

Facilitating Regulation: The Dance of Statistical Significance and Clinical Meaningfulness in Standardizing Technologies for Dementia

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Abstract

Regulatory activities are intended to safeguard the health of citizens by ensuring that new drug therapies meet the highest standards of safety, efficacy and quality. Recent initiatives emphasize streamlining and speeding up approval, and are intent on harmonizing standards for international competitive advantage. In Canada and the United Kingdom, a second order of evaluation is necessary in order to have the costs of a federally licensed drug covered under provincial or state health insurance programmes resulting in wider patient access to potentially cost-prohibitive products. While new therapies can get approved by federal regulatory scientists based upon acceptable evidence from data meeting the standards of safety, quality and efficacy, the determination of the formulary committees, such as the UK National Institute for Health and Clinical Excellence (NICE), or the Canadian Common Drug Review (CDR), take into consideration the economic costs and benefits of the therapeutic agent. This analysis considers the technical-political-social-moral positions taken by various actors involved in legitimizing and contesting the effectiveness of cholinesterase inhibitors (ChEIs) for treating people with Alzheimer's disease. It examines ambiguities in the 'norms of appropriateness and legitimacy' of clinician researchers, and the construction and legitimization of what is appropriate in clinical research and regulatory practices.

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A concentrated international effort to operationalize the measures and standardize criteria for dementia diagnosis began in the 1980s. Even with these new technologies, the heterogeneity

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of the diagnostic subtypes of cognitive impairment has confounded the substantial scientific (and political) activity to pinpoint definitive biological mechanisms that might contribute to the development of effective targeted therapeutic agents (Graham and Ritchie 2006). Nonetheless, with no other symptomatic treatments for dementia available, and despite only modest efficacy shown in clinical trials, the cholinesterase inhibitors (ChEIs) were approved and licensed in the mid 1990s by national regulatory authorities (e.g. the US Food and Drug Administration [FDA], the European Agency for the Evaluation of Medicinal Products [EMA], Health Canada) for the symptomatic treatment of mild to moderate Alzheimer's disease (the most commonly recognized subtype of dementia).

Regulatory approval has raised sensitive issues when advisory boards that make recommendations to publicly funded drug plans arrive at different conclusions. These formulary committees determine whether drugs can be made accessible (i.e. reimbursable) to the elderly under provincial and other health service and insurance programmes, based upon systematic review of the available clinical evidence and pharmacoeconomic critique (PausJenssen *et al.*, 2003). The contrast between standards of scientific critical appraisal established by regulatory authorities, those criteria considered important to evidence-based health technology assessors and by clinician researchers, and the patient desire for versus effectiveness of these treatments, provides a telling portrait of regulatory issues subject to the complex interplay of consumer demands, pharmaceutical marketing and clinician judgements. Efficacy as determined by statistical significance in two pivotal clinical trials does not necessarily translate into clinically meaningful treatment effectiveness in the user population. The licensing decisions of national regulatory authorities purportedly depend on sound scientific evidence that the products meet the highest standards of safety, efficacy and quality, and are subject to international norms and standards (World Health Organization, 2008). The decisions of local appraisal committees to fund treatments are based both on the science and a balancing of the harms, benefits and economic costs, often in light of wider population data subsequent to the initial licensing. Although it is always maintained that final decisions are based on the science, especially on the clinical evidence, differences in interpretation often result in dramatically different conclusions across jurisdictions. Neither level of regulation is without social and political interventions.

This analysis considers the technical-political-social-moral positions taken by various actors involved in legitimizing and contesting the effectiveness of ChEIs for treating people with Alzheimer's disease. If individuals are driven to act according to 'norms of appropriateness and legitimacy' and not just their own self-interest (Black, 2005: 32, citing March and Olsen, 1984), then the construction and legitimization of what is appropriate in the authoritative structures requires unpacking before regulation can be seen to 'work' in an effective, decentred and pluralistic manner.

Objectively establishing dementia: standardizing a common diagnosis for a heterogeneous disorder

With the ageing of the population in the global north, the absolute number of people with symptoms of cognitive impairment and dementia has been increasing. A concentrated research effort at various international sites began in the early 1980s to unravel the aetiology of these disorders, and to establish the prevalence and incidence rates for dementia

and its differential subtypes, in particular, Alzheimer's disease (Jorm *et al.*, 1987). Threatened by a 'potential pandemic' that awaited the greying population of the developed and the developing countries undergoing 'epidemiological transition' (Baker *et al.*, 1995: 65; Osuntokun *et al.*, 1991, 1992), the US National Institute of Aging (NIA) both 'encouraged and supported the development of national collaborative studies to standardize the measurement of cognitive function in Alzheimer disease', in order 'to characterize and measure change among the diverse populations under study', 'to bring uniformity to the study of Alzheimer disease' and to facilitate the pooling of data from the different studies (Buckholtz and Radebaugh, 1994: S215). In 1986, the NIA funded the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), with investigators from university medical centres in the US, France and Canada. The CERAD initiative entered into collaboration with the World Health Organization (WHO) Programme for Research on Ageing, established in 1987 (Morris *et al.*, 1989; Osuntokun *et al.*, 1991).¹

By the late 1980s, international standardization efforts were in full swing. The European Economic Community Concerted Action on the Epidemiology of Dementia (EURODEM), along with groups from the United States, tackled the methodological issues of case ascertainment to facilitate comparison of their findings (e.g. Brayne and Calloway, 1988; Hofman *et al.*, 1991; Lopez *et al.*, 1990, 1994; Rocca *et al.*, 1991a, 1991b). In collaboration with the WHO, the Canadian National Health Research Development Program (NHRDP) spent over \$10 million during the first years of the 1990s (Dalziel, 1994) to conduct 'the largest population-based study to have used a standard approach to ascertain cases and diagnose dementia and to have included community and institutional components' (CSHA, 1994: 909). While EURODEM pooled and re-analysed data already collected, the Canadian Study of Health and Aging (CSHA) standardized all instruments and applied the same research protocol at each of its 18 sites across five time zones (Graham *et al.*, 1996).

