Alzheimer's disease – Delivering disease modifying treatments (DMT)

The South East Clinical Delivery and Network team host webinars to discuss key topics relevant to people leading dementia care across the region. This interactive webinar was led by Prof. Chris Kipps to discuss the potential impact of disease modifying treatments (DMT) for people with Alzheimer's disease.

"There are potentially so many benefits linked to this for people now and in the future. People with dementia have felt ignored for far too long and this will give so much hope and release so much pressure on health and social care" (webinar attendee: Linda Goddard, Alzheimer's Society)

"This is a tremendous opportunity for dementia care. Our equivalent to the first antibiotic" (webinar attendee: Professor Alistair Burns, National Clinical Lead for Dementia)

Aims of the webinar

This webinar focused on the potential impact of disease modifying treatments (DMT) for Alzheimer's disease (AD) on South East clinical pathways was held as part of the Clinical Networks Seminar Series. This was an interactive session gathering views from 92 participants, all involved in dementia care, on how we might need to adapt our local systems to implement new dementia therapies.

The webinar aimed to:

- Share recent AD DMT trial results
- Discus potential impact on the clinical pathway
- Raise awareness of the opportunities and challenges involved in DMT delivery

Areas of consideration

The results of disease-modifying trials in AD, and potential imminent regulatory approval for clinical use of Aducanumab in AD (FDA, USA) have highlighted the need to plan the possible implementation of DMT in clinical practice. This raises a number of clinical, commissioning and policy issues including:

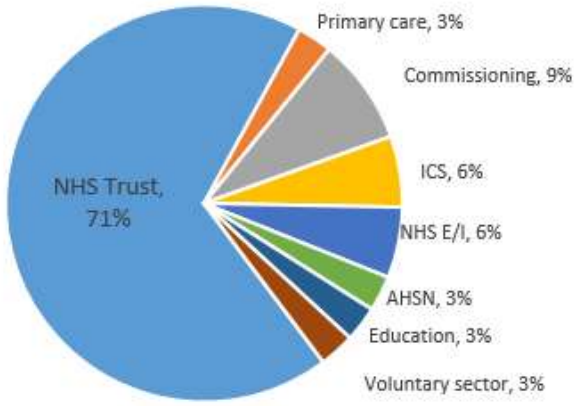
- Use of AD diagnostic tests including biomarkers
- Diagnosis of Mild cognitive impairment (MCI)
- Public interest in disease-modifying therapy
- The clinical pathway
- Training and education
- Resources
- Equity and access
- Pre-symptomatic treatment
- Cost of DMT

Who attended the webinar?

Over 90 people attended the webinar including:

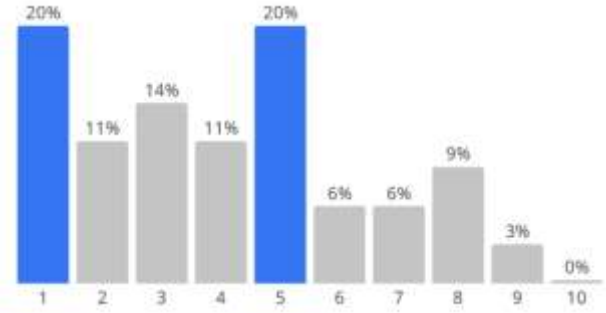
- Medical consultants
- Nursing and Advance Nurse Practitioners
- Psychologists
- Commissioners
- Service managers
- Memory clinical teams
- Pharmacists
- National, regional, ICS and locality managers

South East organisations were represented as shown below.



A short webinar poll asked for an indication of the background knowledge of DMT at the start of the call.

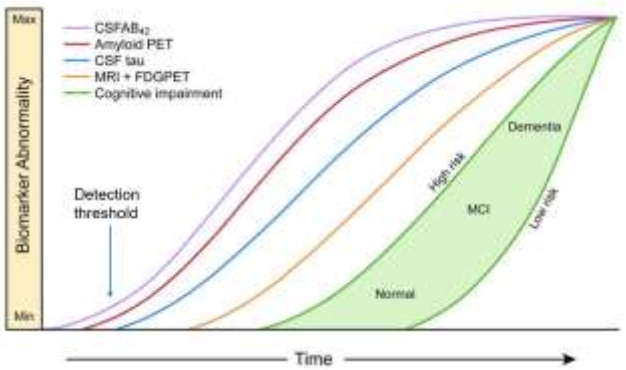
Q: How knowledgeable do you feel about the topic of DMT in AD (1-no knowledge, 10 high level of knowledge)?



