Cochrane Dementia Group turns 21 – older and (slightly) wiser

The Cochrane Dementia Group or, to use its full title, the Cochrane Dementia and Cognitive Improvement Group (CDCIG), was founded in 1995. To mark this 21st anniversary, in September 2016 more than 60 members, contributors and colleagues of CDCIG from around the world celebrated with a conference and party in the group's birthplace, the University of Oxford. As part of the meeting, we participated in some group reminiscence, led by Leon Flicker, one of the group's early editors. As we reflected on the development, achievements and future aims of the group, it became clear that the lessons learned over the years remain relevant to the group and to the broader dementia research community.

For those unfamiliar with it, Cochrane (www.cochrane.org) is a global network that strives to produce credible and accessible information to inform healthcare decision-making by patients and clinicians. The epidemiologist Archie Cochrane recognised the importance of collating all available evidence.[1] The resulting Cochrane Collaboration remains best known for producing systematic reviews and meta-analyses, although its interest extends to many aspects of evidence synthesis, most notably development of methodology. With the number of meta-analyses in the medical literature increasing exponentially, Cochrane reviews are internationally recognised as a gold standard of evidence due to their adherence to strict methodological standards.

Under the umbrella of Cochrane are a series of themed groups. When it started in 1995, Cochrane Dementia had a small team of editors and published a handful of reviews. CDCIG now has a portfolio of over 180 active systematic reviews covering interventions and tests for dementia and other cognitive disorders; an editorial board of 22 from diverse disciplines including geriatric medicine, psychiatry, nursing, pharmacology, psychology and public health; all supported a managing editor, information specialist and search coordinator. This growth is testament to a transformation in the amount and status of dementia research, something which seemed implausible back in 1995 when there were few trials of dementia interventions and little political or public interest.

The timing of the development of the Cochrane dementia group was opportune as the early dementia pharmacological interventions were evaluated with substandard methodology. The first drug to be eventually licensed for the treatment of Alzheimer's Disease, Tacrine, had initial unbelievably positive results reported.[2] However, defects in the trial methodology and reporting were soon noted and a FDA investigation found many irregularities.[3] Subsequently independent positive studies appeared that found more modest effects, as well as hepatic toxicity, effectively summarized in an individual patient data review.[4] The need for more rigorous methodology and more accurate reporting was clear and Cochrane Dementia has always had a role in supporting and campaigning for greater transparency and methodological rigour. Cholinesterase inhibitors now have an established role in the treatment of patients with Alzheimer 's disease although the most recent Cochrane review concludes that effects are modest and often associated with cholinergic side effects.[5] Unfortunately, the field continues to be plagued by trial results that are spectacularly positive[6] yet disappointingly are unable to be replicated.[7]

The story of Tacrine remains pertinent to contemporary dementia research. The massive increase in public interest and in the commercial potential of dementia, has only served to multiply the appetite for stories of 'breakthroughs' and 'cures' for dementia. Core to the purpose of CDCIG is to subject the evidence about interventions to critical scrutiny. Unfortunately, there are few reviews in the portfolio which identify benefits of treatment with certainty. An accusation often levelled at Cochrane is that most reviews end with the same conclusion: "…….there is no convincing evidence to support use of X". We make no apology for subjecting the evidence about interventions to rigorous testing. We are neither nihilistic nor pessimistic regarding dementia treatment, but we believe progress will only come through a clear-eyed approach to current knowledge.

Currently, the greatest scientific speculation and controversy in the field of dementia is not around treatment, but diagnosis. Making a robust diagnosis is an important facet of dementia management. CDCIG was among the first Cochrane groups to publish reviews of diagnostic test

accuracy, offering a suite of reviews describing the accuracy and utility of various approaches to dementia diagnosis. The reviews covered neuroimaging and tissue based assays as well as short cognitive screening tests.[8] This work was timely as it coincided with new diagnostic proposals which suggested the use of imaging and cerebrospinal fluid biomarkers in the diagnosis of dementia and pre-dementia states.[9] Again, CDCIG sounded a note of caution that was not in keeping with the general excitement and enthusiasm regarding biomarkers. The body of evidence to support the use of biomarkers was, and still is, relatively modest in size and the available studies had a number of methodological limitations.[10] Our formal evaluation quantitative of sensitivity and specificity found that certain dementia biomarkers had accuracy metrics that were less than would usually be required to recommend use of a test in clinical practice.[11]