International researchers visited one another; epidemiologists, geneticists and clinician researchers shared methods, biological samples and clinical data to ascertain biological mechanisms, prevalence and risk factors for the disease. The early 1990s was an exciting and heady time, with data arriving from around the world and weekly announcements from collaborating labs of new gene loci and potential risk factors. While the epidemiologists and clinicians were standardizing protocols, instruments and clinical diagnostic criteria, the studies on biological mechanisms continued to encounter the illusive materialities of a heterogeneous disorder. Despite remarkable international collaborations, the biological markers at best indicated susceptibility, but none predicted Alzheimer's disease with certainty. St George-Hyslop *et al.*'s (1987) autosomal dominant model of transmission implicating chromosome 21 was followed by Schellenberg *et al.*'s (1992) chromosome 14 finding. Goate *et al.*'s (1991) segregation of an amyloid precursor protein gene mutation, and the discovery that the Apolipoprotein E4 allele affecting cholesterol transportation on chromosome 19 (Corder *et al.*, 1993; Pericak-Vance, 1991) could, at best, be associated with a susceptibility for Alzheimer's disease (AD) (Poirier *et al.*, 1995).²

1 The WHO has been addressing issues of ageing in the developing world since at least 1959 (WHO, 1959, 1979).

2 While dementia, including Alzheimer's diseases, are heterogeneous disorders characterized by multiple gene mutations being identified as a single disease, Apolipoprotein E represents a converse complexity known as pleiotropy, that is, a single gene that has multiple phenotypic effects (Cacabelos, 2008; Wachbroit, 1998); those harbouring

New sequencing technologies and sophisticated imaging techniques (Baron, 2006) monitor physiological changes in neuronal activity (Selkoe, 2006) and prospective bioassays, molecular mechanisms and genetic markers (Blennow and Zetterberg, 2006; Goate, 2006) aimed to ‘crack the amyloid code’ (Hardy and Cullen, 2006; Mandavilli, 2006) and the mystery of tau pathologies (Lee and Trojanowski, 2006). Yet, a hundred years after the original bench work of Alois Alzheimer in 1906 that identified the neurofibrillary tangles, amyloid plaques and arteriosclerotic changes, no cure has been found. Slippage between the suspected pathological biomarkers for AD and a clinical diagnosis that depends on a combination of bio- and sociomarkers of individual cognitive, social and behavioural manifestations, disrupts nosological certainty (Graham and Ritchie, 2006). Early complaints of diminished energy and enthusiasm, loss of interest in activities previously cherished, lability of mood, or increased anxiety are often non-specific. Healthy elderly people and persons in the early stages of AD, particularly in cases of late-onset, often overlap substantially. Early diagnosis of cognitive impairment is not always predictive of later dementia, and some people diagnosed with cognitive impairment have been found on five-year follow-up to no longer be impaired (Tuokko *et al.*, 2003). There appear to be many different and unpredictable patterns of cognitive change in those with sub-clinical cognitive deficits (Larrieu *et al.*, 2002; Ritchie *et al.*, 1996). Debatably, a new and somewhat premature labelling, as a nosological entity, of mild cognitive impairment, has been driven as much by research heuristics and the potential of a worried-well demographic market for drug development and profit, as by any clinical and aetiological distinction (Corner and Bond, 2006; Graham and Ritchie, 2006).³ New imaging techniques that match social performance to brain pathology are research fields under investigation rather than reliable diagnostic tools that can be used with confidence. There is a growing awareness of the danger of using biomarkers as surrogate endpoints in clinical trial outcomes (Ledford, 2008).

The efforts to standardize in the 1980s and 1990s resulted in the development of new diagnostic criteria for dementia and its subtypes. Emerging criteria met with criticism and were subsequently modified, absorbed into other criteria or dismissed. Standardization necessarily demanded a higher degree of clarity and accuracy in the definition of subtypes accomplished with a new generation of operationalized and criteria-related classification systems. Despite some minor differences, both the European *ICD-10* (WHO, 1993) and the US *Diagnostic and Statistical Manual of Mental Disorders* (APA, 1987, 1994) describe dementia as a progressive degenerative disorder characterized by decline from a previously higher level of functioning with multiple cognitive deficits and impairment in occupational or social functioning. McKhann and colleagues (1984) cornered the criteria for Alzheimer’s disease, and a subsequent working group captured vascular dementia (Román *et al.*, 1993) despite some early opposition.⁴ The Lund and Manchester Group (Neary *et al.*, 1998) and

the Apo E4 allele may be susceptible to hypolipidemia, at higher risk for atherosclerosis, myocardial infarction and Alzheimer’s disease while being at reduced risk for age-related macular degeneration (Zarepari *et al.*, 2004). Apo E2, on the other hand, is associated with being protective for Alzheimer’s disease.

3 A special volume of the journal *Philosophy, Psychiatry and Psychology*, vol. 13, no. 1 (March 2006), edited by Julian Hughes, examines the labelling of mild cognitive impairment in a collection of papers and commentaries.

4 The State of California vascular dementia criteria queried the ‘imperfect biological validity’ for the theoretical concepts of areas of cognition for brain function, and therefore does not state type or number of deficits other than ‘deterioration from a known or estimated prior level of intellectual function’ (Chui *et al.* 1992: 477); the NINDS-AIREN vascular dementia criteria require ‘cognitive decline demonstrated by loss of memory and deficits

the NINDS (National Institute of Neurological Disorders and Stroke) Work Group (McKhann *et al.*, 2001) each developed criteria for frontotemporal dementia, and the criteria for dementia of the Lewy-body type has been pursued by the Newcastle group (McKeith *et al.*, 1992, 2004, 2005).

The growing precision in diagnostic subtyping contributed to higher accuracy between clinical and pathological findings, although the rigorously selected clinical research populations were not likely to be matched in community contexts (Burville, 1993; Mendez *et al.*, 1992; O'Connor, 1990). The selection of study populations for clinical trials to minimize background variability and noise has resulted in the charge that clinician researchers select their study subjects to favour treatment efficacy in clinical trials. These types of controls, however, are chaff in the wind once a drug is licensed and marketed. The effectiveness of the ChEIs has proven more illusive in these post-approval circumstances. Alzheimer's disease,⁵ still seen as the dementia syndrome's most prevalent subtype despite the encroachment of these newly emerging diagnoses, has become a spectre to fear for seniors, disproportionate to the estimated 5–8% probability of being diagnosed (CSHA, 1994). Some 24.3 million people live with dementia in the world today and there are 4.6 million new cases every year; almost 60% of these individuals live in developing countries, with this figure predicted to rise to 71% by 2040 (Ferri *et al.*, 2006). Caring for people with dementia is expensive, surpassing the combined costs of many other illnesses, including heart disease and cancer (Dalziel, 1994; Ernst and Hay, 1997; Ostbye and Crosse, 1994). Although the definitive biological mechanisms for Alzheimer's aetiology may not have kept pace with the clinical and public demand for an effective therapeutic agent, any new product that can offer a hint of symptomatic treatment or delay commands a captive market.

