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

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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"

"Polio pioneers"—some of the many children who took part in trials of poliomyelitis vaccine

polio vaccine on 161 children to the Immunization Committee, a scientific advisory committee to the National Foundation for Infantile Paralysis.[2 3] The foundation, created in 1938 by President Roosevelt and his law partner, Basil O'Connor, was a lay governed organisation based on grassroots fundraising and volunteer effort. For 15 years a portion of the dimes and dollars collected in the annual "Mothers' March" had been devoted to research: epidemiological studies of poliomyelitis, identification and classification of the three strains of the virus, development of practical culture methods. These projects had strong support among scientists, but for the foundation's staff and volunteers they were necessary stepping stones to the development of an effective vaccine.[4] Salk's work seemed promising to O'Connor, and to Thomas Rivers, the dean of the foundation's scientific advisers. The children had shown no ill effects and the levels of polio antibodies in their blood had risen. Almost immediately, O'Connor and Rivers began planning for a major field trial.[4 5]

Several of the senior virologists on the Immunization Committee, notably the Nobel laureate John Enders of Harvard and Albert Sabin of Cincinnati, thought these plans precipitate. They questioned the relation of antibodies to permanent immunity and doubted the safety of a vaccine prepared from virulent poliovirus, whatever "inactivation" method was used. Enders described Salk's work as "most encouraging" but cautioned that "the ideal immunizing agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk"[6]—that is, an attenuated strain that would create immunity by producing a subclinical case of the real disease, as in the classic cowpox/smallpox model.[3 5]

Despite these objections, O'Connor believed that his organisation had a mandate from its volunteers and donors to proceed.[3 5] As Harry Weaver, the foundation's director of research, wrote: "The practice of medicine is based on calculated risk .... If [we wait until more] research is carried out, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so."[4]

The virologists' critique was only one obstacle to the field trial. Since paralytic polio was a disease of relatively low incidence, the experimental population would consist of school age children, the group with the highest case rate; the foundation decided to target the first three grades in the 272 counties with the highest incidence of the disease. Volunteers from the foundation would work through state and local health departments and schools to gain parental consent and deliver the children for injection.[7 8] The use of a placebo control group seemed to be too much of a "calculated risk," one that parents, teachers, and health officials would reject; in Salk's words, "a 'beautiful' ... experiment over which the epidemiologist could become quite ecstatic but [which] would make the humanitarian shudder."[9]

The foundation enlists support

On 9 November 1953, O'Connor announced that the field trials would begin in the spring and that an "observed control" plan would be used, in which one group of children would receive vaccine, while others in the same age group would not be injected but only observed.[10] Hart Van Riper, the foundation's medical director, asked the nation's health officers for advice and support.[11] Carrying the imprimatur of medical expertise, yet necessarily responsive to public fears, the health departments constituted a potential counterweight to the virology community.

Within a month, departments in 38 states had responded, most enthusiastic about the prospect of a vaccine and ready to use the observed control plan. A number of state officials, however, saw it as a problem that the project was sponsored not by scientists but by a lay organisation. They questioned the impartiality of an evaluation run by the foundation and the rigour of the proposed design.[3 12]

To meet these objections, and those of the doubting virologists, O'Connor and Van Riper asked Thomas Francis of the University of Michigan to direct an independent evaluation of the trials, supported by funds from the foundation, but otherwise autonomous.[3 4 13 14] Francis, a highly respected virologist who had conducted field trials of influenza vaccines, was supportive of the killed virus preparation. "I think I shall do it," Francis admitted in a letter on 29 December[15]; but before taking the job, he mobilised support among the state health officers to engineer a change in the trial design.

Two types of controls

In a public statement on 8 January 1954, the foundation still adhered to the observed control plan; but on 15 February, six days after Francis was formally appointed to head the evaluation, O'Connor announced that two types of controls would be used in the field trials: "observed controls" in 34 states and "placebo controls" in 11: "a combination of the two procedures [will] assure a valid evaluation of the trial vaccine."[16 17] This change in plans was the result of a month of manoeuvring on Francis's part.

He had requested an "advisory group" meeting on 11 January. This new group was entirely distinct from the foundation's scientific advisory committee, which

was excluded from these deliberations. As well as the senior staff of the foundation, a selected list of state health officers, paediatricians, clinical polio specialists, statisticians, and virologists attended. Their charge was not to debate the merits of Salk's work but to take the vaccine project from the laboratory into the field. Part of the January group later became an advisory committee for the field trial evaluation, and the state health officers constituted a separate body to advise on "technical aspects" of the project.[1 18 19] Because the health officers were divided, Francis's role was critical.

The 11 January meeting began with briefings from the foundation's staff on plans to date. Rivers assured the group that the foundation would do its best to guarantee the safety of the vaccine.[18] After general discussion, the group subdivided for the afternoon into three groups designated as "clinicians," "statisticians," and "health officers." Though each of the groups made several recommendations, I will focus here only on their statements regarding trial design. The clinicians' report assumed the use of observed controls, and the statisticians' group, unsurprisingly, recommended the use of "a blind injected control" wherever the "proper facilities" made such a design possible.[18]

Francis himself joined the "health officers" group. He listed in his notes several health departments that would support an injected, or placebo, control design: Massachusetts, New York, Michigan, Ohio, Illinois, California. Each was a populous state with a well organised health department headed by a nationally respected physician. Perhaps, he mused, a "double study" could be done in these states: placebo controls in the second grade, observed controls in the first and third grades.[20]

