
Debate

Clinical trials – a brave new partnership: a response to Mrs Thornton

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Author's abstract

In this commentary on the previous paper it is explained that screen-detected Duct Carcinoma In Situ is effectively a new disease of unknown natural history. It is therefore impossible that 'the doctor knows best' and it is therefore both in the patient and the public's best interests that such cases are submitted to the rigours of the randomised controlled trial.

Inevitably this brings the ethical dilemma of how to explain to patients the uncertainty and how to involve them in a rational decision to take part in the randomised controlled trial. It is argued that as well as there being a collective benefit for future generations of women, that we should resolve this problem now, the individual woman is likely to benefit from being treated according to a strict protocol.

Nevertheless the time of diagnosis is paradoxically not the best time for a patient to become aware of these matters and it is about time that the lay public and the opinion formers recognised their responsibility to become acquainted with the benefits and the needs of the randomised controlled trial in anticipation of the day when they themselves will be patients.

'Even if the open windows of science at first make us shiver after the cosy indoor warmth of traditional humanising myths, in the end the fresh air brings vigour, and the great spaces have a splendour of their own'.

Bertrand Russell, 1925 (1)

Most of the lay public and sadly many of our political leaders have never been exposed to the open windows of science and thus have never been shaken out of their complacent beliefs in the myths of received wisdom. Hazel Thornton, a highly intelligent and articulate person finds herself shivering at this open window, forced to contemplate the scientific process as a result of the diagnosis following mammographic screening of the enigmatic condition, referred to as Duct Carcinoma *In Situ* (DCIS). Having got to know Mrs Thornton

well, I have it from her first-hand that this experience has in a perverse way been invigorating and has opened up vast new perspectives for her personal experience. Encouraged by myself and other clinical scientists she suddenly finds that she is invited to scientific meetings to express her views, is offered privileged space in such learned journals as the *Lancet* (2) and has had the opportunity to sit down and discuss these issues with some of the finest brains in the business. This alone demonstrates the openness of the scientific process that welcomes dissenting voices, as without dissent there can be no progress.

It is indeed a cosy myth that the doctor knows best and that for every patient, for every disease, there is a best treatment. This belief, perpetuated by a peculiar conspiracy of the public and the profession together, has effectively held back the progress of medicine for 100 years, delaying its entry into the scientific era and making it extraordinarily difficult to draw the line of demarcation between orthodox and 'alternative' medicine (3).

Nevertheless I have been one of the first to recognise that the application of the scientific method and its expression through the medium of the randomised controlled trials brings with it unique problems of medical ethics (4). To illustrate my thinking on this point I would like to quote from a publication of mine in the *Lancet*: 'We have to face up to this extraordinary dilemma, the need for randomised controlled trials is now recognised by all clinical scientists and the Department of Health acknowledges that such trials are essential for assessing the effects of health technologies and for controlling the introduction of new therapeutic regimens into the National Health Service in Britain. There is a moral obligation for the public to join such trials, but at the same time there is an ethical imperative that they should only do so, with fully informed consent, yet the seeking of informed consent shortly after the diagnosis of a life-threatening condition is on the one hand cruel, and such cruelty negates the ethical imperative of beneficence and on the other hand a charade' (5). I therefore absolutely agree with Mrs Thornton that achieving 'informed consent' within two weeks of

Key words

Clinical trials; informed consent.

the diagnosis of DCIS in a woman who thought herself well until submitting to screening mammography, is an absurdity! We continue to pay lip service to this charade which I believe has more to do with protecting the doctors from litigation in America or from vilification in the press in this country, than with protecting the patients. It is difficult enough for the lay person to understand disease processes, medical treatments and the need for randomised controlled trials when they are perfectly well but imagine what this imposes on them when they are suddenly faced with the disease, whose over-treatment could lead to unnecessary mutilation and whose under-treatment could lead to premature death. I share Mrs Thornton's view that most consent within clinical trials conducted in the politically correct manner is ill-informed consent, yet until now few have had the courage to state this in public. In this respect Mrs Thornton and I are allies but our responses to this challenge are diametrically opposed, which is no surprise as we emerge from the two distinct cultures of our society, with differing backgrounds in the liberal arts and the biological sciences. Mrs Thornton's response is a plea for less science and less disclosure and mine is a plea for more science and a more open and honest dialogue with our partners (the patients) in our search for better treatments for patients with cancer.

Having dealt with the generalities of the matter I think the specifics of the clinical trial into which Mrs Thornton was invited to participate beautifully illustrate the paradoxes and double standards that apply when you retreat from the scientific method in clinical medicine. The problem with screen-detected DCIS is that we are uncertain of its natural history. It is likely that say only 1 in 4, if left untreated would progress to invasive cancer with all its lethal potential (6). Over-treatment in such cases would lead to unnecessary mastectomy. However, under-treatment in the minority of cases could lead to unnecessary death. This cruel dilemma is neither the fault of the surgeon nor the fault of the clinical scientist but a defect in the screening process itself. Although mammographic screening in women over the age of 50 can lead to a relative reduction in cause-specific mortality from breast cancer of the order of 20 per cent, one of the costs of this activity, which the patients have to shoulder, is the detection of DCIS together with the uncertainty of its management (7). This has to be added to the cost/benefit analysis of the screening process and not added to the cost/benefit analysis of a randomised controlled trial (*vide infra*). It is those who made the value judgement on behalf of society, that mammographic screening is a worthwhile activity, who should shoulder the blame for the dilemma about the treatment of screen-detected DCIS.

