This response was submitted to the consultation held by the Nuffield Council on Bioethics on *Dementia: ethical issues* between May 2008 and July 2008. The views expressed are solely those of the respondent(s) and not those of the Council.

Alzheimer's Research Trust

QUESTIONS ANSWERED:

Q1

ANSWER:

The Alzheimer's Research Trust (ART) conducted an informal survey of our supporters in September 2007. ART asked the supporters to rank the symptoms of Alzheimer's according to how distressing they are to a partner, relative, carer or a person with Alzheimer's disease. The survey suggested that memory loss and aggression are the most distressing symptoms with wandering, following, incontinence and hallucinations also considered distressing, but less so.

Q5

ANSWER:

Ultimately the most important developments in AD research are those that will lead to new treatments to slow progression or even prevent the disease. Great progress has been made and a number of compounds are in late stage development with many others in early clinical trials. A cautious optimism is warranted but we have three concerns – first although the pipeline looks interesting, most compounds in a drug development pipeline fail; second that a very considerable weight has been placed on amyloid as a target for therapy and thirdly that pre-clinical models of AD and related dementia are not sufficiently well-developed. With regard to the first concern; this is a matter shared across biomedicine and not unique to AD. Specifically in relation to AD however we note the difficulty of performing trials in elderly, often frail, people; the absence of biomarkers for disease progression and the difficulty therefore of measuring efficacy; the necessity of long term and large trials with a correspondingly large cost (estimated at more than £20m per year per trial). With regard to the second concern – the weight of research focussing on amyloid as a target – there is clearly a risk should anti-amyloid trials fail (and early results include a failure of compounds targeting amyloid production, amyloid aggregation and amyloid clearance). Further potential therapeutic and indeed symptomatic targets need urgently to be identified. With regard to the third concern – models of AD are based almost exclusively on inducing autosomal dominant mutations in AD-related genes into mice. Often multiple mutations and genes in the same animal. Although this is clearly the most straightforward route to developing animal models the results have shown that the ensuing phenotype does not match the human condition. As these are the only models currently it is appropriate that they be used to further research and drug development but their limitations should be acknowledged and more efforts put into refining these and developing other models. In addition to research directly targeted towards drug

development, which despite the caveats and concerns noted above, is progressing rapidly, we note three other areas of research that show promise for translation to improvements in care and treatment: Firstly there are recent developments in biomarkers for early diagnosis and disease progression which will ultimately improve the care, diagnosis and treatment of people with dementia. These are resulting from progress being made in neuroimaging including both structural and molecular imaging and from gene and protein based studies in blood and CSF. Some of these biomarkers are already being used in clinical trials and in some European countries in clinical practice. A proposal has been made to incorporate biomarkers into formal diagnostic procedures and we expect the use of biomarkers to become widespread in clinical practice in the near to medium term. If effective biomarkers have the potential to make earlier and more specific diagnoses possible and to more accurately measure progression. Secondly very large scale genetic studies are underway to try to elucidate the causes of AD. These may have a long-term impact on the field but in the shorter term may help to understand why some people with AD have certain sets of symptoms. The Alzheimer's Research Trust, for example, is funding a study to determine how a person's genotype could effect the development of psychosis including aggression, depression and hallucinations. Many other approaches are possible to try to understand the origins of non-cognitive symptoms in dementia and once it is possible to determine which patients are likely to develop each symptom, symptomatic treatment might be customised for the best possible benefit and to limit side effects. Thirdly we acknowledge the important contribution of research into the provision of care and into support for relatives. Although this is not an area that the ART chooses to concentrate on, as a funding organisation we do support research into the evaluation of existing medical interventions. See for example Q31 for our comments on anti-psychotic medication. In summary our assessment is that the single most important developments arising from research are likely to be treatments designed to slow or prevent disease or novel symptomatic treatments. These are long-term research goals but with a not-unrealistic chance of being achieved to some extent within 5-10 years. In the shorter term research into biomarkers and into non-cognitive symptoms and their treatment are important translational research targets.

Q6

ANSWER:

The Alzheimer's Research Trust believes diagnosis of dementia should be given as soon as it is possible to do so with some confidence or accuracy. Currently the continued decline of dementia is inevitable and allowing patients who want to be told and families as much time as possible to prepare is important. Understanding how this progression happens can be useful in helping someone with dementia anticipate and plan for change (Ref 3). In the future drugs that can delay cognitive decline will be available. At that time, the earliest possible diagnosis could change the course of the person's life by providing additional years of mental capacity. Ref 3: Knapp M, Prince M. Dementia UK. 2007.

Alzheimer's Society.