Disease Modifying Treatments for dementia - the story so far…

Progression of disease

Dementia develops over many years in a series of pathological stages that precede the clinical features of the condition.



Jack CR et al. Lancet Neurology, 2013

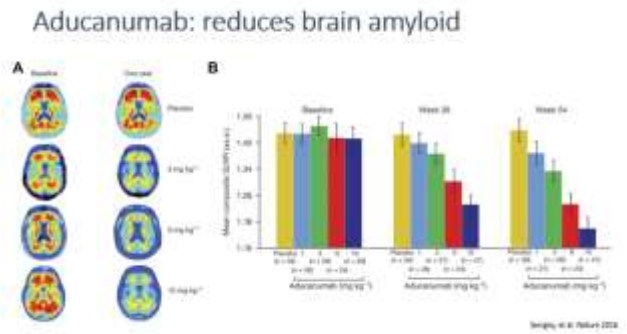
In initial stages amyloid protein deposits start to build up in the brain. These deposits form sheets with subsequent damage to tau protein (a major constituent of nerve fibres) producing the hallmark plaques and tangles seen in AD pathology.

The early stages are asymptomatic, but over time, the earliest features of disease can be detected using diagnostic biomarkers (cerebrospinal fluid and imaging). Clinical symptoms emerge later, with many pathological changes already having taken place in the brain.

Removal of amyloid

Several therapeutic compounds which remove amyloid from the brain have been identified over the last decade. Working from the premise that amyloid deposition leads to later tau abnormality, and in turn, to clinical disease, it is anticipated that adequate removal of amyloid might influence disease progression.

One such example compound is Aducanumab (Biogen). Clinical trials have shown that Aducanumab removes brain amyloid, and that this is related, in part, to the dose and duration of drug administered.

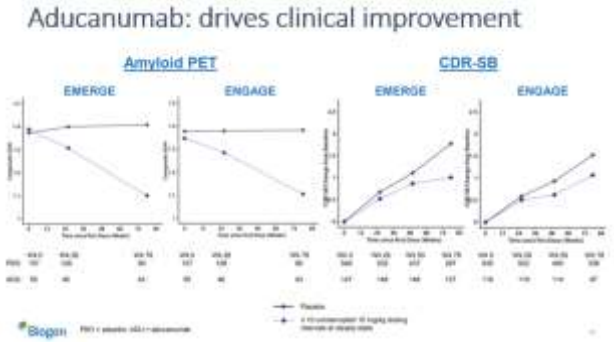


In practice, most trials of disease-modifying therapy in Alzheimer's disease have failed, and in fact, by 2018 it looked as though amyloid removal as a therapeutic strategy was not going to be viable.

Aducanumab review

Initial results of the Aducanumab (ENGAGE trial) were disappointing, but reanalysis of this data in combination with data from a separate trial (EMERGE) suggested potential benefit in individuals who had sufficient exposure to the highest doses of Aducanumab. The precise results of this trial re-analysis are controversial (see this link for original data). The analyses from EMERGE and ENGAGE (high dose and long duration) showed both biochemical (amyloid removal and change in biomarker profiles) and clinical benefit (reduction in functional decline).

The CDR sum of boxes (CDR-SB) is often used as a functional measure of 'ability' over a time period. A positive change in CDR-SB is needed for a drug trial to be considered useful in clinical practice. Initial data from the Aducanumab trail was not conclusive.



Biogen, Inc 2019

Therapeutic drug approval typically requires demonstration of meaningful clinical impact - biomarker evidence of improvement alone is usually not sufficient for licensing.

