Debate

Clinical trials – a brave new partnership?

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Author's abstract

The need for informed consent is considered from the patient's viewpoint by an examination of the shortcomings of the UK Ductal Carcinoma In Situ (DCIS) trial and its failure satisfactorily to accrue both profession and patient. The impersonal, negative aspects of the informed consent process in the research situation are contrasted with the positive benefits of confidence fostered by the traditional doctor/patient relationship. The need for new research with a partnership between patient and profession, the necessity for rigorous re-assessment of treatments and care both within and outside of trials to avoid waste by the perpetration of unnecessary treatments together with the need for evaluation of the efficacy of treatments employed outside of trials, especially in 'new' conditions, to foster progress and maintain public confidence in the profession, is advocated.

'Human kind
Cannot bear very much reality.
Time past and time future
What might have been and what has been
Point to one end, which is always present.'

T S Eliot. *Four Quartets*. Burnt Norton (1)
The question asked in 1986, 'Do we need informed consent?' (2), has elicited numerous responses from the professions. Professor Baum also asked: 'But whose attitudes to informed consent are more important – those of the doctor, the lawyer, the ethicist, or the patient? We have heard much more on this from the first three but know little about the attitude of patients, present or potential' (2). Response from the patient is less well documented and more difficult to assess. This examination of the question is offered from the patient's viewpoint, following my being asked to participate in the UK Randomised Controlled Trial for the Management of Screen-detected Ductal Carcinoma *In Situ* (DCIS) of the Breast in September 1991. It is offered in the hope that it may assist in identifying

the drawbacks to the current system where informed consent, whilst accepted as being necessary, has been shown to be a grave stumbling block for the profession and public alike.

My original observations (3) resulted from the necessity (for me) of justifying my refusal to participate in the UK DCIS Trial. Regrettably, were I to be invited today my answer would be an even more emphatic 'No!' An examination of my reasons may therefore prove to be fruitful. The possibility of achieving 'informed consent' for this trial in two weeks was absurd: the suspicion that the unbalanced treatment options were unreasonable troubled me. The request was made at a very stressful time when, after two weeks of anxious waiting, I was told I had a carcinoma. When most in need of support I was sent away to inform myself, feeling isolated from the medical team who seemed at that moment to be a research team more interested in future generations than in my own plight. It suddenly seemed that my belief that the physician's primary concern should be for me was ill-founded. I felt isolated, selfish, let down, ill-prepared for considering the options for this unknown disease of DCIS which would obviously affect my life and health. The impersonality of this trial proposition seemed to be attempting to deprive me of one of the most important factors of healing, continued confidence in 'my' team, whilst accentuating negative aspects of chance rather than choice. My worries about the unbalanced and excessive treatment options for a non-invasive cancer were exacerbated by my research findings, leading me to the sad conclusion that 'informed consent' was impossible and that the best anyone could hope to give would be 'partly informed consent' but more likely 'ill-informed consent'. Having declined to participate, my perturbation led me to continue to examine the matter.

We all use the best example to illustrate our case: hyperbole and exaggeration have their place for vivid illustration, and both advocates of clinical trials and patients seeking to understand 'informed consent' are no exception! The clinician/researcher is free to choose from his or her wealth of experience of these matters for a good example but the patient will have the choice thrust upon her by her own unique set of

Key words

Informed consent; DCIS; multi-centre trials; confidence; patient's viewpoint.

circumstances. My disease was asymptomatic DCIS and the UK DCIS trial was the one in which I was invited to participate. Furthermore, I fell into the category of <1.5 per cent target figure of women screened who shall be subjected to an open surgical biopsy (4) and it is from this viewpoint that I am offering my observations.

Anger at double standards

Proponents of clinical trials naturally express anger at the double standards which obtain and the injustice of a situation whereby those who do not practise within a trial are able to treat patients without the need for informed consent but according to their own beliefs of what is best for each individual patient, even though this may be perpetuating unknown and sometimes toxic treatments, thereby inhibiting progress towards the prevention and cure of breast cancer. The reality is that there is surely a wide spectrum of attitudes amongst these clinicians and a wide variety of reasons for non-participation. Is it somehow more laudable for the trialist who uses overtreatments to test toxic treatments? And withholds treatments in the control arm? Because he *needs* to know?

