Fully informed consent is impossible in surgical clinical trials

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Clinical trials are a cornerstone of advancing quality in all areas of medical practice. They may be especially challenging in surgical specialties where potential risks of surgery, including novel interventions, can be catastrophic. Yet they are most important in surgery because the prognosis for quantity and quality of life for many of the major diseases we surgeons treat are poor to fair (e.g., glioblastoma multiforme, pancreatic cancer and ulcerative colitis). If we did not conduct properly designed randomized controlled trials (RCTs), we would be passively committing our future patients to a standard of care both they and we should not accept. The results of positive trials may translate into substantial improvement in quantity of survival or quality of life for surgical patients.[1] Negative trials, although disappointing, provide data that may result in alteration of clinical practice, which protects patients from receiving potentially toxic treatments that have no material benefit.[2]

Consent for an investigative procedure has 3 distinct but interrelated elements that are essentially the same as for purely therapeutic procedures: disclosure, capacity and voluntariness.[3] In this brief commentary, I reiterate widely held concerns about informed consent and take the argument one step further by suggesting that truly informed consent is essentially impossible and almost never obtained from research subjects in clinical trials in surgery.

If we look first at disclosure, it is impossible for investigators to list every possible material risk to a patient embarking on an experimental therapy. There are a number of reasons for this, but arguably the most relevant is that investigators simply cannot foresee every possible significant risk of a new treatment. There are numerous examples in the clinical trial literature. When the first RCT of high-activity brachytherapy for de novo glioblastoma was performed, it was based on good science and much excitement from promising clinical results observed in phase I and phase II studies.[2] In this particular RCT, 2 patients suffered devastating middle cerebral artery strokes presumably due to radiation fibrosis and resultant occlusion of the artery lying in close proximity to one of the implanted radiation catheters.[4] Both patients survived for brief periods in a markedly compromised condition after this event, a complication that investigators would not have been expected to discuss with their patients.

Furthermore, it is quite likely that investigators overplay the potential benefits and underplay the potential negatives of a novel therapy, especially the degree of uncertainty about the experimental treatment's ability to provide material benefit. This suspicion is corroborated by a recent study in which investigators analyzed in detail 277 consent forms for phase I gene transfer protocols and, indeed, found that the consent forms were overly optimistic.[5] This propagation of the "therapeutic misconception" in clinical trials has been found in other studies.[6]

With regard to capacity, patients who have just been told they have a devastating condition such as esophageal cancer can hardly be expected to be in a psychological state of mind compatible with understanding all of the additional information the clinician investigator is about to tell them concerning a clinical trial. Patients' trust in the doctor is obvious, but the relative unimportance to the research subject of factual information is less obvious. This phenomenon has been found in qualitative research in which patients were interviewed about what factors led them to consent to major cancer surgery.[7] The overwhelming finding was that patients base their decision to go forward on trust as opposed to

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factual information about risks and benefits. In an analogous study, patients were asked if they were concerned about medical error before undergoing major brain-tumour surgery.[8] Again, when asked to talk about medical error, patients chose to talk about trust, indicating that this may be the major factor guiding patients' decisions to go forward with major medical interventions.

The final element is voluntariness, which means that the patient is able to act in his or her best interests without undue influence or coercion. Obvious sources of undue influence come from the patient's loved ones (e.g., parents, spouse, children), friends, employers, and others who are championing their view of what is right for the patient. The most insidious form of undue influence, however, comes from the research subjects themselves, based on what they perceive others want, including the doctor. This is a form of subtle self-coercion, which again partly stems from profound trust in the doctor. Trust in one's doctor may cause off-loading of major decision-making to the medical person in authority, who has evolved as one who is seen to be looking out for the patient's best interests. If the doctor is suggesting or even offering to put the patient into a clinical trial, the patient may wish not to offend the doctor or may feel that entering the trial must be the right thing to do, or both. Just as clinician-investigators must be wary of subtle coercion and conflicts of interest within themselves,[9] so must research subjects be wary not to fall into a similar situation on the other side of the scalpel, so to speak.

Given all the forces at play, some obvious and some not, it is exceedingly difficult to achieve full disclosure to surgical research subjects, to ensure they are at full capacity to comprehend all the materially important information, and to obtain a state of complete and unconditional voluntariness. It must simply be accepted that fully informed consent is rare and generally unattainable in most surgical clinical trials. We must all be aware of this and not be disheartened by it, but we must continue to make every effort to achieve as close to informed consent as is possible in every situation.

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