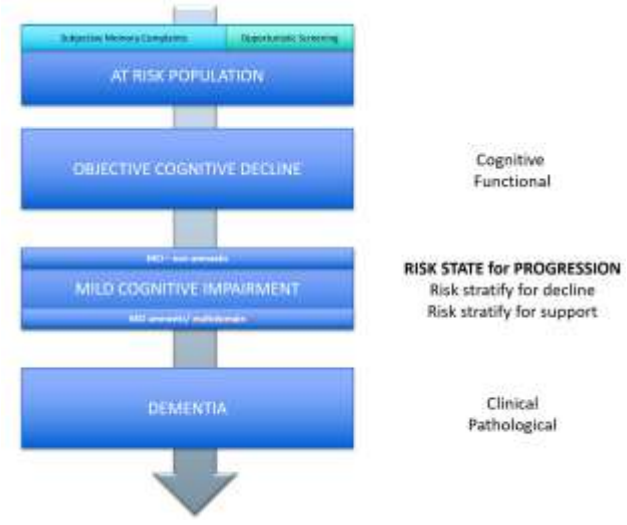
The US Department of Health and Human Services Food and Drug Administration (FDA) are reviewing Aducanumab for clinical use. A decision is expected by 7th June.

Regardless of the FDA outcome for Aducanumab, this is a clear direction of travel. There is increasing evidence that a drug of this type, if given in adequate dose for long enough to the right group of people, is going to have a positive clinical impact.

In the UK, NICE have launched a working party to appraise the clinical and cost effectiveness of aducanumab within its marketing authorisation for treating mild cognitive impairment (MCI) in early Alzheimer's disease. Publication is expected in May 2022.

Clinical pathways

Clinical pathways flow from large at-risk populations to smaller populations with varying levels of confirmed cognitive impairment. Cognitive decline moves from subjective levels to more objective (measurable) levels and encompasses the categories of Mild Cognitive Impairment (MCI) and for a proportion of individuals, dementia. This can be measured clinically and pathologically.



Symptoms are usually initially assessed in primary care, and other non-dementia causes, or concerns ruled out where possible. Specialist service referral for more detailed history and cognitive assessment may follow. Most people will have imaging performed as part of the diagnostic work-up. Some will also have advanced diagnostic testing including neuropsychology, cerebrospinal fluid biomarkers and specialist imaging techniques (including amyloid PET imaging).

The aim of this pathway is to identify those people with no dementia, possible dementia (MCI) or confirmed dementia (Alzheimer's or other type).

What would be different in the new pathway?

The proposed DMT are likely to be used initially (if licenced) in early MCI due to Alzheimer's disease (AD) and early AD.

Aducanumab would be administered by monthly infusion following demonstration of amyloid in the brain (amyloid PET scan or presence of cerebrospinal fluid biomarkers) to symptomatic individuals. Other compounds in clinical trials offer subcutaneous administration but have yet to demonstrate clinical efficacy.

Regular monitoring is required (in trials, imaging every 3 months) to identify side effects including local brain swelling and minor bleeding (ARIA-E and ARIA-H). Where identified, treatment is paused pending resolution of these side-effects.

In the longer term

- Blood biomarkers may be useful for screening
- Self-administered treatments (via subcutaneous injection) may be available.

There is no current proposal to treat asymptomatic, amyloid-positive individuals.

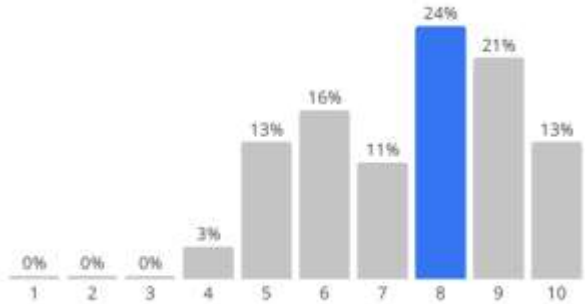
How many individuals might be affected by a DMT pathway?

In England 298,000 people are estimated to have brain amyloid that might respond to treatment. In the South East this equates to 48,000 people with amyloid pathology who have MCI or mild AD. Treatment and monitoring costs (assuming a base cost of £26,000 for Aducanumab) are estimated to be in the order of £1.2 billion (plus drug delivery costs).

Discussion

Following the DMT update, the group was asked their opinion on the potential impact on local dementia pathways of the introduction of a disease-modifying therapy for Alzheimer's disease.

How big would you estimate the impact of the introduction of DMT to be on the clinical pathway and care provision (1-no impact, 10 – maximum impact)?



The webinar was opened for comments and discussion. These have been grouped below.

"this could improve lives greatly"

Impact on: Public and patient perspectives

Previous press headlines have indicated the media and public appetite for dementia treatments.