Q7

ANSWER:
Perception related to cancer Currently dementia is perceived very similarly to how cancer was perceived thirty years ago. At the time, cancer was untreatable and there was no hope; therefore, people did not talk about the disease or the diagnosis. Once cancer research had progressed to the stage that survival was possible, the stigma associated with it radically changed. A YouGov poll commissioned by the Alzheimer's Research Trusts has shown that 39% of people over the age of 55 fear dementia more than any other condition. Comparatively, only 30% of those polled are most concerned about cancer. In addition, 26% of the UK population are more scared of dementia than any other medical condition. Dementia stigma & misunderstanding We do not understand how stigma arises or which aspects of dementia it is related to. It may be related to the disease as a whole or, for example to behavioural symptoms. At the same time, there is a large amount of misunderstanding. Often the early symptoms are considered a normal aspect of ageing and not a symptom of disease, thus delaying diagnosis and treatment. It is essential to promote a better understanding of dementia. Better understanding might reduce the stigma associated with the disease and would encourage earlier diagnosis. Dementia is under diagnosed in the UK; between half and two thirds of people with dementia never receive a formal diagnosis and it takes an average of 32 months to receive a diagnosis after the first symptoms have been reported. This compares to 14 months in Italy and only 10 months in Germany (Ref 1). An improved understanding of dementia is required in both the general population and in the health and social services. Only 68% of British doctors agreed that early treatment could delay the progression of the disease in comparison to 92% in France and 91% in Italy (Ref 1). Ref 1: Bosanquet N, Haldenby A, Rainbow H. NHS Reform. Feb 2008.

Q9

ANSWER:
People with dementia should be included in everyday life as much as possible for social, emotional and mental stimulation. People who feel lonely have a significantly raised risk of developing Alzheimer's disease (Ref 2). In the past, scientists have associated social isolation with and increased dementia risk but this study by Professor Robert Wilson related the social isolation to loneliness through analysing people's perceptions of their loneliness. The study followed more than 800 elderly patients over a four-year period. Participants' feelings of loneliness were measured on an annual basis as they rated from one to five whether they agreed with certain statements. The team found that the risk of developing Alzheimer's disease increased by 51% for each point of the 'loneliness score' so that those with the highest loneliness score of 3.2 had about 2.1 times the risk of developing Alzheimer's disease compared to those

with a low score of 1.4. Ref 2: Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry. 2007 Feb;64(2):234-40.

Q24

ANSWER:
The state owes investment in research to the hundreds of thousands of people with dementia and their families, and all the many hundreds of thousands who will otherwise get this disease in the future. This is on the ethical basis that 700,000 people in the UK live with dementia, which costs the economy £17 billion (Ref 3) and is expected to hit £35 billion within 20 years (Ref 4). In addition, YouGov polls commissioned by the Alzheimer's Research Trust have shown that 42% of the UK population, or 25 million people, know someone close to them with dementia. The same poll has shown that 82% of the UK population support an increase in dementia research funding. Ref 3: Knapp M, Prince M. Dementia UK. 2007. Alzheimer's Society. Ref 4: McCrone P, Dhanasiri S, Patel A, Knapp M, Lawton-Smith S. Paying the Price: The cost of Mental Health Care in England to 2026. The King's Fund. May 2008.

Q29

ANSWER:
Achievements The most important aspiration of research in dementia is the development of drugs that could delay the onset or decline. Delaying the onset of dementia by five years would halve the number of UK deaths due to dementia (Ref 3). There has been a significant underinvestment in disease prevention. The UKCRC UK Health Research Analysis of the top 11 largest government and charity funders of health research showed that only 2.5% of their research portfolios are dedicated to prevention (Ref 5). However, the public identifies preventing ill-health as the single most important area for research into ageing. More than twice as many people chose research into prevention over research into cure (Ref 6). In order to find a cure, treatment or prevention, more basic research is essential. Basic research into understanding the causes and mechanisms of disease is the most likely route to discovering new drug targets. See also response to Q5 Funding Allocation The amount of funding for dementia in relation to other diseases should be allocated based upon the costs to society. Dementia costs more than cancer, heart disease and stroke combined. The current economic cost is £17 billion per year (Ref 3); this will rise to £35 billion within 20 years (Ref 4). Achieving a balance in mechanisms for distribution of research funding is vital. A predominant mechanism should continue to be investigator-led research application and peer-review. However we support recent initiatives by the MRC and other funders to target research funds to translational targets including early trials, biomarkers, clinical cohorts and model development. Within each it is important to ensure that dementia research is well represented and reflects national priorities as highlighted by the costs of dementia compared to other disease areas. Ref 3: Knapp M, Prince M. Dementia

UK. 2007. Alzheimer's Society. Ref 4: McCrone P, Dhanasiri S, Patel A, Knapp M, Lawton-Smith S. Paying the Price: The cost of Mental Health Care in England to 2026. The King's Fund. May 2008. Ref 5: UK Clinical Research Collaboration. UK Health Research Analysis. May 2006. Ref 6: Ipsos MORI. Public Consultation on Ageing: Research into Public Attitudes Towards BBSRC- and MRC-Funded Research on Ageing. July 2006.