A therapy: but does it work? Techniques to establish regulatory efficacy fall short of effectiveness

In 1983, what was probably an exaggerated importance of the cholinergic deficit in Alzheimer's disease was described in *Science* (Coyle *et al.*, 1983) and was met by heightened attention. Drug development for a treatment approach that could augment cholinergic neurotransmission was underway. The *New England Journal of Medicine* reported an open-labelled Phase II placebo-controlled crossover clinical trial in 1986, where remarkable improvement had been obtained for a new class of anti-dementia drugs equivalent to levodopa in Parkinson's disease (Summers *et al.*, 1986). The journal editors, however, remained presciently cautious, warning that:

Any therapeutic strategy that relies on the integrity of the cholinergic neuron for its efficacy in a degenerative brain condition like Alzheimer's disease is ultimately flawed. There must come a time, as the disease continues to progress, when cholinesterase therapy will not be effective. (Davis and Mohs, 1986: 1287)

in *at least two other* domains' (Roman *et al.*, 1993, emphasis added); the NINCDS-ADRDA Alzheimer's disease criteria require 'deficits in two or more areas of cognition' without specifying memory loss (Lopez *et al.*, 1994).

⁵ I have endeavoured to emphasize throughout this article that the subtypes of dementia, such as Alzheimer's disease, are not singular entities but rather they are more usefully understood as heterogeneous and pleiotropic disorders. An individual can manifest several subtypes at once (Mitnitski *et al.*, 1997). As such, it is more accurate to talk of Alzheimer's diseases, but I have resisted my inclination to call them such here and remain largely within convention, albeit a confusing one.

Significant scientific flaws in Summers' research eventually led to an inquiry on conflict of interest between industry and academia (Kodish *et al.*, 1996; Whitehouse, 2003), the partial retraction of the paper, and the requirement by the US FDA for proof of equivalency in placebo-control using an appropriate cognitive measure (Leber, 1990; Thal, 2002).

It took more than a decade before the cholinesterase inhibitors became available for the symptomatic treatment of mild to moderate Alzheimer's disease. The EMEA licensed donepezil in March 1997; Health Canada granted regulatory approval in October 1997. Although a first-generation ChEI (tacrine) had been approved by the FDA in 1993, safety concerns surrounding its severe liver toxicity (Marx, 1987; Watkins *et al.*, 1994) prevented it from achieving regulatory approval in Canada or the UK. With the wider approval of a second-generation safer alternative, tacrine was no longer recommended in the United States, although the fact that the tacrine trials were designed in parallel with the FDA guidelines remains a strong indictment of such close industry–regulator relationships. The co-generation of the criteria used to determine tacrine's efficacy during its primary clinical trial (Knopman *et al.*, 1994) set the standard for FDA regulatory approval that all subsequent trials have been patterned after (Leber, 1990, 1997a, 1997b).

The US FDA was moving away from a command-and-control regulatory structure and beginning to entertain wider stakeholder involvement. The FDA worked closely with the sponsor and researchers involved in the tacrine trials to establish the outcome measures to be used to determine efficacy for the dementia drugs. In 1990, the FDA committee outlined the regulatory criteria for establishing efficacy for these new anti-dementia therapies (Leber, 1990, 1997a, 1997b). Stating the need to be responsive to their duty to protect the public, and concerned that pharmaceutical companies might not be rigorous enough in their testing procedures, the FDA put in place a requirement for objective, valid and reliable efficacy measures to ascertain statistically significant outcomes based on standardized tests (Leber, 1990, 1997a, 1997b). Two primary outcomes to determine efficacy were agreed upon for the tacrine clinical trials: statistically significant improvement in at least one symptom domain (i.e. cognition), such as that measured by the Alzheimer's Disease Assessment Scale–Cognitive (ADAS–Cog) (Rosen *et al.*, 1984) and a clinician-based global impression of change (Knopman *et al.*, 1994; Schneider *et al.*, 1997).⁶ The US FDA had opened an avenue to approve a drug based upon *clinical judgement* of observable improvement in some functional performance and global impression of change in the individual.

The FDA, researchers and manufacturers agreed that treatment response would be based on a significant improvement using a standardized objective measurement tool and a clinician's impression of global cognitive, behavioural, functional and social change. With a desperate elderly population awaiting some action: 'the trials were never intended to be "ecologically valid" experiments in which ordinary, representative patients were treated and assessed; rather they were intended to get the drugs approved for marketing' (Schneider, 2006: 11).⁷

6 Feldman *et al.* (2006) suggest that cognition or behaviour domains could be substituted for the Global Impressions of Change, thereby compressing the number of criteria necessary for ascertaining improvement even further.

7 It has been estimated that 90% of those being treated for mild or moderate Alzheimer's disease in California, for instance, would have been excluded from the industry-run clinical trials (Schneider, 2004). The non-representative nature of these data did not prevent the research results being used to make decisions on effectiveness, costs and clinical meaning.

The ADAS–Cog subscale became the *de facto* standard primary outcome measure for AD trials, with treatment response based on a 4-point improvement on the 70-point scale (Rosen *et al.*, 1984). Based on the ADAS–Cog and clinical impression of a modest treatment effect in a short-term (24 week) double-blind randomized placebo-controlled clinical trial sponsored by Eisai, the producer of donepezil, and its co-marketing partner Pfizer, donepezil was approved throughout the world in 1997 (Rogers and Friedhoff, 1996; Rogers *et al.*, 1998). The promises of tacrine in the early 1990s had already primed a market that demanded a symptomatic treatment without the tacrine side-effects. The ADAS–Cog and clinician-based assessment of change showed just enough statistical significance for the treatment to meet regulatory approval. The instruments became part of the standardized package to measure the progress (decline) of AD in subsequent comparator and post-marketing clinical trials. Donepezil (Aricept®), as the first of the so-called second-generation ChEIs to address the serious adverse drug effects of tacrine, was first past the gate for Pfizer to dominate the substantial world market.⁸ In Canada, donepezil was soon followed by two other ChEIs, Novartis’ rivastigmine (Exelon®) in November 2000 and Janssen-Ortho’s galantamine (Reminyl®) in July 2001.⁹

Standardization and therapeutic reform during the twentieth century has been the route to regulate, if not quite assure the public, that patient care is supported by the findings of sound biomedical science instead of quackery and opinion (Marks, 1997). There has been some discomfort, however, that this trend towards evidence from large-scale epidemiological population studies and sophisticated statistical analyses neglected ‘biologic logic’ and ‘clinical judgment’ (Feinstein, 1987, 1994). For Feinstein, treatments had to be relevant, applicable and ‘clinically meaningful’, to the physician’s practice and the particular individual patient, not a population statistic. By the late 1990s, researchers began developing tools that were sensitive to clinically meaningful outcomes (Kielhofner and Barrett, 1998; Mallinson *et al.*, 1996). While the FDA left the door open for other measurements of functional and clinical meaningfulness, such as activities of daily living and quality-of-life scales, the simple usability of the CIBIC (Clinician’s Interview-Based Impression of Change) ensured its easy adoption. Designed to standardize the clinician’s global impression of change, it allowed clinician *impression* to appear quasi-quantified, thereby charging it with the authority of statistical significance. The dementia research community was beginning to catch up (Joffres *et al.*, 2000; Rockwood *et al.*, 2002; Winblad *et al.*, 2001), although not fast enough to meet the NICE regulators.

