## Appendix D – Clinical specialist statement template

**Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111)**

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Peter Connelly**

**Name of your organisation NHS Quality Improvement Scotland**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes, Consultant Old Age Psychiatrist, Perth and Kinross.
- a specialist in the clinical evidence base that is to support the technology? Previously Chair, SIGN Guideline Group for the Management of People with Dementia (SIGN 86)
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? Chair, Old Age Faculty, Royal College of Psychiatrists

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS?

Dementia is neither well recognised nor well treated. There is a high level of stigma about the symptoms and signs of dementia in an older population and consequently there is a long period, on average 18 to 24 months, during which people with dementia do not present for diagnostic assessment. Unfortunately by this time there are often irreversible changes in the relationship they have with family, friends and

wider society groups. Unquestionably the advent of cholinesterase inhibitors in the late 1990's led to substantially changes in demand for diagnosis and treatment, with the typical patient presenting to services with an MMSE 23 to 24 i.e. above the threshold for cholinesterase inhibitor treatment. Despite this and despite recent stimulation for earlier diagnosis e.g. HEAT Targets in Scotland, improvements in rates of diagnosis remain very slow. For those presenting late crisis intervention is frequent. Coordination of care is often patchy and delivery of community based interventions dependent upon staffing levels which are often poor. The UK government has accepted that age discrimination is at its greatest in the field of mental health and people with dementia are further disadvantaged by societal stigma.

Is there significant geographical variation in current practice?

The issues of postcode prescribing of cholinesterase inhibitors have been well highlighted by the Alzheimer society and others. None the less this hides a variation in diagnostic practice depending upon the accessibility of Neuroimaging and neuropsychological testing. An increasing body of literature is in favour of an increasing overlap between cerebro vascular disease and Alzheimer's pathology, with the consequence that it is now more difficult to be certain of "pure" Alzheimer's disease as a diagnostic entity, especially in people over 80, where co morbidity is extremely common.

One factor determining geographical variation is the rigidity with which HTA111 is put into practice. A recent study has shown that approximately 20% of those treated under previous NICE guidance are now no longer eligible for treatment, though this is balanced to a large extent by the prospect of treating people with an MMSE of 10 to 12. In practice few people commence treatment at the lower end of the spectrum. The limitations of the MMSE are well recognised as is inter rater variation and the difficulties of obtaining consistent scores is well recognised particularly as dementia progresses. In areas where the MMSE is used as the sole criterion for prescription, many people with "moderate" dementia are denied treatment.

Comments about the geographical variation in availability of Memantine apply to a greater extent than cholinesterase inhibitors. In many areas of the country this drug is effectively unavailable or prescribed only through a torturous process of evaluation, usually as a last resort with decisions normally taken by non specialists. As with cholinesterase inhibitors a substantial variation in response is noted. Although some people appear to have dramatic improvement effects is more a therapy or in combination with cholinesterase inhibitors are usually modest. Increased agitation can occur. There is a widely held view that Memantine may reduce agitation and aggression but clinical trial evidence with behaviour change as a primary outcome has not yet been published although at least one major trial is currently being undertaken in the UK.

Are there differences of opinion between professionals as to what current practice should be?

Professionals feel that these drugs are under used. Although the effects on cognition, function and behaviour are modest in scale and limited in range alternatives are either

ineffective across these domains or lack availability. Cognitive simulation therapy has been evaluated in relatively small populations and at present delivery is dependant upon intensive input from trained therapists. Reality orientation therapy has shown some promise but can be tolerated poorly by participants. However, there is a widely held view that the advent of generic forms of cholinesterase inhibitors will lead to more widespread and possibly inappropriate use of particularly within primary care.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

One point raised in the justification for restrictions being placed on the use of cholinesterase inhibitors is that there are adequate alternatives. The reality is much different. Therapies are either ineffectiveness or lack of availability. Interventions such as cognitive stimulation therapy have been evaluated in relatively small populations and at present are dependent on intensive input from trained therapists. Reality orientation therapy has shown some promise but can be tolerated poorly by participants.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In addition to their modest effects on cognition cholinesterase inhibitors also have some effects on behaviour, albeit studies showing this tend to deal with people who are not particularly behaviourally disturbed and indeed one trial on a population with high baseline agitation showed a lack of effect. However pharmacological interventions such as memantine or non-pharmacological interventions including aromatherapy also have modest effects. In addition the effectiveness of long term exposure and side effects remain unevaluated. Consistency is emerging however about the reduced need for antipsychotic medication when people with dementia continue to receive cholinesterase inhibitors or Memantine. There are suggestions that a combination of a cholinesterase inhibitor and memantine may be more effective that either alone although no clear answer to this will emerge until the publication of the DOMINO-AD study.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