A consideration of *why* clinicians fail to co-operate in clinical trials could therefore be constructive. It was reported at the second European Organisation for the Research and Treatment of Cancer (EORTC) Consensus Meeting on Ductal Carcinoma *In Situ* of the Breast in September 1991 (5) that: 'A more ominous development seems to be an increasing reluctance of both physicians and patients to accept entry into these trials. The reasons for this appear complex and were much discussed'. Co-incidentally, at the time of this consensus meeting I expressed my concerns as a patient being invited to participate in the UK DCIS Trial (3). Perhaps a simple definition of an acceptable trial for a doctor is one where, having genuine doubts about the best treatment, he is able to take full responsibility for the suitability of each treatment offer.

The UK DCIS trial is not simply a matter of, say, comparing a new drug with the current standard treatment. To quote the protocol (6): 'It is conventional in clinical trials to compare in the control arm the best standard therapy for a given disease with a novel treatment. However, screen-detected DCIS is effectively a new disease in the UK. Therefore there can be no standard treatment for use within the control arm'. The standard treatment for *symptomatic* DCIS is mastectomy, effecting near 100 per cent cure. This trial, after conservative surgery, compares in a factorial 2×2 design nothing further; tamoxifen for five years; radiotherapy; radiotherapy plus tamoxifen. Is the doctor's reluctance due to his inability to take responsibility for submitting patients to this trial, because he knows that the natural history is not known, there is no

standard treatment, that there is a radical cure for symptomatic DCIS, that the risks of treatment are considerable for healthy women with a 90 per cent chance of surviving 10 years (5); that only one out of four patients will progress to an invasive cancer in her lifetime; that there is an excellent chance for salvage upon recurrence; that the latest findings show that DCIS is heterogeneous histologically, radiologically and biologically and that this diversity may have implications for patient management? At this stage he may feel that analysis of retrospective studies is preferable. To be free of trial constraints will enable him to conquer the mountain by incorporating the latest worldwide findings into his thinking rather than working on the plateaus of prescribed activity between the review points of the trial. Since the protocol of the UK DCIS trial was devised in December 1989, evidence has emerged indicating that the risk of local recurrence is greater with the more aggressive comedo sub-type, but wide participant-entry criteria for this trial takes no cognisance of this. This trial therefore carries the possibility of perhaps under-treating with the 'nothing further' control arm, whilst offering the possibility of over-treating some of the 75 per cent of women who will not progress to an invasive phase during their lifetime with a full course of radiotherapy plus tamoxifen for five years. Does this not demonstrate the 'need to know' rather than ought to know? It certainly flouts the laid-down principles of screening (7) that the natural history of the disease should be well known; treatment of a disease at an early stage should be of more benefit than treatment started at a later stage, and the chance of physical or psychological harm to those screened should be less than the chance of benefit. And it offers the potential hazard that women might undergo unnecessary procedures for the diagnosis and treatment of cancer *which might not have entered an invasive phase during their lifetime*. Such precipitate and flawed trials will attract neither profession nor patient, do harm to the acceptability of trials in general, are an unacceptable drain on resources and do not meet standards of quality demanded today.

The opportunity to question the trial doctor is limited

The patient's opportunity for questioning the 'trial' doctor is limited. He must be committed to persuading patients to enter the trial, even though, during the course of that trial he may have shifted his viewpoint from being honestly able to say: 'I do not know which treatment is best for you' towards the belief, based on emerging findings, that he may at least 'prefer' a particular treatment for a particular patient. It seems to me to be ethically preferable that a doctor should be able to so modify his beliefs and be able to justify his preference whilst explaining that,

with a new disease, there is insufficient scientifically adequate evidence to support that belief, at the same time taking into account the preferences expressed by his patient in the light of her own case history, circumstances and attitude. The patient who declines to go in the trial is told that it will in no way affect the way in which she is treated: she is, however, deprived of being treated by a doctor who can openly discuss his preferences, because the doctor is involved in the trial.

Is it too selfish for a patient to expect her consultant to be solely concerned with *her* welfare when she has just been told that it was a carcinoma? Total concern for *her* will seem to have been replaced by a concern for future generations. The two weeks given her will seem like a no-man's-land of floundering ignorance when she must decide if she can join this army of recruited participants where she does not understand the sophisticated weapons being employed against an enemy which presents itself in a multiplicity of forms. She enters the battle already mutilated and is told she may carry on the fight with nothing, a sophisticated weapon in either hand or in both hands. We are admonished to study history: did not the dynamism and confidence of Henry V at Agincourt inspire his small, tired army to respond with hope, valour, confidence and courage against the odds? Battles are not won by those with the most sophisticated weapons and despair and doubt in their hearts. 'To win the war against fascism in the early 1940s, there were not enough volunteer soldiers, and conscription, with the denial of self-determination, was essential. To win the war against cancer by the end of the millennium offers a different challenge. The enemy is heavily disguised and hides among our healthy allies. Conscription and the loss of autonomy are no longer politically correct. The answer therefore lies in a partnership between doctors and patients, more of whom need to volunteer for trials' (8). So the fault may not lie in the apathy, ignorance and unwillingness of the volunteers, but in lack of solidarity within the profession?