8 Approximately 5.4% of Canadians aged 65 and over were diagnosed with mild or moderate stage Alzheimer’s disease in 1991 (Graham *et al.*, 1997).

9 These medications remain, to date, the only treatment options for mild to moderate AD in Canada, and for moderate AD in the United Kingdom, but not without ongoing controversy. The revised NICE ruling in November 2006 recommended ChEIs for the treatment of moderate Alzheimer’s disease only, removing the funding for ChEIs for those with mild AD. On 10 August 2007, the High Court ruled that this was discriminatory. Company lawyers had successfully argued that quality of life of both patients and caregivers had not been taken into consideration, and neither had the cost of long-term care. In September 2007, NICE reissued their guidelines that clarified the steps that clinicians should take to assess moderate dementia, as well as the need to ensure equality of access, but maintained that the three ChEIs are recommended as ‘options in the management of patients with Alzheimer’s disease of moderate severity only’ (<http://www.nice.org.uk/nicemedia/pdf/TA111QRGSept07.pdf>).

NICE requests evidence of effectiveness: pharma doesn't deliver

Donepezil was licensed in the United Kingdom on 17 March 1997. The cost of the drug, at £2.50 a day, affected its uptake. The National Institute for Health and Clinical Excellence (NICE) is the independent organization that provides guidance in public health, health technologies and clinical practice in the UK. NICE draws upon an extremely formal and largely transparent¹⁰ process of consultation with expert scientists, consultant physicians, patients, drug companies and the Department of Health, for health technology assessment and to advise on health guidance. Most importantly, because its recommendations serve as guidance to health care practices which are funded by the National Health Service (NHS), its decisions take into account issues of cost and harm–benefit.

In its first guidance, *Technology appraisal no. 19*, issued in January 2001 after careful and extensive review of the evidence, NICE cautiously recommended the ChEIs for people with mild or moderate Alzheimer's disease, but noted that the evidence was not convincing that the modest improvement among some patients, shown in outcomes used in the existing trials, could be translated to significant real-world benefits (NICE, 2001). All NICE guidance documents are scheduled for regular review, depending on new evidence. The review date was set for December 2003. Pharma was given a clear heads-up and three years to provide stronger evidence of the ChEIs' effectiveness.

NICE pointed to limitations in the methodologies and study design of the clinical trials. Clinical effectiveness was based on the evidence from five industry-sponsored randomized controlled trials for donepezil, five for rivastigmine and three for galantamine, three systematic reviews for the former two and one for galantamine. Manufacturers' unpublished studies were also provided. NICE noted that the existing comparative studies were not helpful for drawing conclusions, that extrapolation from the six- and twelve-month RCTs rather than observational evidence was used to suggest what amounted to uncertain cost savings on later nursing home care, and that there was a lack of outcome measures and evidence available to adequately assess improvement in patient and carer quality of life. NICE recommended that future research include better methodologically aligned comparative studies with both drug and non-drug interventions, that attention be given to response during the course of treatment and to identifying characteristics of those who respond to the drugs, and that protocols needed to be developed to withdraw those not benefiting from the treatment.

NICE spelled out what it would require as evidence from future studies in order to be able to continue to recommend (and for the NHS to fund) the ChEIs. It made clear that the drug companies would need more convincing evidence for the effectiveness and clinical significance¹¹ of their products if they wished their products to continue to be nationally available and free of charge for some 400,000 individuals with Alzheimer's disease indicated for treatment.

Technology appraisal no. 111 was released in November 2006 (NICE, 2006), over two years after the review had been completed and after an extensive consultation process and

10 Some evidence is submitted as 'commercial in confidence' to the institutes by the manufacturers and, while it is made available to the appraisal committee, it is removed from publicly disseminated versions of the assessment report. Kendall and McGoey (2007) describe, for example, strategies employed to deal with conflicts of interest and publication bias in producing NICE guidelines.

11 This parallels Feinstein's (1987, 1994) 'clinical meaningfulness'.

additional data supplied by the companies.¹² Original submissions from the companies (Eisai Ltd, Lundbeck Ltd, Novartis Pharmaceuticals UK Ltd, Shire Pharmaceuticals) arrived in September and October of 2004. In March 2005, NICE released its first appraisal as a consultation document, with recommendations not to recommend the ChEIs based upon lack of cost effectiveness. Further submissions were made in October and November 2005. Consultations were also undertaken on extra manufacturer analyses based upon individual patients' outcome data, issued in November 2005, and on the second appraisal document issued in January 2006 (NICE, 2006: 39; Schneider, 2006). Considerable public and private interest in these treatments was evident from the 18 profession/specialist and patient/carer groups that made submissions. Eight Commentator groups were involved, including the British National Formulary, the NHS, the Alzheimer's Research Trust and the Research Institute for the Care for the Elderly.

In 2001, NICE had not been convinced of the clinical significance for effectiveness of the dementia therapies and requested that more specifically defined sub-group analyses be conducted. Industry and its clinician researchers had been served notice that new data should deal with the methodological and substantive analytical limitations of previous studies, and most especially address quality-of-life measures of outcomes and sub-group analyses of response to treatment. By 2005, industry still had not come up with these data.

The release of the revised appraisal and dementia guideline was preceded by an unusual early press release on 11 October 2006, a month before its publication. NICE was recommending that the NHS only fund the ChEIs to treat moderate-stage Alzheimer's disease, and no longer those with mild AD (NICE, 2006). A significant number of people would be affected. In Canada, for instance, mild dementia affects 2.3% of those aged 65 and over, a market that would no longer have free access to the only purported treatment. While the NICE guidance allowed that the data had continued to support 'small gains in scores on cognitive and global scales for people with mild to moderately severe Alzheimer's disease...'. The Committee noted that the evidence available for long term effectiveness of the ChEIs using outcomes such as quality of life and delayed time to nursing home placement, was limited and largely inconclusive' (2006: 39).