Dementia is the most feared condition in the over 50's population. If available, patients, carers and family members are likely to increase the demand for information and access to treatment. It may be difficult to match this with the licencing conditions that will are likely to be placed on administration by regulatory agencies such as the MHRA and NICE.

- How will media information and expectation increase the level of anxiety in the population?
- Previously a lack of dementia cure has reduced presentation with memory concerns. Will the prospect of a disease-modifying therapy reverse this trend?
- How will we manage the increased demand on our services?
- Cognitive decline can be difficult to separate from more benign ageing changes. How do we manage the 'worried well'?

- How we will provide information and education materials with our public including guidance on eligibility criteria?
- Will people with other types of dementia e.g. vascular dementia also present requesting treatment? Will these groups require additional support in light of treatment options for other dementia but not theirs?
- The proposed DMT are for use in early MCI due to AD and early AD. How will we manage and support people who are already in a later stage of the condition?
- There is a significant burden for carers of people with dementia for whom there has been little respite thus far. Will this group be also desperate for information and guidance?
- Will the arrival of DMT change the public health conversation on population screening?

"I think there will be a wave of distress from Carers who are desperate to have help and treatments that work for the people they love"

Impact on: Pathway design

Estimated numbers and required level of activity mean that this pathway is unlikely to be simply absorbed into current pathways.

- Given the potential size and scale of impact, is a new clinical pathway for DMT delivery needed?
- MAS services often offer assessment and screening and where appropriate commencement of medication for primary care follow up. How will infusion and monitoring (observation and imaging) alter this pathway?
- Many people will have been given a diagnosis and been discharged from memory services. How will we mange demand from re-referrals?
- Do we need a regional pathway rather than several local pathways?
- Do we need to consider the separation of organic and functional pathways within OPMH and MH services?
- How will we incorporate post diagnostic support for this group?

"Even if a drug is not available for years - this is still an excellent opportunity to improve services. Our patients should be able to have access to biomarkers already!"

Close collaboration between services and an MDT approach including GP, OPMH, MAS and neurology services, would enable shared expertise in this emerging pathway. Care delivery close to home would also be supported where appropriate.

- How do we design and embed an MDT approach to DMT assessment and delivery?

"Regional research centers already assess and investigate people with aMCI/mild AD as part of multinational research trials, enabling patients to access CSF/ amyloid PET with regular monitoring with MRI etc. It seems to me that these centers would be best placed to deliver any new treatments, at least in the first instance"

Impact on: Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) has a broad definition and variable use in dementia clinics. It has been used to defer formal dementia diagnosis where clinical suspicion of dementia is present, and monitor decline until further diagnostic clarity is possible. Current rates of MCI are not known but anecdotally range between 0 and 30%. This is an opportunity to optimise diagnosis of MCI within the dementia pathway and give greater clarity to people living with uncertainty.

- If MCI is to be used as an eligibility criterion, how should we best define this in clinical practice.

Impact on: Education and training

Initially a new pathway will require skilled teams with new levels of activity including:

- Lumbar puncture to obtain cerebrospinal fluid (CSF)
- Drug infusion (2 hours)
- Monitoring of side effects (immediate and delayed)
- Identifying and acting on unexpected imaging findings (at diagnosis, and during monitoring)

"We need to consider training for current trainees re practical procedures such as LP/ Scan experience. At the same time, we need to brush up existing skills and use this time to prepare our clinicians for embracing change"

Impact on: Testing and Imaging services

Dementia diagnostic testing is requested by a range of services across the region including, OPMH, neurology and primary care teams.

The introduction of DMTs will drive an associated increase in testing requirements.

- Access to amyloid (PET) scanning (to detect the presence of amyloid) is currently limited to research. How will an increased need be met across the South East?
- What level of additional scanning will we need to commission and how do we ensure equitable access?
- Is there an opportunity for mobile services (imaging, lumbar puncture, infusion) to support equitable access across the South East?
- Imaging for dementia diagnosis is not seen as a priority. Will this have an impact on capacity? What may need to change?
- Image reporting for dementia is carried out by specialist neuroimaging staff. Do we have sufficient expertise and capacity across the South east?
- There is limited access to CSF biomarker testing as an alternative for PET imaging.
- Blood biomarkers are not yet available but may be a possible screening tool prior to imaging in future.

Impact on: Safety

Earlier diagnosis is challenging. Trials in early stage Alzheimer's disease, where there are clear protocols for assessment and imaging available to research teams, have shown that clinical diagnosis is incorrect 20-25% of the time.