CDCIG has always strived to be more than just a passive collector of evidence and the group has had a role in raising standards in conduct and reporting of science. As an example, we supported our work on dementia test accuracy to create specific reporting guidance for the dementia field (STARDdem).[12] This was complemented by template protocols for those wishing to conduct dementia test accuracy reviews[13] and methodological papers looking at the science of dementia test accuracy analyses.[14] We hope that these materials will bear fruit over time, although we note that recent high profile reviews of biomarkers have not followed best practice recommendations.[15]

Although CDCIG's early intervention reviews were largely of drug trials, these no longer make up the bulk of our activity, again reflecting the broadening of interest in dementia across researchers of many different disciplines. Highly accessed content from last year includes music therapy[16], reminiscence[17] and cognitive stimulation.[18] Several of our reviews with 'positive' findings are of psychosocial interventions, e.g. multicomponent interventions to prevent delirium.[19] Psychosocial interventions can also come with vested interests and have lagged behind drug trials in the quality of trial design and reporting (although the landscape is changing). Hence, Cochrane's systematic review methods, emphasising the importance of assessing risk of bias, are just as pertinent. Increasingly

dementia studies are looking at the effects of complex (systems based) interventions and adopting appropriate methods for synthesis of these data is another current interest in the group.

Using reviews of existing research is useful to summarise what is already known but can also be a powerful tool for guiding future primary research. Historically, variations on the review conclusion of "more research is needed" are at least as common as "there is no convincing evidence", and equally frustrating for readers. One of CDCIG's current aims is to improve reviews by drawing more specific implications for future research. This is a theme of a recent programme of work looking at modifiable risk factors for dementia. There is much interest in whether lifestyle modifications could alter the course of cognitive decline and CDCIG have collated the evidence with an emphasis on some of the more recently proposed modifiable risk factors. Titles include computerised cognitive training, dietary and exercise interventions and whether discontinuation of medications such as antihypertensives has an effect on cognitive decline.[20] Not all the reviews in the suite are complete but a common theme is emerging. For certain interventions, pooled data suggest a signal of potential effect, but the summary estimates do not reach statistical significance. Positive trends in the data are encouraging but are not enough to change practice. Hoping not to confine ourselves to the anodyne "more research is needed", CDCIG is now working with methodologists and statisticians to explicitly define *which* research questions would benefit from further original data, *what* should these studies look like and *how* much data are needed to give a definitive answer.

Along with publication of systematic reviews, all Cochrane review groups are tasked with the creation and maintenance of a register of clinical trials in their area of interest. In 2008, with the support of the Alzheimer's Association, CDCIG created ALOIS, a register of dementia trials, containing bibliographic and other information on controlled trials in dementia and related areas, that is updated monthly (www.medicine.ox.ac.uk/alois). ALOIS is the focus of pioneering public engagement work, recruiting volunteers, many of whom were carers and former carers, to help populate ALOIS by extracting characteristics of trials. Cochrane Dementia has established a

reputation for consumer/patient involvement in evidence production. The information specialist within the group now co-leads Cochrane Crowd (http://crowd.cochrane.org) a crowdsourcing platform, with a community of over 3,500 volunteers who have helped identify almost 30,000 reports of randomised trials across many healthcare areas. Cochrane Crowd builds on all that we have learnt over the last 8 years in terms of providing better opportunities for people to be able to contribute meaningfully and usefully to the work of Cochrane.

