**Post-Print**

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# Impediments to "T2" research: is ethics really to blame?

Peer commentary

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Ever since the emergence of the field of research ethics, concerns have existed about the possibility that regulation of research might "cripple", if not eliminate, research in important fields (Beecher 1959). In recent years research ethics review has been accused of impeding basic and translational research and of being responsible for driving medical research from the industrialised West to "less heavily regulated" regions (e.g. Russia, Africa, China, India, Latin America and Brazil) (Asprey 2010). Indeed, while research ethics committees are sometimes criticized for existing primarily to serve the interests of research scientists and academic and commercial organizations, these committees and other regulatory structures have also been characterized as "regimes of ethical control" which seriously threaten both scientific progress and academic freedom (Boden, Epstein, and Latimer 2009).

Sofaer and Eyal join this chorus, arguing that post-approval ("T2") translational research is particularly affected by excessive regulation and overly bureaucratic ethics review. This is an interesting question, as T2 research has not typically been the focus of complaints about ethics review (which have tended to focus on more on regulatory impediments to research on "vulnerable" populations" such as children and the mentally ill, on restrictions to the use particular research technologies or resources such as human tissue collections and on the bureaucratic impediments to collaborative (including multi-site and multi-national) research (Boden, Epstein, and Latimer 2009; Asprey 2010)).

Unfortunately, Sofaer and Eyal provide little empirical data to support their claim, and their argument that ethical review is stifling T2 research appears to be based more on polemic and bioethical and biomedical editorials than on carefully considered evidence. Moreover, their argument that this is the major ethical issue in T2 research both ignores the fact that T1 research (i.e. the evidence upon which T2 research is based) may itself be ethically and epistemologically problematic, and diverts attention from the range of other, more significant, impediments to T2 research including discordant commercial, academic and government priorities, changing scientific paradigms, the globalization of research and consumer demands for "high tech" basic and T1 research.

First, while major distortions of clinical research due to commercial involvement are now rare, the involvement of the pharmaceutical and biomedical technology industries in medical research may still influence the generation of T2-type evidence. Clinical trials conducted by drug companies are designed to meet regulatory requirements for safety and efficacy with a view to attaining government approval and funding, and those deciding whether to register or subsidize medications do not always demand

much T2 information or reward such research. (It is important to note, however, that the process by which new medicines and biologicals are assessed and decisions made about approving government subsidization differs enormously between countries, with some countries requiring substantive cost-effectiveness, quality of life and translation data and others requiring just evidence of efficacy from Phase 3 studies). It is not surprising, therefore, that commercially funded research tends not to ask (T2) questions about substantive outcomes such as long-term survival, quality of life, feasibility of implementation or cost-effectiveness. It is also understandable that drug manufacturers may be reluctant to conduct studies with the potential to demonstrate either lack of efficacy or unexpected side effects. (Mitka 2003). Indeed, many "post-marketing" studies are currently designed largely to expose clinicians to new medicines or expand the marketing potential and patent life of a medicine by identifying new clinical indications (Relman and Angell 2002).

So-called "academic" research may be similarly prone to neglect T2 research. For one thing, medicine has always existed in a commercial environment and the distinction between "academic" and "commercial" research is no longer clear cut. Indeed, many universities and academic medical centers now position themselves as "partners" with private industry and do not necessarily demand, or even want, complete control over the design, conduct or dissemination of research (Bekelman, Li, and Gross 2003). T2 research is, therefore, not likely to be an "academic" priority if it is not a commercial priority. And even if academic research is independent of the pharmaceutical and biotechnology industries, there is still enormous pressure from governments which, in their funding priorities, may privilege "high-tech" basic science and T1 research that generates new intellectual property (Caulfield and Ogbogu 2008).

The demands for "high tech" research are also fueled by scientific progress and changing scientific paradigms, such as genomic medicine and pharmacogenomics (in which drugs are designed not for populations of patients, but rather for individuals with particular genetic profiles). This changes not only the nature of diagnosis and treatment ("personalised medicine") but also the relevance of particular kinds of research. In this context, randomized controlled trials are difficult and expensive to conduct (especially where more than one aberrant pathway or target has been identified and where combinations of targeted agents may be necessary) and meta-analyses have little meaning (Frueh 2009). Indeed, it may be the case that, as a result of such changes in our understanding of disease and treatment, the focus will shift not only away from T2 research, but away from clinical trials more generally, and towards basic research focused on the individual. The globalization of clinical research also raises issues about the generalisability of findings (including T2 findings) from one location to another (Glickman et al. 2009).

It is not only governments, universities and pharmaceutical companies that determine the direction of biomedical research. Consumers and patient advocacy groups are increasingly interested in ensuring that the research agenda generates the products and clinical outcomes that matter to them. Like governments and pharmaceutical companies, consumers seem to increasingly favor "high tech" basic and T1 research. "Personalised medicine", for example, is considered to be a priority by consumer groups and has received strong political support in many countries (Petersen 2009). The great excitement among consumers for the breast cancer treatment trastuzamab (Herceptin) which is tailored to cancers in which there is overexpression of the HER2 oncoprotein, provides evidence for such consumer support of "high tech" and individualized therapies and related research (Sparano et al. 2010).

We would argue, therefore, that while ethics review processes are potentially obstructive, they are not necessarily (excessively) so. Moreover, while it is possible that evidence may be found that research

regulation has constrained important T2 research, it seems unlikely that this is currently the case and to focus on adverse consequences of ethics review may divert attention from far greater threats to T2 research—threats that undermine the very possibility of T2 being on the research agenda. What is needed, therefore, is a more dialectical approach to thinking about T2 research, by which we mean, first, an approach which recognizes the complexity of social reality and accounts for *all* of factors impacting upon T2 research (and their interactions) and, second, an approach that allows for ongoing dialogue as new ethical and epistemological issues emerge.

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