The focus of treatment is inevitably community based. Over 80% of prescriptions are issued by primary care, normally through shared care protocol. The presence of shared cared protocols is not uniform across the country. In many cases old age psychiatrist physically issue the prescriptions though this does lead to patient safety problems associated with dual prescribing, particularly if treatment with a cholinesterase is not recognised when a person with dementia is admitted to a general hospital. However, there are advantages in old people's mental health teams being constantly aware of those who are receiving cholinesterase inhibitors and there are good arguments that coordination of prescription through specialist care ensures follow up is optimum.

There is an increasing trend to move away from routine testing of people, particularly at higher levels of MMSE. Patients who retain insight realise that they are

deteriorating and become extremely distressed by the testing procedure, whilst psychiatrist often feel that they have little or nothing to offer in additional medical care so that the distress is simply counterproductive.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

At a practical level, the increasing awareness of the interaction between Alzheimer's pathology and cerebro vascular pathology makes certainty about diagnosis difficult and consequently specialists are becoming less rigid about making attempts to diagnose "pure" Alzheimer's disease. In addition there is evidence for benefit in treatment of dementia with Lewy body and Parkinson's disease dementia. They appear to have beneficial effects in the treatment of visual hallucinations, what ever the underlying pathology might be. As a result a small but perhaps increasing number of prescriptions are initiated by non psychiatrist and there is some concern that GP's are more willing to prescribe when the recommendation is made by a non psychiatrist that by a psychiatric specialist.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

In the UK the two main sets of guidelines are NICE 42 and SIGN 86. Not surprisingly the NICE guideline and NICE guidance are similar but in Scotland more weight seems to be given to changes in function, behaviour and personality when assessing the severity of dementia. Consequently in Scotland there is more of a tendency to make a diagnosis of "moderate" dementia even if the MMSE exceeds 20. However, in Scotland there is still widespread geographical variation in prescribing.

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is a considerable amount of concern about what might happen when generic compounds are introduced. Only the minority of GP's are confident in making a diagnosis of dementia and there is concern that inappropriate prescribing for "memory complaints" will become the norm, coupled with short term assessment of benefit and inappropriate withdrawal from people who feel no better. At this point psychiatrists anticipate the GP will refer the patient to them as having trialled cholinesterase inhibitors unsuccessfully and questioning further management options. Since cost effective arguments will be substantially modified by the appearance of generic

compounds there is a concern that psychiatric services will be overwhelmed, particularly since early diagnosis and treatment is mandated by the English national dementia strategy and similar work in Scotland.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There is no clear guidance on the combination of clinical features which might indicate that withdrawal of a cholinesterase inhibitor or memantine is appropriate. The MMSE is particularly unreliable at its lower end and prone to fluctuate. Cessation of medication at an arbitrary cognitive point is particularly worrying especially if the decision is made on a rating at a single point of time. A withdrawal syndrome for donepezil and for memantine have both been described and the effect illustrated by one study often quoted as being an indication of donepezil preventing behaviour problems which may simply show the effects of donepezil withdrawal. In practice discontinuing medication might make the difference between a person being able to continue residing in the community with support and requiring entry into care. The discontinuation of medication in reaching a threshold of dysfunction contrasts markedly with Parkinson's disease where medication regimes becomes increasingly complex as mobility declines or stroke where preventative strategies also become more intense once the stroke has happened.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

Neither cholinesterase inhibitors nor memantine are a panacea for the problems of Alzheimer's disease. Clinicians would acknowledge that their effects on the patient are in the main modest though some people now continue to reside at home 10 years after therapy was introduced. Their effectiveness on changing the population's viewpoint on dementia however has been much more significant. A desire for early intervention is now considered normal and the restriction of prescription is considered a very retrograde step by old age psychiatrists. When the first cytotoxic was introduced there was no expectation that all cancers would be cured and there needs to be a recognition that the effects of any intervention in a population with dementia are going to be modest though at an individual level some dramatic improvements do occur. In this light even person centred care does badly. The management of dementia is a matter of carefully knitting together a number of interventions each of which contributes a small amount. Cholinesterase inhibitors and memantine need to be part of what we can offer throughout the course of someone's dementia. One must remember that economically the costs of dementia soar when it becomes severe. Maintaining someone outwith this category whilst they die of something unrelated is considered a good therapeutic outcome by doctors and by carers.

