

An Academic Viewpoint on Clinical Trial Designs for Disease Modification in Alzheimer's Disease: Challenges

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Conceptual problems

- With the disease
- With the science
- With the investigational products
- With the methodology
- With the drug development process

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What is Alzheimer's disease?

- That described in 1907?
- Amyloid disorder vs tau disorder
- Does the influence of amyloid decline with time?
- Natural history
- When does it start?

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Science or fiction?

- Have we reviewed what we know to date – e.g. what is PIB suggesting
- How good are the current biomarkers?
- Elaborate modes of action
- How good are the animal models?

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Investigational products

- Difficult to develop
- Single targets may not influence AD, but be useful in combination
- May not work

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Particular issues

- Using long term symptomatic designs and scales
- Using many surrogate endpoints – with a particular reliance on carers
- Confounding factors: relative contribution of different AChEIs, memantine and ApoE4
- Managing drop outs

Potential ways forward

- Better management of participant expectation and understanding of what 18 month studies mean
- Using function and time to next stages/harder end points may help
- Emphasising executive factors and correlating to activities of daily living
- Using person-centred clinical targets (e.g. GAS)
- Starting studies in non-demented biomarker defined AD

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Difficulties in the process

- Haste
- Financial imperatives – “positive” phase II safety study to negative phase III pivotal
- Unimaginative advisory boards
- Inertia in the academic/industry/regulator dialogue based on fixed ideas and vague expectation
- Problems translating science to the individual clinical response

Conclusions

- Is AD actually all that we have made it?
- Maybe amyloid disease is an early event and clinical AD is due to something else
- Maybe we are trying to answer too many questions at once
- A regrouping of what we have already learned could reveal some better clinical endpoints; e.g increasing dependency can be measured and costed
- Maybe posing new questions may reveal new answers

“only those who risk going too far can possibly know how far they can really go”

T S Eliot

Thank you for your attention

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