A storm of protest ensued across Britain immediately after the announcement. Personal testimonials appeared in newspapers from elderly citizens with heartrending accounts of how donepezil had staved off the progressive course of the disease, 'I felt I still had my husband', and gratefulness that 'We had had two years of a really happy and good life on it' (BBC News, 2006). The Alzheimer's Society (2006) announced that 'NICE fails dementia'. The President of the Alzheimer's Research Trust, Dr Clive Ballard angrily responded: 'We're astonished and appalled by this decision' and accused NICE of 'fundamental errors' (Day, 2006). Ballard 'called for ministers to intervene'. Not surprisingly, the British Pharmaceutical Industry (ABPI) condemned the decision 'on the grounds of commonsense and of basic humanity' and raised the spectre of sending 'negative signals to those engaged in cutting-edge medicines research', that their industrious and innovative research would be for naught

12 Strategies to delay the release of this report are not without significant cost to the NHS and profit to the pharmaceutical companies, whose drugs were able to maintain national subsidization during the year and a half's delay. In the United Kingdom, with an estimated 400,000 people diagnosed with Alzheimer's disease of whom about 40% are diagnosed with mild AD, the cost of ineffective dementia treatment at £2.50 a day is not insignificant.

(Medical News Today, 2006). ABPI threatened that: ‘This decision makes it harder for companies to justify devoting the enormous sums of money and resource necessary to research and develop new medicines’ (Medical News Today, 2006).¹³

Treatment response: finding a way to show that the ChEIs work

Despite only ‘modest’ benefit, and with higher rates of adverse events and discontinuation of treatment compared to placebo (Lanctôt *et al.*, 2003; Perras *et al.*, 2005), the evidence of statistical significance has been deemed sufficient by many clinician researchers to advocate for an end to placebo-control trials. For many clinical trialists, the evidence is clear that the ChEIs work.¹⁴ The public indignation at the decision by NICE in 2006 to discontinue NHS funding of ChEI therapy for those with mild AD was reinforced by clinicians who saw themselves as representing their patients’ desires as much as standing up to the principles of best evidence. Indeed, considerable debate among physicians and health technology assessors has existed over the clinical meaningfulness and effectiveness of ChEIs (Courtney *et al.*, 2004; Kaduszkiewicz, 2006; Kaduszkiewicz *et al.*, 2005; Rockwood and MacKnight, 2001; Rockwood *et al.*, 2006), putting the health technology assessment committees that decide on the adoption and subsidization of treatments in the awkward position of inevitably rankling one side or the other. Citing the need for better evidence and the absence of clinically meaningful results, NICE’s decision was on the side of rationing the public purse—it asked for evidence that the ChEIs had some tangible effects. After five years, without the necessary evidence, an economic cost–benefit formula determined that those with mild AD showed insufficient benefit to warrant subsidized treatment.

Clinicians recognized that something different was needed to mark treatment success in order to get the ChEIs included in difficult provincial formularies and insurance regimes. A large publicly funded clinical trial to address the NICE (2001) request for outcomes of institutionalization and progression of disability that would address effectiveness concluded that, while there were small improvements in cognition, there was no difference in institutionalization or disability (Courtney *et al.*, 2004). Other groups had already begun looking beyond cognition for other domains and endpoints to establish decline and improvement, using new templates and standardized packages (Fujimura, 1996; Latour and Woolgar, 1986: 238). They looked to the world of everyday practices (Graham, 2001; Rockwood and Graham, 1997; Timmermans and Berg, 1997). Identifying and targeting everyday

13 The finality of this decision remains contested. Eisai Limited, the UK subsidiary of Eisai Co., Ltd, and Pfizer Ltd., backed by the Alzheimer’s Society launched a first ever judicial review of NICE, charging it with acting ‘irrationally and unlawfully’ in not funding the treatment for people with mild Alzheimer’s disease. On 10 August 2007, the High Court upheld the NHS decision, but did find NICE at fault for discrimination surrounding the assessment of people with disabilities, including those with learning, linguistic and communication difficulties. NICE amended its guidelines accordingly. Eisai Ltd. launched an appeal against the High Court Ruling, which they were granted on 6 December 2007. Eisai’s main charge was that NICE had provided them with a read-only economic model on which NICE had based its cost-effectiveness economic decision, breaching principles of procedural fairness. On 1 May 2008, the Court of Appeal ruled in favour of Eisai, which had 42 days from release of the cost-effectiveness model to review its calculations for errors and reliability. At the time of writing, Eisai are then to ‘submit their findings to the NICE Appraisal Committee who will be required to review their recommendations in light of any such fresh evidence’ (Eisai, 2008). NICE emphasized that: ‘we have not been asked to amend or withdraw the current guidance on the use of these drugs to treat Alzheimer’s disease: the drugs continue to be recommended only for people at the moderate stage of the disease’ (NICE, 2008).

14 Not all clinician researchers maintain this position however. See, for example, Schneider (2004: 2101).

symptoms of decline and improvement to measure the ChEI's treatment effects took on heightened importance as clinical meaningfulness appeared on the radar for ascertaining effectiveness. Tying memory loss and social and behavioural decline into events viewed as significant and meaningful by people with dementia and those who care for them meant consulting an entirely different set of actors beyond clinicians. Clinicians were beginning to recognize that they needed a new set of instruments to ascertain these patient-centred and recognized target symptoms (Rockwood *et al.*, 2002).

A person with Alzheimer's disease can be expected to decline by about 4–6 points a year on the ADAS–Cog scale (Aisen, 2000; Mulnard *et al.*, 2000). This 4-point decline is 'clinically relevant', that is, it maps to loss of family members' names, remembering who visited the day before, behavioural and functional loss (Winblad *et al.*, 2001). In 2001, Winblad and colleagues proposed a redefinition of treatment success for responders to dementia therapies. In light of the many distressing symptoms beyond a decline in memory, Winblad and colleagues decided that 'Alzheimer's disease is more than just memory loss' (2001: 656) and 'that benefits in areas such as behaviour or functional activities *alone* are legitimate therapeutic goals'. They recommended revising the definition of treatment response so that long-term (one year) stabilization, maintenance, or preservation of cognition, function *or* behaviour, be considered 'improvement'.¹⁵ Any statistical test that corrects for multiple comparisons would be able to question the credibility of such an apparent domain-dredging technique.