Percentages are people

Is this why there are so few volunteers? No one doubts the enemy must be conquered. Could it be that the generals and their tactics do not inspire us or have our confidence? Where is the charisma of the cold clinical trial? Why does the scientist so often ignore, forget or deny the benefits of the intangibles of hope in a common cause, confidence and inspiration? Despair never won battles! Statistics are cold. Percentages are people! Do we want our generals with faces lit by the green luminescence of the computer screen, pushing buttons for our treatments? Would we rather not fight with them, each according to his circumstances and abilities but appreciating the uncertainties? Is this not the partnership we are looking for?

Who is the heavily disguised enemy among our healthy allies in this war against cancer? Perhaps these independent-minded ones are sceptical of the published outcome of trials (9), concerned by the misleading results of trials due to sample bias (10), resistant to the constraints of trials, resentful of the embargo they put on emerging preferences, unhappy at the reduction in their clinical freedom to tailor the treatment to their individual patients. They do not necessarily practise in the cosy comfort of their own unjustified certainties: they may rather wish to have scope to modify their opinions in the light of emerging data rather than wait for review points of trials to be able to do so. Could we not ascribe to them the noble desire to take total responsibility for their patients' care? The nirvana of total certainty is a myth. Have the myriad of past trials provided certainties? They usually indicate the way forward to the next generation of trials!

Room for new research

'There is clearly room for new research, comparing the outcome in clinical trials of patients with the common adult tumours and of similar patients treated on an *ad hoc* basis outside trials' (8). Currently the NHS is grappling in the market-place of purchaser/provider where limited resources demand efficient, appropriate and effective methods of care, with consequent priority for good research, to achieve quality of care and quality of life for the patient. The need for rigorous assessment of any new treatment to avoid piecemeal introduction of advances and perpetuation of those that do not work has now been declared by the government (11). This policy can be applied to ensure that quality is maintained and valuable resources are not wasted either within trials or outside of them. The rigidity of the current concept of 'informed consent' is an inhibition to advancement which is best illustrated by two extremes. The humanly inappropriate formal consent procedure used in the USA in the ISIS-2 trial of streptokinase and aspirin in acute myocardial infarction so slowed recruitment and delayed completion of the trial that it was responsible for many thousands of unnecessary deaths, although this simple trial is a beautiful example of 'the uncertainty principle' being exercised, resulting in enormous progress with an inexpensive treatment. The UK DCIS trial is the absolute antithesis of the ISIS-2 trial: the patient is healthy, not acutely ill; there is no hurry for action but time for consideration; there is near ignorance of the new condition of DCIS, not the understanding of heart attacks; the complexity of the disease, treatment options and wide participant-entry for the DCIS trial contrasts sharply with the clear issue being examined in the ISIS-2 trial. What these two trials both demonstrate in full measure is

our inability to define an acceptable level of informed consent for all situations, although few would argue about the need for it, and that bad trials are an equally bad stumbling block to progress, and just as wasteful of resources. There is clearly a need for technological and ethical examination of multi-centre trials by a national committee. A simple alternative to the potentially destructive DCIS trial, as suggested by Charles Hamilton (12), lies in careful documentation of individual patients and their pathology and close observation; in that way the natural history of the disorder will be learnt, high-risk groups identified and public confidence maintained.

Today's question should be: 'How can we achieve a partnership agreement between profession and patient so that patient care and research and development make progress?'

Hazel Thornton is a semi-retired Director/Company Secretary. She was invited to participate in the UK Randomised Controlled Trial for the Management of Ductal Carcinoma In Situ (DCIS) of the Breast, in September, 1991. This invitation resulted in a paper entitled Breast Cancer Trials: the Patient's Viewpoint, which was published in The Lancet in January 1992, followed by others in different journals, and correspondence and involvements worldwide.

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News and notes

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