Be that as it may, Hazel Thornton's response to this dilemma would be to study the natural history of the disease on the one hand and a retrospective

analysis of the results of previously treated cases on the other hand. I would agree in principle with the first approach, but has Mrs Thornton thought this through? To study the natural history of DCIS would entail no intervention whatsoever, and imagine the public outcry if on having detected the characteristic microcalcifications on a mammogram the clinician sat back and monitored the mammographic images at, say, yearly intervals, until a proportion progressed to invasive duct cancer. Even I couldn't subscribe to that in practice.

Retrospective analyses of previously treated Duct Carcinoma *In Situ* are already available and have generated sufficient uncertainty to persuade the experts that a clinical trial is necessary (8). Although we accept that the disease can be cured by a mastectomy in all cases, this still brings us back to the point that the majority of these cases will have been over-treated but at present we don't know which these are. Furthermore, previous series of trials of DCIS concern the treatment of clinically detected variants of the disease, which are extremely rare and probably have a different natural course from those which are sub-clinical and screen-detected. When Mrs Thornton makes the plea for clinicians to be free of the constraints of a trial to allow them to 'conquer mountains rather than working on plateaus', she has rather uncharacteristically sunk to the level of political rhetoric. The majority of surgeons are completely free of constraints within clinical trials and this freedom from constraint led to the persistence of the Halstead radical mastectomy for early breast cancer up until the 1970s, when clinical trials demonstrated the safety of an ultra-conservative approach. So in other words Mrs Thornton is making a plea for the return to the cosy indoor warmth of inductive reasoning, which held back my subject for more than 100 years. I am afraid that once we open the windows of science they can never be closed, short of a return to the days of the Spanish Inquisition.

Later on in her paper she suggests that an alternative to the trial and presumably an alternative to the study of the natural history using its true meaning would be a wide local excision of the mammographic abnormality alone with the careful documentation of the individual patient and her individual pathology ... and then what I ask? After about five years we might have accumulated enough cases of different histological sub-types to be followed up for ten years, after which time we might have learnt to characterise the minority that have the potential to progress to invasive disease from cells presumably left behind after the wide local excision. It would then take a longer period of time to collect a large enough sample of these sub-types to conduct the trials of radiotherapy or tamoxifen, the whole process taking thirty years or more. In contrast the factorial 2×2 design* of the United Kingdom Co-ordinating Committee on Cancer Research

(UKCCCR) trial enables us to address all these questions at the same time, using the same cohort of patients, which should allow us to provide an answer in at least half the time of Mrs Thornton's approach, which effectively is an uncontrolled study of wide local excision alone. I ask readers to decide which is the flawed design?

The randomised controlled trial has been described as one of the fairest risk-limiting practices used by human societies (9). The UKCCCR trial would only expose 25 per cent of its patients to the risk of under-treatment, whereas Mrs Thornton's design would expose 100 per cent of patients to the risk of under-treatment. Under-treatment risks lives whereas the worst over-treatment in the UKCCCR study would involve a course of radiotherapy and tamoxifen which even with the most pessimistic interpretations of available data couldn't possibly have the lethal effect of invasive carcinoma of the breast. After a slow start the UKCCCR trial is now recruiting well and is likely to achieve its target on time. Trials of a similar design are currently recruiting well in the European Organisation for the Research and Treatment of Cancer (EORTC) in Europe and the National Surgical Adjuvant Breast Project (NSABP) group in the United States of America. The world overview of this international activity will speed up the answer and provide sufficient statistical power for sub-group analyses. I have freely acknowledged the ethical dilemma in recruiting patients to such trials but in all fairness it must be recognised that attempts to inhibit or torpedo this activity have ethical consequences as well. Without these trials women worldwide with screen-detected DCIS might continue to receive under-treatment or over-treatment with unnecessary loss of life and unnecessary loss of breast.

Once again I acknowledge Mrs Thornton's courage in bringing these issues into the public domain and once again I throw down the challenge to lay groups, such as the Women's National Cancer Control Campaign, and Europa Donna to join the clinical scientists as partners in our quest for improving the treatment of patients with cancer.

'Impeding medical research no less than performing it, has ethical consequences. Not to act, is to act' (10).

Stop press

At the time of correcting the final draft of this text the first report of the NSABP trial comparing lumpectomy alone with lumpectomy plus radiotherapy for DCIS appeared in *The New England Journal of Medicine* (11). The conclusion of this study with a maximum follow-up of five years was that breast irradiation after lumpectomy is more appropriate than lumpectomy alone for women with localised DCIS. The working party of the UKCCCR trial are now urgently discussing whether they

should drop the non-irradiated arm of the trial, whilst continuing the tamoxifen-only randomisation. Mrs Thornton should now, urgently, be reconsidering her prejudice against radiotherapy.

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*A factorial 2x2 trial allows you to address two questions in an RCT with the same cohort of patients. Generic design:

	COLUMNS	
	W	X
Y	CONTROL (C)	A+C
Z	B+C	A+B+C

To analyze effects of 'A' compare outcomes between columns W v X.

To analyze effects of 'B' compare lines Y and Z.

Actual design:

	W	X
Y	WIDE EXCISION	+ TAMOX
Z	+XRT	+ TAMOX + XRT

NB: A 4-way analysis has half the statistical power of the 2x2 analysis.