Clinical Research: Problems and Possibilities

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Finding myself in my occasional role as guest editor for this issue of *Oncology News* and it being the NCRI supplement issue this month, I take the opportunity of continuing a theme I touched on in an editorial at about this time last year, brought to mind by the abstract of Prof Peter Selby's invited lecture on Clinical Research and Healthcare Outcomes. Two statements jogged my memory. Firstly, "The benefits of clinical research have historically only been available for a minority of patients". Secondly "Research active healthcare systems generate better outcomes for patients". He also mentions in the latter context the notion, which he considers falls short of convincing evidence, that individual patients in a healthcare institution do better if included in randomised trials.

My comment in the previous editorial was that "This reductionism can build a parallel universe where clinicians know well how best to treat patients who would be eligible for an RCT, but arguably short changes the many who would have been excluded". I have recently been following the fortunes of a good friend who landed a job as a research nurse largely on the basis of one multicentric, supranational clinical trial. It is a cruel game I play with her that whenever we meet I enquire whether she has managed to recruit a patient yet. The fun might now be spoiled in that most recently and after several months on the job, a potential participant was apparently identified, but not yet consented. It is not a rare cancer that is involved here either: one of the top three, by incidence, in fact.

The dilemma of choosing how far to go in designing reductionist experiments, as against realistic ones, is not the sole preserve of clinical trials researchers. It pops up in the basic science research laboratory where, for instance, those who work with primary cultures tend to sniff at the rest of us who use cell lines. They do so with reason, but not necessarily with justification. Much of the biochemistry of life was originally elucidated in micro-organisms. The surprising conservation of genes through evolution makes that possible. It tends to be the middle ground where fine detail matters that causes controversy, such as extrapolations from animal to man.

Stratifying drug development trials into four phases, it is hard to knock phase I studies; tolerability is an obvious first step as is dose escalation. Phase II trials are usually small and loosely controlled, if at all; adequate to identify some measure of efficacy. Perhaps the minimal control element might however be a bonus rather than a deficiency in viewing the results. It is the climax of the process with the phase III RCT where the difficulties lie; in the exertions to achieve homogeneous groups so that only one variable (or as near to one as possible) is up for assessment. They do indeed supply essential evidence, but evidence that needs a sceptical reception. It is perhaps for the statisticians and study designers to seek the solutions, by having the wherewithal and being happy to deconvolute complex data and less inclined to insist on relatively simplistic experimental designs with rigid inclusion limits in order to ease interpretation. A simple aid to gathering as much information as possible is to follow the adage 'randomise early, stratify late', even if that means excluding some subsets from some analyses where they clearly do not belong.

Phase IV, so called ongoing development, problem identification and the emergence of extensions to the original use is where a drug or protocol meets the real world. Here I happily find myself singing from the same hymn sheet as Prof Selby. The healthcare system itself needs to be structurally research-minded in order to supply much of that valuable Phase IV data on which the development of real strategies for real patients who could not be consented into a trial, have an array of co-morbidities and inconvenient staging or presentation of the cancer that constitutes their most pressing problem. Or indeed cancer might exist but not be the most pressing problem.

Clinical research meets investigative healthcare in the realm of audit. This process combines elements of research method with the quality control procedures required of any organisation that is trying to deliver a 'product' of best quality to fulfil the legitimate and reasonable expectations of the end user … the patient, that is, not the doctor or other healthcare practitioner.

So let us hope that the inevitable reorganisation of both academia and the NHS will leave the former able to provide valuable scientific input and the latter to have the time space and money to keep clinical research moving at the increasingly breakneck speed required to keep up, both with those expectations and the rest of the world. ■

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