ARIA (Amyloid-related imaging abnormality) is the major side-effect identified from clinical trials of amyloid removal from the brain. This manifests as

local brain swelling (ARIA-E) or as micro-haemorrhage (ARIA-H). This may be asymptomatic, but may also present as a focal neurological deficit. Depending on where is in the brain it will have different effects. Management of ARIA requires both routine monitoring and the ability to respond to emerging side effects in a timely fashion.

- Will new and unexpected side effects increase presentation in primary or emergency care?

Impact on: Cost

Current DMT in development are not expected to cure the disease, but would be expected to slow progression of disease, and potentially delay need for formal care.

"Off-setting costs is very important, but it depends on whether a system-wide approach is considered i.e. saving costs for whom, where and what part of the pathway?"

- This is not cheap.
- Depending on the agreed duration of treatment costs may be incurred over several years.
- What is the cost of not doing it? Dementia care currently costs the system £34.7 billion and we have an ageing population.
- Will early diagnosis and treatment reduce post diagnostic care and social care costs?
- Will delayed presentation for nursing or residential care release costs from another part of the system?
- Will there be a decrease in other care pathways and costs e.g. frailty?
- The cost (financial and quality) of informal care is often forgotten (and hard to calculate). Will the quality of life for carers and family increase?
- Will the new pathways be manageable under current block contract arrangements or do we need a new commissioning model?
- Increased imaging may identify unexpected findings requiring further investigation and referral to other pathways?

Impact on: Reputation

This is a huge opportunity and will raise the profile of dementia, dementia care services and staff. We do not want this to fail. We have an opportunity now to consider opportunities and plan.

- How can we plan new pathways across South East teams, organisations and populations?
- How do we learn from each other to understand what is working and what needs to improve?

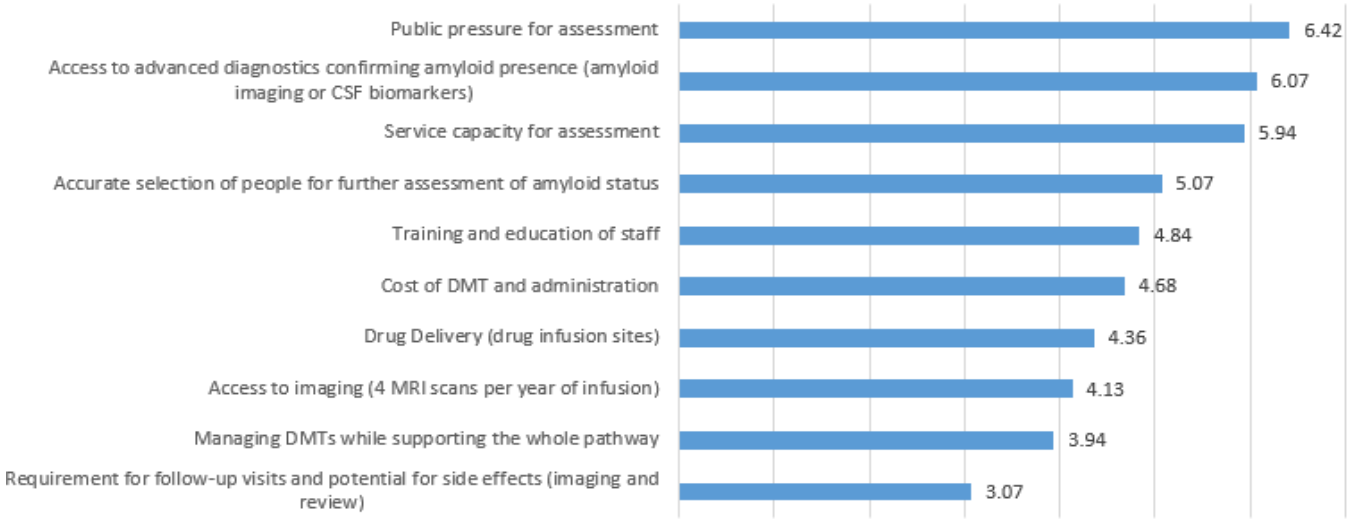
In Summary

The webinar was held as a starting point in local conversation, and sought to raise awareness of the issues that will need to be considered in the roll-out of a DMT for Alzheimer's disease into clinical care.