Rewriting the design

When the "health officers" met in the afternoon of 11 January, Francis found the group willing to endorse an even broader design. The participants included Francis, health officers from California, Illinois, New York, and Massachusetts, and two friendly virologists. Their report began emphatically: "It was the consensus of the group that [placebo controlled] studies were necessary … that rather than limit the controlled study to the second grade it would be better to take the first three grades of school and select individuals … on an alternate basis."[17]

The Health Officers' Advisory Committee which met in Atlanta at the end of January was a select group of doctors from eight states who were supportive of placebo control. Francis told the group that he had decided to accept the job of directing the evaluation "with the understanding that a number of the states have indicated that they would like to, and would be able to, carry on injected [placebo] control studies." The majority of the states, 36, preferred to adhere to the observed control design. Francis suggested that if a shortage of vaccine developed (which seemed quite likely at that point) supplies should be reserved for the placebo control areas; the group agreed with a formal recommendation that those areas be given "priority on available vaccine." Someone asked whether the placebo control plan would make it more difficult to obtain the parents' consent. The group decided that it could rely on the widespread fear of the disease; members agreed that "it would not be difficult to sell as there is a high attack rate in the three grades [and] there would still be a 50% chance of a child receiving the vaccine."[19]

In Francis's mind, the placebo control study was now his primary interest, and he reiterated this point in the summary report. Indeed, he seems to have stage managed the January meetings to reorient the project in that direction, selecting likely allies among the health officers and using their support to rewrite the trial design. "The best Departments are committed to this [placebo control] plan," Francis told Van Riper. "The assurance and faith of those committed must be maintained."[21] Although it might be necessary to exploit parents' fears to obtain their consent and to allow large numbers of children to face the polio season without protection, the use of a randomised and blinded controlled trial would effectively counter the criticisms of scientists such as Enders and Sabin, legitimise the sponsorship of the lay governed foundation, and gain the support of the leaders of the medical community, exemplified by the nation's leading state health officers.

A national event

But the observed control trials were not a sideshow to the main event, an unnecessary "deviation" from good methodology. Thirty six health departments, representing a large segment of public opinion and the rank and file of the medical profession, were committed to that plan and their participation was necessary to the field trial. If the Salk vaccine trials were to succeed, it was essential that they be a great national event, enlisting volunteers, doctors, and parents in one united effort that represented the culmination of 15 years of work and faith. Given the climate of scientific doubt that surrounded the killed-virus vaccine, it was essential that the field trials offer public, as well as scientific, validation of its effectiveness.

The National Foundation for Infantile Paralysis had tried to reconcile its scientific and political problems by working through the state health officers, but this group—each official facing the conflicting demands of professional training and public constituency—was itself divided. O'Connor then enlisted Francis and his impressive credentials, who, rather than pacify the advocates of placebo controls, chose to ally himself with them. The ensuing negotiations shaped a dual statistical design that reflected the multiple meanings of the trial: as scientific demonstration, political statement, and mass participation event.

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Efficient management of randomised controlled trials: nature or nurture

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A randomised controlled trial sets out to do just one thing—to discover the truth. Pick up any medical journal, and you can read about the need for a good randomised clinical trial to answer a burning clinical question. A trial that will inform, enhance, and, when applicable, change clinical practice. Experienced research committees prioritise the clinical questions that need answering to ensure the health of the nation. They also set guidelines on what constitutes good clinical practice within a research context.[1] Furthermore, the scientific and clinical communities ensure that good scientific modelling is central to trial methodology. How a trial actually happens and how the conclusions that affect clinical practice are arrived at are often less prescribed.

Little is written about the day to day and strategic management of such trials. There are no clearly defined operational models established or any code of practice for managing a randomised controlled trial. The apparent lack of recognition for the role of efficient management in the effective delivery of a trial needs to be addressed. Randomised controlled trials need to be managed like any other organisation. Many clinical trials fail to deliver because of the lack of a practical businesslike approach to getting the job done.

Summary points

- Although the scientific validity of a randomised controlled trial is subject to intense scrutiny, the actual management of the trial often receives little attention
- The knowledge and expertise gained on running earlier trials are not widely disseminated, so new trials are begun from scratch
- Trials need to be marketed properly to ensure that sufficient numbers of participating centres and patients are recruited
- For the day to day running of the trial, robust systems and procedures must be designed that are efficient, effective, and flexible (generic models that can be customised)
- A trial team is needed for the efficient management of a trial and to ease the burden on collaborating groups

Reinventing the wheel

The past 50 years has produced many successful clinical trials, which have changed clinical practice. However, the knowledge and expertise gained on how to run those trials have not been widely disseminated. Again and again, trials are begun from scratch. Often there is nothing but the scientific question along with the enthusiasm and commitment of the principal investigator to make it happen.

A system of "mentoring" and training is being developed by the Medical Research Council and Health Services Research Collaboration to help alleviate needless duplication and provide a network of support for trial teams—in effect, a little "nurturing." In mentoring an experienced trial coordinator works alongside a recently appointed coordinator, giving support and guidance through the setting up phase of a trial on areas unique to clinical trials. The system can also offer ongoing advice and aftercare. Courses on clinical trial management are being developed and will provide training for new and experienced coordinators. The expertise developed in a clinical trial should be valued and not lost as a result of a lack of career structure or a recognised body that could offer direction to individual trialists.

What makes a trial happen?

A randomised controlled trial has a basic scientific methodology. During the long phase of developing a