Nevertheless, this reconstruction of the definition of responder made it 'possible to see that cholinergic inhibitors are achieving success in the treatment of Alzheimer's disease' (Winblad *et al.*, 2001: 661). By making 'staying the same' equivalent to improvement, the clinical trialists could conclude that the ChEIs 'have all demonstrated efficacy for up to 6 months', and that 'cholinergic treatments offer clinically meaningful, long-term (12 months or more) benefits in cognition, functional abilities and behaviour' (2001: 662).¹⁶

Structural and corporate forces directed (and paid for) the recalibration and adoption of new measurement instruments, in the guise of models of human compassion and patient empowerment. The virtues of the powerful are turned upon those with less power when there are profits to be made (Badiou, 2001). The constructions of measures and empirical evidence to determine whether the drug worked met the needs of the producer. With the revised definition of responder, maintenance in any *one* of the three domains (cognition, function *or* behaviour) was all that was needed to 'be considered improvement'. The turn to qualitatively meaningful, individually responsive assessments appears somehow entangled in a larger market agenda. Applying the authoritative capital of consensus recommendations, Winblad and colleagues could bypass those research activities that were directed at developing new tools by simply weakening the criteria that already existed to

15 'Responders' are 'those with "improvements" in any of these areas [Activities of Daily Living, behaviour, caregiver burden, quality of life and resource utilization, in addition to cognition] and those who experience a delay in progressive decline. Relative stabilization . . . is an important outcome. . . . We propose redefining "responders" to Alzheimer's disease treatment as those patients who maintain baseline scores (improvement over baseline ≥ 0 points) for 1 year on appropriate scales, assessing cognition and/or functional abilities, and/or behaviour' (Winblad *et al.*, 2001: 662).

16 The advertising materials from the drug companies (Pfizer, Janssen-Ortho and Novartis) that market these drugs recommend that patients remain on them for life, despite little evidence from longitudinal study.

ascertain response (and, in fact, patients). The contingent and political nature of epidemiological facts demands that we recognize and not ignore the partial nature of the aggregated assemblage. Some truths are better than others, but always their selection requires careful auditing (Eco, 1990; Strathern, 2000).

Treatment response (particularly its variability) is uneven and difficult to tag for clinical meaningfulness. Attaining consistency in statistical significance across the various tools used to measure the domains (cognition, function, activities of daily living) involved in this multidimensional, heterogeneous socio-neurodegenerative process challenges methods and theories. Technology appraisers insist that it is not possible to select out responders given the small treatment effect of the current ChEIs; there is too low a signal-to-noise effect, and no sub-group tail can be identified. Progressive decline is not apparent in all domains at the same time, nor is it at a constant rate. Variable rates of decline are associated with age (Wolfe *et al.*, 1995) and stage (Stern *et al.*, 1994), and social and biologic factors together provide a constellation of patterns of change that might be marked as decline or improvement (Graham *et al.*, 1999). An individual in the moderate stages of AD (e.g. ADAS-Cog of 35) may decline at approximately 12 points a year, while those with very mild or severe AD (ADAS-Cog of 15 or 60) may decline at a much slower rate (5 points a year) (Thal, 2002, citing Stern *et al.*, 1994), but there is much variability in these ‘standards’.

Many clinician researchers in the dementia community insist that statistical significance (although small) has been proven, and that it is unethical to continue conducting placebo-control trials.¹⁷ The FDA Advisory Committee on Psychopharmacological Drugs reviewed the assessment scales used for the four anti-dementia drugs that were then available in the US (Thal, 2002). The committee recognized that the use of historical controls for comparison when decisions are made not to use placebo-control trials introduces methodological bias. Historic controls differ substantially in age and stage from the study treatment groups; comparisons are difficult. Indeed, as noted previously, sponsors select subjects with rapid decline:

... since success of a trial depends upon the treatment–placebo differential. Since ChEIs tend to stabilize cognition while producing only modest improvements in cognition, the presence of a rapidly declining placebo group means that a greater treatment–placebo differential may be seen in a moderate population than in patients with milder or more severe disease. This allows for the demonstration of a larger treatment effect size [than systematic reviews would find]. (Thal, 2002: 389)¹⁸

While the US regulatory authorities require difference between treatment and placebo, the European authorities (EMA) ‘look at the proportion of subjects classified as “responders”’ (Thal, 2002: 389). Winblad’s definition turns on the position that European

17 The ethics of conducting placebo-control trials when ‘acceptable’ agents are available hinges upon whether their efficacy and effectiveness is disputed. When ‘belief’ camps register uncertainty in the professional communities, then a situation of clinical equipoise exists requiring further investigation (Freedman, 1987). But the camps authorize and oppose different tools of philosophy, clinical assessment and critical evaluation for their technology assessment. This is further complicated by the perception of the public and many scholars of conflict of interest of many of the clinicians whose research is contracted or sponsored by the pharmaceutical companies.

18 Lanctôt *et al.* (2003) report a pooled mean global response of 9% for AChEIs.

regulators accept that benefits in behaviour or function *alone* are legitimate therapeutic goals. The EMEA is clear ‘that improvement in ADLs and on a Global Scale are sufficient for registration’ (Thal, 2002: 389). Improvement in any one of several criteria was now sufficient to ascribe treatment effect to ChEI.

Clinical research, industry and ethics

National regulators (e.g. the EMEA, FDA or Health Canada’s Therapeutic Products Directorate) are responsible for ensuring that a new drug is safe and that it works in the manner and in the population on whom it has been tested during the pre-market, clinical trial stage. Approval is supposed to be based upon sound scientific evidence of safety,¹⁹ efficacy and quality. After a drug product’s approval, physicians are free to prescribe a medication using their best clinical judgement. This is the terrain of off-label prescribing and indication creep. The object for drug companies after getting a drug licensed is to market the product, a process that requires product endorsement by key clinicians, gained most often through their research experience with the drugs. Clinician researchers who are the initial study investigators have the most experience with these therapies, and become key spokespeople and ‘educators’ on the drugs for the wider population of health care providers.²⁰

In Canada, as elsewhere (e.g. Björkman *et al.*, 2005), provincial formulary committees and national organizations such as the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health (CADTH) perform health technology assessments that examine factors such as effectiveness, cost-effectiveness, quality of life and/or patient use, and ethical and social implications at the post-licensing stage. Monitoring of adverse events at this stage allows for the identification of signals and underlying patterns of problems that smaller clinical trial samples would not provide. In a recalcitrant denial of openness and transparency, however, industry continues to resist independent analysis of their often extensive corpus of data, often collected for years after a drug approval through post-marketing or seed studies.