Q31

ANSWER:

The regulatory framework in the UK is perceived to be robust, if not potentially restrictive with areas of concern being ethical review, clinical trials regulation in Europe, organ retention, legislation surrounding mental capacity and privacy of personal information. Overall our view is that valuable research is not prevented but can be hampered and that clarity and some refinement of processes would be valuable. Ethical review: we welcome some of the change in practice and legislation over recent years and broadly speaking the proliferation of independent review boards has been reduced and review boards have become more transparent and responsive. However we believe that the current review process remains cumbersome for both animal and human research. For human research the ethical review process appears geared towards trials and we are aware of a view in our research community that there is scope for some streamlining for research that involves little or no risk of harm to participants. For animal research, so vital to progress in dementia, the bureaucracy involved risks seriously hampering research in this area in the UK. Clinical trials regulation: we are concerned that the regulation surrounding therapeutic interventions research in UK and Europe is perceived as so restrictive that increasingly the pharmaceutical industry is turning to Eastern Europe and further afield. We worry that this is transferring ethical responsibility, is unlikely to result in an overall decrease in risk of harm to research participants worldwide and may hinder research efforts in this area. Organ retention: we broadly welcome many elements of the change in legislation and practice surrounding organ retention. We particularly welcome the emphasis on consent and involvement of potential donors and their relatives and others. However we note with some concern the grave penalties now attached to process in organ retention, including the potential for criminal prosecution. We note also with concern the resource cost – both financial and managerial – attached to process. Both add to a sense in the UK science, health and education communities that organ retention has become prohibitively risky in the UK. If this is a consequence of the change in process then it would be to the serious detriment of people with dementia now and in the future. We do not believe that a change in the regulatory framework is needed but we would welcome further investment of time and other resource from funders such as the MRC and NIHR to ensure that organ retention for research is a continued activity in the UK and that organisations conducting this research are empowered to meet the appropriately enhanced due-process. Mental capacity – see response to Q30 Personal information and privacy; we are aware of the current alarmist narrative

surrounding personal information; particularly that held by centralised organisations including government. We are concerned that this may significantly impair research particularly if it leads to further legislation in this area, to more restrictive interpretation of existing legislation or to guidelines further restricting the use of personal information. Health records represent one of the most important resources for research. Examples of successful outcomes of research based on health records, particularly in Scandinavia abound. The UK electronic and other medical records represent one of the greatest untapped resources for dementia research. However, ambiguity about the ability of researchers to access records and the ethical framework surrounding the use of anonymised data is significantly hindering work in this area. We feel strongly that the use of anonymous or anonymised clinical records should be permitted wherever possible and that an ethical framework providing clarity and guidelines for best practice but with an assumption in favour of permitting such research would be valued by both the public and scientific communities. Finally we note that it is unlikely the Human Fertilisation and Embryology Bill (HFEB) would have been passed without the support of medical research charities and it is likely that similar issues will develop in the future. The HFEB highlights the need to inform the public about scientific issues and their importance. Only with a fuller awareness of the issues involved can society provide informed consent and come to a consensus on ethical issues.

Q30

ANSWER:
Research volunteers are essential for research to progress and treatments to be developed. Volunteers are important in every step of research from basic studies through to health services research and late stage evaluation trials. The value of research volunteers can not be over-estimated. It is our understanding from direct experience and from surveys that the public wish to participate in well conducted, ethical research and that frailty, age and impaired capacity of potential participants at the time of the research should not be a barrier to participation. Whilst the rights and dignity of participants must be respected and risk of harm must be assiduously be avoided, the prevalent view, held by almost all of the public, is that there is an imperative to do research that may lead to benefits for others, now or in the future. Avoiding research on participants who lack capacity through dementia is prejudicial to the elderly and to the mentally and neurologically unwell and is in our view unethical. We think that the safeguards to conducting research in those lacking consent are rigorous in the UK and have been considerably strengthened in recent years through the Mental Capacity Act, Adults with Incapacity (Scotland) act and the processes surrounding organ retention. Arguably the UK may now represent the most refined and regulated arena for conducting research with people lacking capacity. We welcome this but caution against further legislation or regulation. A period of stability is now essential to allow these developments to bed down and for researchers to become fully familiar with the processes. Further regulation in this area is likely to become restrictive, is unlikely to further the

