in 33 states used an "observed control" design: participating children in the second grade (ages 7-8) received injections of vaccine; no placebo was given, and children in all three grades were then observed for the duration of the polio "season."[1]

The use of the dual protocol illustrates both the power and the limitations of the randomised clinical trial to legitimate therapeutic claims. The placebo controlled trials were necessary to define the Salk vaccine—introduced by a lay organisation that has taken an activist position against the counsel of its virological advisers—as the product of scientific medicine. The observed control trials were essential to maintaining public support for the vaccine as the product of lay faith and investment in science. Here I examine the process by which the trial design was negotiated and the roles of the several actors.

A problematic vaccine

On 23 January 1953, Jonas Salk of Pittsburgh presented the results of his tests of a "killed virus"