Those conducting these studies are the experts chosen for the consensus conferences where clinical practice guidelines are developed. Initiated in 1977 by the National Institutes of Health (Keating and Cambrosio, 2003: 316), many of the expert participants in these

19 Although I have concentrated on efficacy and drug effectiveness in this article, I do not want to dismiss some serious concerns about the safety of the cholinesterase inhibitors. Tacrine, as has already been mentioned, was not approved in Canada because of early concerns around liver damage (Watkins *et al.*, 1994) that did not satisfy the Canadian regulatory authorities. With regards to donepezil, galantamine and rivastigmine, statistically significant higher rates of adverse events that include anorexia, diarrhoea, dizziness, headache, nausea and vomiting compared to controls are reported. Higher withdrawals of patients from trials on treatment compared to placebo have been noted (Perras *et al.*, 2005). Patients on galantamine and rivastigmine were more likely to stop treatment due to adverse events when compared to patients on donepezil. The FDA Safety Information and Adverse Reporting Program posted an advisory in 2005 regarding the results of two randomized, placebo-controlled trials of two years’ duration of patients with mild cognitive impairment that reported 13 deaths in the galantamine treatment group compared to 1 death in the control group (www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Reminyl). The warning they posted stated that: ‘The deaths were due to various causes which could be expected in an elderly population.’

20 The validity and reliability of clinician judgements remain contested, however, given that clinicians arrive at different judgements regarding improvement and decline than do their patients or those who care for the person (Rockwood *et al.*, 2006).

conferences tend to be researchers funded by the pharmaceutical companies that sponsor their clinical trials. These experts are a familiar group, knowing one another through collaborations and conferences, and arriving at recommendations based on consensus drawn often from their own data. In the literature, these guidelines become taken for granted and referenced as fact. Most often they favour final recommendations for standard of care using the drugs they were responsible for studying. The members of these committees do not take their task lightly, but they also come to the meetings with already-arrived-at opinions, and there is seldom an attempt to bring dissenters to the table (Willison and MacLeod, 1999). Winblad and company's consensus appears to have redefined the markers for treatment success without critical debate or presentation of negative data or dissenting opinion.

Formulary committees have the task of determining whether to include new drugs, and retain old ones. They sort through often methodologically compromised or incomplete data, decide on the appropriateness of outcomes, determine whether risks and harms have been addressed, and consider potential ethical dilemmas that move the discussion to issues of social justice, utility and community responsibility (Bassett *et al.*, 2001; McAllister, 2000; Wright, 2002). This is not without some considerable political interference (Evans and Bosely, 2006). Certainly the conflict of interest and ties between university-based clinical research, drug trials and industrial sponsorship have received considerable attention in the first years of this decade. Drug companies contract some 60% of medical researchers (Caulfield, 2001) and the pharmaceutical industry spends more on medical research than the National Institutes of Health in the United States (Lexchin *et al.*, 2003). Research and industry agendas do not, nor should they, coincide (Talon *et al.*, 2000). Yet a systematic publication and prescribing bias has been found favouring the products of the funding industry (Mintzes *et al.*, 2003). Studies that produce findings that go against the grain of these interests are subject to intense public and professional scrutiny and condemnation.²¹ Evidence for efficacy of the dementia treatments has come almost exclusively from industry studies. The close ties between clinical trial researchers and industry is seen in the remarkable cross-referencing of authors of the studies and membership representation of the expert advisory committees. In 1996, more than three-quarters of the expert scientific advisors to British drug regulatory authorities had financial interests in the drug being approved (Abraham, 2002). Yet physicians, as stewards of their patients' health, have a primary responsibility for their care and treatment, trusted to 'first do no harm'. Clinical research, as an experiment, often poses some threat of risk, harm or benefits. It may well be that regulations that ensure the protection of the fiduciary relationship between patient and physician need to be made into laws in order to be effective (Lemmens *et al.*, 1998).

21 The AD2000 Collaborative Group (Courtney *et al.*, 2004) study, one of the few publicly funded clinical trials of the cholinergic drugs, met with considerable opposition while it was being conducted and sparked such a vitriolic attack from the sponsored clinical trial community, as well as the various national Alzheimer Societies, as to be worthy of a special session for reflection and wound-licking at the 2006 Madrid 10th International Conference on Alzheimer's Disease and Related Disorders. Meant to examine the effectiveness of the ChEIs in typical patients, there were some flaws to the study design and final execution of the study related primarily to inadequate power. The NHS was already funding the ChEIs by the time the trial started, negatively affecting the ability to meet recruitment and sample size targets in a placebo-control trial. The study found no difference in its two main endpoints, time to institutionalization and loss of critical activities of daily living. Its major decriers continued to rail against the conducting of a placebo-control trial, although that charge has been rebutted (e.g. Schneider, 2004). For those interested in such responses, Fujimura (1998) has an excellent analysis of such scapegoating activities with regard to the science wars.

Science, clinical judgement and everyday life

To understand dementia, to move into the world of the person with dementia, we need to understand their ‘micromoral worlds’, the ‘local knowledge and daily practices concerning the body and self’ (Kleinman, 1995: 123; see also Graham and Bassett, 2006). But we need to consider, as well, the wider structural forces that help shape this local knowledge, when and why ‘locals’ are called upon for their knowledge, and who does the translation. And herein lies an ambiguity. The move by some research clinicians towards taking an interest in their patients’ life stories and experiences in order to better recognize and target symptoms of decline and improvement seems to counter the technological trend to biomedical platforms, where ‘physicians no longer rely on narratives of symptoms offered by patients during a medical encounter but turn instead to an expanding collection of diagnostic signs’ (Keating and Cambrosio, 2003: 10). Surely, after all, the biomedical powerhouses of Alzheimer’s disease research reside in expensive laboratories, gene sequencing and sophisticated imaging techniques, not in qualitative techniques for ascertaining life events. But it turns out that the goal of this counter-technology clinical movement is, in fact, to give their own impressions statistical significance. Regardless of a direct request from NICE in 2001, and despite attention to contextual representations of subtle cognitive impairments and the generation of work differentiating the subtypes of dementia in multiple post-marketing clinical trials, the clinician researchers neglected to identify individual responder subtypes.