As we look forward, we recognise that systematic review is evolving in line with methodological and technological advances. Reviews of dementia treatments compared to a control will remain core work for the group and we are excited that potential new treatments are emerging from early phase work. The process of the systematic review is likely to change with techniques like semi-automation allowing improved efficiency. However, the methodological precision and complete impartiality that has defined Cochrane reviews will not change. To meet the needs of an ever changing health-care system, it seems likely that CDCIG will also evolve. A direction of travel is to complement traditional review work, with more sophisticated reviews that incorporate economic evaluation; qualitative data and multicomponent network analyses. Communicating this science is key and we will continue to share important reviews through various social media. We would welcome users to follow us on twitter @CochraneDCIG. CDCIG's greatest strength lies in the researchers, clinicians, information scientists and lay public who contribute to our work. We are happy to welcome new members, particularly those with a passion for evidence based healthcare who are not afraid to challenge the status quo in dementia research. Happy Birthday Cochrane Dementia, here's to the next 21 years.

1. Cochrane AL. Effectiveness and Efficiency. Random Reflections on Health Services. London: Nuffield Provincial Hospitals Trust; 1972. (ISBN 1-85315-394-X). 1972 (Reprinted in 1989 in association with the BMJ).

2. Summers WK, Majovski LV, Marsh GM, et al. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. N Engl J Med. 1986; 315:1241-5

3. Division of Neuropharmacological Drug Products Office of New Drug Evaluation (I) Center for Drug Evaluation and Review. Special report. Tacrine as a Treatment for Alzheimer's Dementia — An Interim Report from the FDA. N Engl J Med 1991; 324:349-352

4. Qizilbash N, Whitehead A, Higgins J, et al. Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. Dementia Trialists' Collaboration. JAMA. 1998; 280:1777-82.

5. 5. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006;:CD005593.

6. Doody RS, Gavrilova SI, Sano M, et al Dimebon investigators Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet. 2008;372:207-15.

7. Chau S, Herrmann N, Ruthirakuhan MT et al. Latrepirdine for Alzheimer's disease Cochrane Database Syst Rev. 2015:CD009524.

8. Quinn TJ, Fearon P, Noel-Storr AH et al. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within community dwelling populations. Cochrane Database Syst Rev. 2014;4:CD010079

9. Dubois B, Feldman HH, Jacova C et al. Revising the definition of Alzheimer’s disease a new lexicon. Lancet Neurol 2010; 9: 1118–27.

10. Noel-Storr AH, Flicker L, Ritchie CW et al.. Systematic review of the body of evidence for the use of biomarkers in the diagnosis of dementia. Alzheimers Dement. 2013;9:e96-e105

11 Ritchie CW, Smailagic N, Noel-Storr AH et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2014:CD008782.

12. Noel-Storr AH, McCleery JM, Richard E et al. Reporting standards for studies of diagnostic test accuracy in dementia: The STARDdem Initiative. Neurology. 2014;83:364-73

13. Davis DH, Creavin ST, Noel-Storr A et al. Neuropsychological tests for the diagnosis of Alzheimer's disease dementia and other dementias: a generic protocol for cross-sectional and delayed-verification studies. Cochrane Database Syst Rev. 2013; 28;CD010460.

14. Wilson C, Kerr D, Noel-Storr A, Quinn TJ. Associations with publication and assessing publication bias in dementia diagnostic test accuracy studies. Int J Geriatr Psychiatry. 2015;30:1250-6.

15. Dyere SM, Flicker L, Laver K et al. The clinical value of fluid biomarkers for dementia diagnosis. Lancet Neurol. DOI: http://dx.doi.org/10.1016/S1474-4422(16)30238-1

16.Vink AC, Bruinsma MS, Scholten RJPM. Music therapy for people with dementia. Cochrane Database Syst Rev.2003:CD003477

17. Spector A, Orrell M, Davies S, Woods RT. Reminiscence therapy for dementia. Cochrane Database Syst Rev.2000:CD001120.

18. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev. 2012:CD005562

19. Siddiqi N, Harrison JK, Clegg A et al.Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database of Syst Rev.2016:CD005563

20. Jongstra S, Harrison JK, Quinn TJ, Richard Edo.Antihypertensive withdrawal for the prevention of cognitive decline. Cochrane Database Syst Rev.2016:CD011971