- There is a strong possibility of a disease modifying treatment being approved although timing remains uncertain
- Population selection will be based on evidence of amyloid presence in the brain
- This innovation will prompt
  - Significant change to clinical pathways
  - Substantial public interest
  - Major cost

Webinar attendees were asked to consider what they thought the impact of DMT might be on their service or area.

Q: Please rank the following in terms of their likely impact on your service or work role?



Attendees were also given an opportunity to comment on areas of impact.

Theme	Free text comments
Public pressure for assessment	Increasing the number of worried well wanting assessment
	More people will want testing and GPS likely to refer sooner
	Hope for the patients, softer public approach re AD, which so far means a sentence
	delay whilst drug goes through NICE approval process?
	I think it will be a great innovative success
	Mindset of commissioners and clinicians re diagnosis becoming more important and early recognition
	The general public's expectations (as per newspaper headlines).
	Length of time to realise benefits of DMT
Access to advanced diagnostics confirming amyloid presence (amyloid imaging or CSF biomarkers)	The reliable scanning for amyloid within the brain, to ascertain that there is amyloid present. At the moment, most patients within our clinic in the NHS, with AD diagnosis, only receive a CT, possibly MRI scan.
	How will we be reliably scanning for amyloid and at what cost?
	Availability of regular MRI slots for monitoring demand likely to exceed ability to supply
	Access to investigations to confirm amyloid pathology
Service capacity for assessment	Via gp
	Neurology vs Psychiatry and location of both services
	more waiting list
	System capacity for such a volumetric change even if skills are refreshed
	Infusion treatment - how this will affect our already bursting at the seams dementia services
	managing expectations introducing the 'triaging' system to sort those who might benefit

Theme (cont)	Free text comments (cont)
Accurate selection of people for further assessment of amyloid status	Benefits is only for those with AD?
	Finding people early enough that they will receive the greatest benefit
	Acceptance of MCI/early AD as treatment meriting an therapy with risks and not insignificant costs.
	understanding and positive acceptance by those referred into the memory clinic
	Clinical pathways do not currently identify or retain patients with a MCI
	Developing protocols to allow use
	Determining who will benefit and getting them on the meds
	identifying appropriate patients
Training and education of staff	Cost Time and clinical skills, manpower - required for diagnosis of definite amyloid disease,
	Staffing
	Staff training Cost
	Training of staff Cost
	Skills of clinicians
	The resources to monitor as dementia does not appear to be a priority for funding
	managing follow up and side effects with this number of people
	facilities to monitor treatment
Cost of DMT and administration	Cost would be an issue but should be offset against the reduction/delay in support.
	Needs an entire unified process - imagine at high cost it will be rationed
	Cost
	Funding issues
	The cost, has there been any research on the possible saving vs traditional treatment
	cost and setting up services
	Funding!
	Administration via control/cost
	Cost
	Cost
	Cost
	Cost
Drug Delivery (drug infusion sites)	How will the infusion be delivered, will it then require hospital trips and monitoring, or will this be done in a clinic?
	Capacity to deliver the drug, i.e. IV administration. This is due to the numbers involved.
	Resources for drug delivery
	Estates/resources for drug delivery
	facilities to deliver treatment
Managing DMT while supporting the whole pathway	Diverting money away from other evidence based sources of support.
	Expensive treatments that will support small numbers of people only. Would be better to focus more resources on prevention with improving lifestyle and reducing risk factors.
	May impact on capacity in MH services if more monitoring is needed
Requirement for follow-up visits and potential for side effects (imaging and review)	Potential volume number of patients and coordination of treatment, monitoring response
	The resources to monitor as dementia does not appear to be a priority for funding
	managing follow up and side effects with this number of people
	facilities to monitor treatment

"Thank you, incredibly interesting discussion"

"A great session, thanks very much - lots of food for thought there..."

"A really interesting webinar and great news that we now have a treatment that is very likely to have a significant benefit to those living with dementia and their carers"

Post meeting note:

This webinar was held on 19th May 2021. On the 7th June 2021, the FDA approved Aducanumab for use in Alzheimer's disease.

NICE have launched a development project: To appraise the clinical and cost effectiveness of aducanumab within its marketing authorisation for treating mild cognitive impairment (MCI) in early Alzheimer's disease which is due to report in May 2022 (see NICE webpage)