What, in your view, are the most important outcomes, and were they measured in the trials?

The clinical trials not surprisingly evaluated cognition, function and behaviour together with global outcome measures. Behaviour change was rarely a primary outcome. Measures of social integration, quality of life, carer burden and stress have

not been systematically evaluated as primary outcome measures. Descriptions of the effects of cholinesterase inhibitors in dementia with Lewy bodies, Parkinson's disease and the treatment of hallucinations have also led to services relaxing their concentration on the measurement of improvement through cognitive or functional scales and a more holistic overall assessment including social integration, behaviour change, maintenance of personality and interpersonal interaction in assessing effectiveness.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Cholinesterase Inhibitors appear to be well tolerated in clinical practice in both short and long term treatment. Cardiac complications, including heart block, can appear but in cases where people have been responding well the insertion of a pacemaker can control this problem. The drugs appear to be less well tolerated by people with symptomatic cerebro vascular disease though this is by no means uniform.

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The following are a number of small scale studies indicating that there may be different responses in different patient groups.

**Connelly PJ**, Prentice NP, Cousland G, Bonham J (2008) A randomised double blind placebo-controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *Int J Geriatric Psychiatry* **23**: 155-60

**Connelly PJ**, Prentice NP, Fowler KG. (2005) Hypertension, white matter change and response to cholinesterase inhibitors. *Int J Geriatric Psychiatry* **20**: 623-628

**Connelly PJ**, Prentice NP, Fowler KG. (2005) Predicting the outcome of cholinesterase inhibitors. *Journal of Neurology Neurosurgery and Psychiatry* **76**: 320-324

Connelly PJ, Prentice NP (2005) Current smoking and response to cholinesterase inhibitors *Dementia and Geriatric Cognitive Disorders* **19**: 11 – 14

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?

In my practice cholinesterase inhibitors in particular have been of enormous benefit in changing how we approach people with dementia and what we offer them for the future. I would urge NICE to revise its policy to allow cholinesterase inhibitors to become available for people at all levels of severity of established dementia and Memantine either singly or in combination at later stages especially if the patient is unable to tolerate a cholinesterase inhibitor because of physical side effects. The reduction in the use of antipsychotic drugs and the consequent associated mortality must not be under-estimated and reducing this iatrogenic mortality is now a clear goal for the government. Cholinesterase inhibitors and memantine should play a clear part in this process. The arguments in cost effectiveness are going to diminish with the advent of generic drugs and delaying judgement until that time simply imposing unnecessary hardship on people who have dementia now. I would urge NICE to act swiftly in recognising the wider societal aspects of these drugs when considering their revised guidance.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Issues of implementation have to be seen in tandem with service developments consequent on the implementation of dementia strategies in the UK.

As noted above there remains a major issue over the advent of generic compound. At present primary care services are not developed to an adequate level or on a sufficiently widespread basis to allow routine diagnosis and management of people with dementia. Whether primary care represents the best locus for diagnosis and initial management remains a source of debate amongst professionals despite governmental desires. The key for other conditions such as schizophrenia, multiple sclerosis, stroke etc is to get the patient into contact with secondary services at as early a stage as practical. Although considerable improvements need to be made secondary care services are currently best placed to coordinate initial management

once a diagnosis is suspected and the benefits of early involvement of specialists cannot go unacknowledged. There are good arguments for specialist services being provided from primary care environments to encourage engagement and reduce stigma, but there are obvious resourcing issues attached to this. The training and education of primary care staff, including GP's including improved diagnostic acumen, skilled diagnostic disclosure, detailed post diagnostic counselling and appropriate coordination of care would be a major undertaking in the UK and the use of cholinesterase inhibitors and Memantine would be a clear part of this.