safeguards for people with dementia and if it results in decreased involvement of people with dementia in research is likely to be prejudicial and harmful. We welcome the efforts being made by the Department of Health and the NIHR to enhance participation in research. One example of this is the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN), a part of the UK Clinical Research Network (UKCRN), stemming from the success of the National Cancer Research Network (NCRN). Within three years of establishment the NCRN had succeeded in more than doubling the rate of cancer patients being included in clinical research studies. We look forward to similar enhancement of participation in dementia relevant research through DeNDRoN. The Alzheimer's Research Trust and Alzheimer's Society are working together to increase participation in research through brain donation. Together we have launched the Brains for Dementia Research project to develop a network of UK dementia brain banks. One of the motivators for this considerable investment was our awareness through our two organisations of the importance both potential participants and scientists place on brain donation and yet the difficulty in achieving this. Patients and families regularly contact both charities with the desire to donate their brain to research and yet find it difficult to do and at the same time the scientific community is concerned by the decrease in availability. This Brains for Dementia Research project is designed to resolve these bottlenecks in donation and access in the best possible ethical environment.

Q32

ANSWER:

We would highlight of particular concern the widespread use of anti-psychotic (or neuroleptic) medication in people with dementia, especially in nursing homes. In the US and Europe, up to 60% of people with dementia residing in care facilities are prescribed antipsychotic medication (Refs 7, 8, 9). A study by Professor Clive Ballard, King's College London, suggested 90% of people with dementia in care homes are being prescribed these drugs (Ref 10). These drugs are widely used as the first line pharmacological approach to treating neuropsychiatric symptoms. Most people with dementia develop neuropsychiatric symptoms, such as aggression, agitation and psychosis at some point during their illness. However, better training and psychological management approaches can replace the need for anti-psychotic and similar treatments without significant worsening of behavioural symptoms. Research funded by the Alzheimer's Research Trust and led by Prof Ballard shows that for most patients with Alzheimer's disease withdrawal of medication tends to improve functional and cognitive status. Antipsychotic medication may have some value in the maintenance treatment of more severe neuropsychiatric symptoms but this must be weighed against the side effects of therapy (Ref 11). These results stem from an Alzheimer's Research Trust Major Programme Grant: "Neuroleptics: do they accelerate cognitive decline and exacerbate neuronal loss?" It began in July 2001 and ran until June 2006: • 165 participants with Alzheimer's disease living in nursing homes in Oxfordshire, Newcastle, Gateshead, Edinburgh and London, who had been taking neuroleptic

drugs for at least 3 months, took part in a long-term randomized double-blind placebo controlled neuroleptic withdrawal trial. • The neuroleptics in the study were thioridazine (Melleril), chlorpromazine (Largactil), haloperidol (Serenace), trifluoperazine (Stelazine) and risperidone (Risperdal). Patients continued to take their prescribed neuroleptic drug for 12 months or took a matched placebo. • Additional follow up was completed a minimum of 12 months after initial enrolment (range 24-54 months) to determine the impact of continuing or discontinuing neuroleptics on mortality. The differences in survival were particularly striking at 24 months (78% v 55%), 36 months (62% v 35%) and 42 months (60% v 25%). Some patients undergoing treatment for up to 4.5 years were nearly twice as likely to die (1.8 fold mortality risk for a-typical anti-psychotic treatment of up to 54 months). • These findings were first presented at the Alzheimer's Research Trust Network Conference, which took place at the Royal College of Physicians in Edinburgh on Wednesday 28th and Thursday 29th March 2007. A study demonstrated that better training and psychological management approaches can replace the need for neuroleptic treatment without significant worsening of behavioural symptoms (Ref 12). Ref 7: Margallo-Lana M, Swann A, O'Brien J, Fairbairn A, Reichelt K, et al. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatric Psych. 2001: 16: 39-44. Ref 8: McGrath AM, Jackson GA. Survey of neuroleptic prescribing in residents of nursing homes in Glasgow. BMJ. 1996;314:611-2. Ref 9: Alldred DP, Petty DR, Bowie P, Zermansky AG, Raynor DK. Antipsychotic prescribing patterns in care homes and relationship with dementia. Psychiatr Bull. 2007. 31: 329-332. Ref 10: Ballard C, Ayre G, Gray A. Psychotic Symptoms and Behavioral Disturbances in Dementia: A Review. Revue Neurologique. 1999. 155: 44-52. Ref 11: Ballard C, Lana MM, Theodoulou M, Douglas S, McShane R, Jacoby R, Kossakowski K, Yu LM, Juszczak E; Investigators DART AD. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). PLoS Med. 2008 Apr 1;5(4):e76 Ref 12: Fossey J, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ. 2006 Apr 1;332(7544):756-61.