By enrolling clinicians to conduct clinical trials research, industry reaches and recruits prescribing physicians. Clinicians enrol industry to sponsor their particular research by conducting these trials. Clinicians also enrol patients, while extensive direct-to-physician promotion is concurrent with direct-to-consumer advertising²² that enrolls more patients to gather further pre- and post-marketing data on the drug’s effectiveness and safety. So then why didn’t the studies requested by NICE get done? Why were secondary analyses not conducted to determine responder subtypes? Potentially valuable data that might provide a more detailed profile of individual treatment response and effectiveness remains locked away in company vaults as proprietary material. Clinical trial subjects expect that their data, whether qualitative or quantitative, will be analysed and results will be disseminated. That only the positive results get reported limits attempts to gain full openness and transparency in clinical trials.

Clinician researchers have become powerful advocates for equal access to ChEIs on provincial and local formularies. They accept the power of the statistically significant results from the industry trials, and remain highly critical of the methodological critiques of less interested critical appraisal evaluators. While some propose alternative methods to identify symptoms that interpret meaningfulness, there is as yet no acceptable translation into effectiveness.

Conclusion

Keating and Cambrosio tell us that the work of standardization (statistics) and clinical interpretation bring the laboratory and the clinic together, and that ‘technologies of consensus’

²² To date, the United States and New Zealand are the only countries that permit direct-to-consumer advertising, although significant pressure is being put on other countries to follow suit (Mintzes, 2003). Less attention, however, has been given to direct-to-physician marketing by drug companies (Groves, 2006).

mediate regulatory layers (2003: 316). It is debatable, however, whether the ‘interpretive freedom’ (2003: 301) that Keating and Cambrosio ascribe to clinicians is free, or whether these technologies have been entirely successful in either mediating the regulatory layers or maintaining the legitimacy that Black (1998) views as essential to counter charges of self-interest. Rather, independent scientific health technology assessments continue to question the judgement and authority of clinical consensus groups whose decisions, nonetheless, get adopted as guidelines for practitioners (e.g. Feldman *et al.*, 2006; Winblad *et al.*, 2001). The 2006 decision by NICE sent a message that dubious methods would not suffice in Britain, that regulatory licensing of innovative new drugs does not mean that they are effective in the real world, and that industry might need to take better care in precisely identifying for whom their drugs work. There is an apparent need for some regulatory intervention in building an enforceable requirement for better long-term Phase 3b and Phase 4 studies, with registration and monitoring of adverse events as well as real-world effectiveness.

In the first half of this decade, dementia clinician researchers were asked to develop the tools to identify those 9% of people who respond to ChEI treatment. Instead, they worked towards changing the measuring stick, so that maintenance could be recognized as improvement, so that more people could be seen to respond, and towards widening the recognition of disease through new treatable categories for mild cognitive impairment. This performance has compromised the legitimacy of the clinical research process. The norms and standards set by the clinical trials research community were neither accepted nor readily adopted by independent critical health technology appraisers, who continue to ask for real-world evidence of the effectiveness of the cholinesterase inhibitors. When independent evaluators do not see the same end result that the interested clinician researcher sees, then there is cause for inquiry. The regulatory actors, including the data, have been confounded and rendered incommensurable. The public is left questioning the legitimacy of the entire process and asked to pay for hope rather than being supplied with evidence.

Trust in basic science, in regulatory science and in clinical research practices has been forfeited because the actors were not able to come to the table, agree on the instruments and deliver impartial results. The remarkable lack of what Black (1998) describes as regulatory facilitation, and the incommensurability between the various actors’ intentions and outcomes, could not be overcome—for all the money of the pharmaceutical industry, and all of the hubris of clinician researchers who failed to recognize what they were being asked to provide. These major stumbling blocks prevented the actors—despite their continuous generation of research activities and data—from providing the final results. The drugs were innovative for some, but the clinical trials were not. NICE’s first guidance (NICE, 2001) recognized this, despite the very small statistical significance trophy. Subsequently, industry and its clinical trialists failed to address responder subtypes and real-world effectiveness, opting instead to recalibrate the responder category. That they were unable to harness sufficient outcomes speaks to the failure of industry to enrol clinician researchers to perform the studies they needed; to the researchers’ inability to innovate and move beyond the old outcome instruments; and to their hubris in insisting that what they were doing was ethically and methodologically correct when this has been challenged consistently by both health technology groups (Perras *et al.*, 2005; Therapeutics Initiative, 2005) and the wider clinical practice community (e.g. Schneider, 2004). As an alternative, secondary analyses were carried out and results proving unfavourable to treatment were not reported.

Perhaps in the future the scientific community, researchers, industry, regulatory agencies and clinicians might become interested in regulatory facilitation. Interest in patients' stories, in their hopes and expectations will need to be actively targeted to diagnostic subtypes and biological mechanisms. But regulation cannot be seen to loosen in order to provide an expeditious route for the therapeutic agents to travel more easily to a desperate public, and at the cost of their effectiveness. The ADAS is a cognitive assessment instrument—as cognition is being dropped from the dementia criteria in favour of more behavioural outcomes, the ADAS score won't matter; the dementia diagnosis is being de-cognized. Some as yet unknown constellation of new constructs will serve that purpose. To ensure regulatory truth-telling, all the actors need to be at the same table to design studies that address efficacy—especially years after licensing, when the wider population data most certainly are in. Consensus committees cannot be made up of clinicians doing industry-sponsored studies and still be seen to be legitimate. All manner of data need to be brought to the table, and those groups that do so, like NICE, must have thick skin and a strong regulatory stick.

As government-appointed independent assessors carried out their responsibilities, which include both precision in scientific methods and guardianship of the public health purse, a forceful if somewhat awkward collection of both self-interested and authoritatively positioned researchers actively coalesced, and to all intents and purposes, advocated for the ready availability of drugs that appear to work for only a small segment of the people for whom they are prescribed. A complex array of interests operated as a backdrop to persuade by redefining through traditional ostensibly deliberative democratic routes (e.g. consensus meetings). The magician's act, whereby one hand draws the attention while the other changes the cards, was played. The clinician researchers met in authoritative *judgement* over their standardized, objective assessments; these instruments were no longer effective in convincing their critics that the drugs worked. They concluded that the instruments (not the drugs) could be replaced by different techniques directed at recalibration of the individual responders (the patients) themselves. This is an ambiguous turn, where those who identify as scientists return to observational techniques to 'see' people in their everyday life and to analyse softer data, resting on slippery and seductive new techno-humanistic assessments that are being built upon a pack of cards, of hopes and expectations.

One should not lose sight, however, of the primary actor of note, that is, the cholinesterase inhibitors. The central activities of clinician researchers and regulatory authorities, whose actions and partial motivations we have considered, have revolved around the significance and meaningfulness of the effect that these agents have on their primary and secondary targets—people with AD and their carers. Approved and licensed, their effectiveness remains unresolved.

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