Learning from failure

The launch of a new initiative to share data from failed clinical trials of investigational drugs for Alzheimer's disease provides both a promising opportunity to improve drug development in this field, as well as a novel mechanism to learn more from negative trials in general.

The search for disease-modifying drugs for Alzheimer's disease has been beset with expensive setbacks, such as the recent failure of a Phase III trial of dimebon, a compound for which Pfizer paid Medivation a US$225 million upfront fee for global marketing rights in 2008. This field is challenging to work in for several reasons, which include poorly predictive animal models of Alzheimer's disease and a lack of qualified biomarkers that can predict disease progression and drug response in clinical trials (see the review on page 560). A related problem is the lack of understanding of the natural course of the disorder, which is particularly needed for evaluating potential disease-modifying drugs that might be optimally used before symptoms become readily apparent.

So, the recent release of a new database containing information on 11 failed industry-sponsored clinical trials of investigational drugs for Alzheimer's disease, which involved 4,000 patients, is welcome news (see page 505). It is hoped that the database, the largest of its kind to be made openly available to qualified researchers so far, will facilitate the creation of more accurate models of the course of the disease, including potential differences in particular patient subgroups, which in turn could aid the design of more efficient clinical trials. The database developers, the Coalition Against Major Diseases (CAMD) — a consortium of pharmaceutical companies, academic research foundations, regulatory agencies and patient associations, led by the Critical Path Institute — aim to submit improved disease models to regulatory agencies for review. The CAMD is also investigating disease biomarkers, and hopes that the database will expand to include further data from clinical trials of drugs for Alzheimer's disease, as well as those for other neurodegenerative disorders such as Parkinson's disease.

More generally, the CAMD initiative also represents a novel approach to the long-standing question of what happens to data from failed clinical trials. The issue has gained considerable prominence in recent years through initiatives aiming to reduce the potential influence of 'publication bias' — the selective reporting of positive results of clinical trials, which could skew assessments of the effects of a particular therapeutic intervention[1]. As a result, US legislation now requires the registration of all trials beyond the Phase I stage involving products that are subject to FDA regulation at ClinicalTrials.gov, as well as the disclosure of key characteristics and results of the trial in the registry, generally within 1 year of trial completion.

Nevertheless, although such information will now be disclosed, it is often not likely to be readily suited to gaining insights that might help guide decisions about future clinical trials. These include key issues such as whether a trial has failed because the underlying hypothesis was incorrect or because of limitations in the design or implementation of the trial. One recent example of the value of such data is provided by a publication describing Phase I and II trials of an agonist of the melanocortin receptor 4 (MC_4), an anti-obesity target that had been considered to be highly promising on the basis of genetic evidence and studies in animals[2]. Overall, these negative studies provided the basis for the termination of this development programme by the company, Merck, and strongly indicate that other MC_4 agonists would not be likely to be viable drugs for weight loss, which might save the wastage of substantial further resources on such agents by other companies and research institutes.

However, such publications are currently rare, owing to issues such as lack of resources and motivation for authors to write up negative trial results in a form suitable for publication, and lack of interest from journals in publishing such results. In this respect, initiatives such as the CAMD database might also provide the opportunity to develop publications based on the results of multiple negative trials in a therapeutic area such as Alzheimer's disease. Such analyses could be more valuable than results from a single negative trial and more likely to attract the resources and attention needed for publication in a peer-reviewed journal, thereby further helping to allow the investment in failed trials to be harnessed to substantially improve the chances of future success.

1. The evolution of trial registration. *Nature Rev. Drug Discov.* **8**, 755 (2009).
2. Krishna, R. *et al*. Potent and selective agonism of the melanocortin receptor 4 with MK-0493 does not induce weight loss in obese human subjects: energy intake predicts lack of weight loss efficacy. *Clin. Pharmacol. Ther.* **86**, 659–666 (2009).

FURTHER INFORMATION
Coalition Against Major Diseases: http://www.c-path.org/CAMD.cfm
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