Alemtuzumab and the value of neurological research

The announcement by the US Food and Drug Administration (FDA) on Dec 27, 2013, to reject an application for the use of alemtuzumab in relapsing-remitting multiple sclerosis (MS) has caused a stir within the neurological community. Investigators involved in two large phase 3 trials that tested its safety and efficacy expressed discontent; patients’ organisations protested the decision; the drug makers announced their intention to appeal this initial ruling (which is subject to further regulatory review); and even an opinion piece in the Wall Street Journal called for FDA reform, given such “vivid example of the serious problems besetting US drug regulation”. Friction among these stakeholders is common, and reflects the difficulties of the ever more complex process of moving experimental therapies into clinical practice. However, the process will not be streamlined solely by reforming the regulatory agencies.

The CARE-MS I and CARE-MS II randomised trials compared intravenous alemtuzumab with subcutaneous interferon beta in more than 500 and 800 patients, respectively. In both studies, alemtuzumab was more efficacious than interferon beta in reducing relapse rates, and patients treated with the antibody had fewer brain lesions and less brain atrophy. In CARE-MS II, in which participants had ongoing disease activity, alemtuzumab also had a beneficial effect on accumulation of disability; this improvement was not detected in patients with early MS who formed the study population in CARE-MS I. In both trials, the safety profile of alemtuzumab was as anticipated for an anti-CD52 antibody with lymphocyte-depleting effects: infusion reactions, infections, and autoimmunity. In light of these findings, the benefits were deemed greater than the risks by Canadian and Australian regulators, and by the European Medicines Agency, which approved the use of alemtuzumab in patients with active disease. But the FDA concluded that, because of their open-label design, the CARE-MS trials did not provide robust evidence to substantiate safety and efficacy claims.

Weighing up the risks and benefits of new treatments for chronic neurological disorders is a balancing act, but inconsistencies among regulators are becoming habitual. The recent regulatory discrepancies on the approval of new oral drugs for the treatment of MS (ie, cladribine and fampridine) raised similar questions to those now elicited by the alemtuzumab affair: how robust do results have to be in one study so that a second one is not needed? How long does a study need to be to assess safety? What is the most unbiased trial design? These issues refer to the uncertainties inherent to the scientific endeavour, but a more fundamental question is poised to the neurological research community after these incidents: why are the aims of the stakeholders in this long and complex process seemingly so misaligned?

A Series in The Lancet (Research: increasing value, reducing waste) provides the conceptual framework to initiate a discussion of this question. Participants and investigators in the CARE-MS trials will probably agree with the authors of this Series that the “present situation is ethically, scientifically, and economically indefensible” and back their call for a new research governance strategy. Regulatory requirements directly influence researchers’ choice of study design and methods; hence, regulatory agencies ought to be transparent about their rules, ensure that guidance on those rules reaches all stakeholders, and monitor delays and inconsistencies in their procedures. Yet, they are not the only stakeholders that should take any opportunity to minimise waste: all those involved must be accountable for the integrity of the process and its effectiveness. The decision about what study to do is primarily driven by research funders, who should also be more transparent and engage the potential end-users of research in their priority-setting procedures. Awareness of all relevant information and previous knowledge is crucial; however, selective or biased reporting and dissemination of findings are insidious problems for which researchers and journal editors share responsibility.

Neurologists have reasons to celebrate their embracing of rigour in research and evidence-based clinical practice. Notably, they have been instrumental in establishing the Cochrane Collaboration and are driving CAMARADES, an initiative to use systematic reviews of animal studies to speed up translation of preclinical findings. Regulatory inconsistencies show that big challenges remain. As The Lancet Neurology went to press, the final ruling on alemtuzumab by the FDA was still unknown. Even if that changes, it is time to pause and reflect on how to prevent other research endeavours from facing similar troubles. ■ The Lancet Neurology