Streamlining CNS Clinical Research with Digital Endpoints – the Trade-off Between Shorter Versus Smaller Trial Designs

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Introduction

- CNS clinical trials are long, costly and burdensome for patients. For instance, Alzheimer's disease trials need time to detect change in a slow-moving condition and neuropsychiatry trials are large due to disease heterogeneity and placebo responses
- Limited scalability and sensitivity of conventional pen-and-paper endpoints exacerbate these issues (DiMasi et al., 2024; Poleur et al., 2023; Polk et al., 2025). Digital assessments offer a scalable alternative through frequent at-home measurements over multiple domains (Giboin et al., 2025; Poleur et al., 2023; Polk et al., 2025; Rueda-Delgado et al., 2025)
- For example, a digital motor score for Huntington's may save 60% in duration of participation, or 75% in cohort size, relative to a conventional functional endpoint (uHDRS) (Giboin et al., 2025)
- A digital cognitive score for Alzheimer's may save >25% duration of participation and >50% patient numbers, compared to a composite endpoint (ADAS-Cog) (Rueda-Delgado et al., 2025)
- **Question: Is it more beneficial to shorten the duration of participation in a trial, or to reduce the number of participants?**

Methods

- We retrieved industry-led interventional phase 2 studies, July 2020 to July 2025, in Alzheimer's Disease, and Major Depressive Disorder, from clinicaltrials.gov
- Number of participants, duration of study (First-Patient-In until Last-Patient-Out), and duration of participation (timing of latest primary endpoint) were extracted
- Recruitment rate was calculated as (durationOfStudy-durationOfParticipation)/numberPatients
- Trials were excluded if they had mixed sponsorship/phases, or where number of participants and durations were missing or inconsistent
- We project costs and study duration for an illustrative 10-50% reduction in patient numbers, compared to a 10-50% reduction in duration of participation
- **Following DiMasi et al. (2024) we assumed costs to be proportional to the product of the number of participants and duration of study**

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Results

Cohort Size and Trial Duration Descriptives

Study variables	AD	MDD
Number of trials found in initial search	123	74
Number of trials included	77	55
Cohort size	114 (60, 250)	148 (76, 240)
Duration of study (weeks)	98.6 (67.1, 146.7)	69.6 (47.6, 83.6)
Duration of recruitment (weeks)	62.6 (38.1, 85.4)	59.0 (38.2, 76.5)
Recruitment rate (participants/week)	2.2 (1.0, 4.0)	2.2 (1.3, 4.4)

Table 1: Median and interquartile range (in brackets) of study variables.

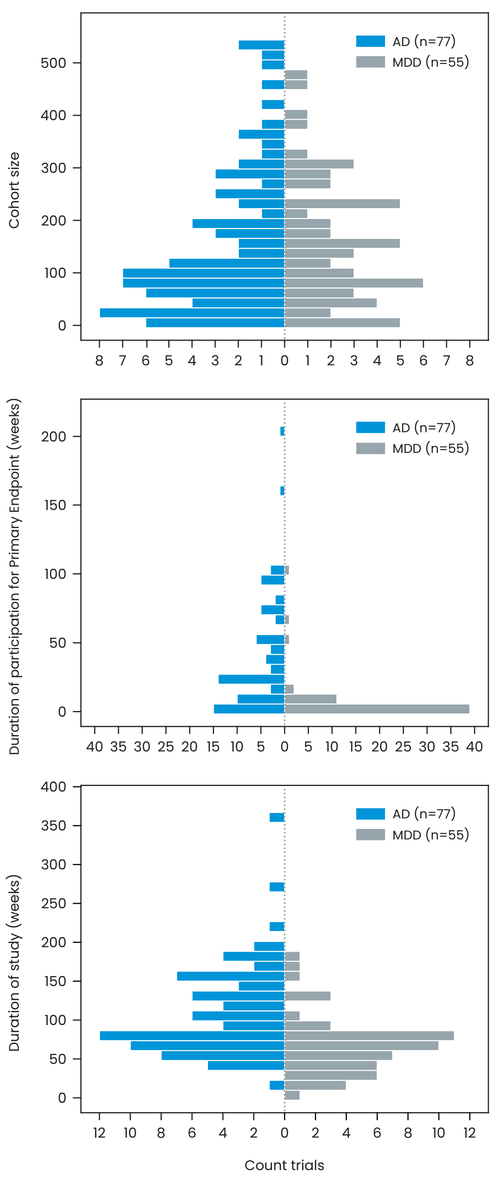

Figure 1: Histograms of cohort size, duration of participation for primary endpoint and duration of study per clinical trial type.

Smaller Cohorts Save More Costs than Shorter Protocols

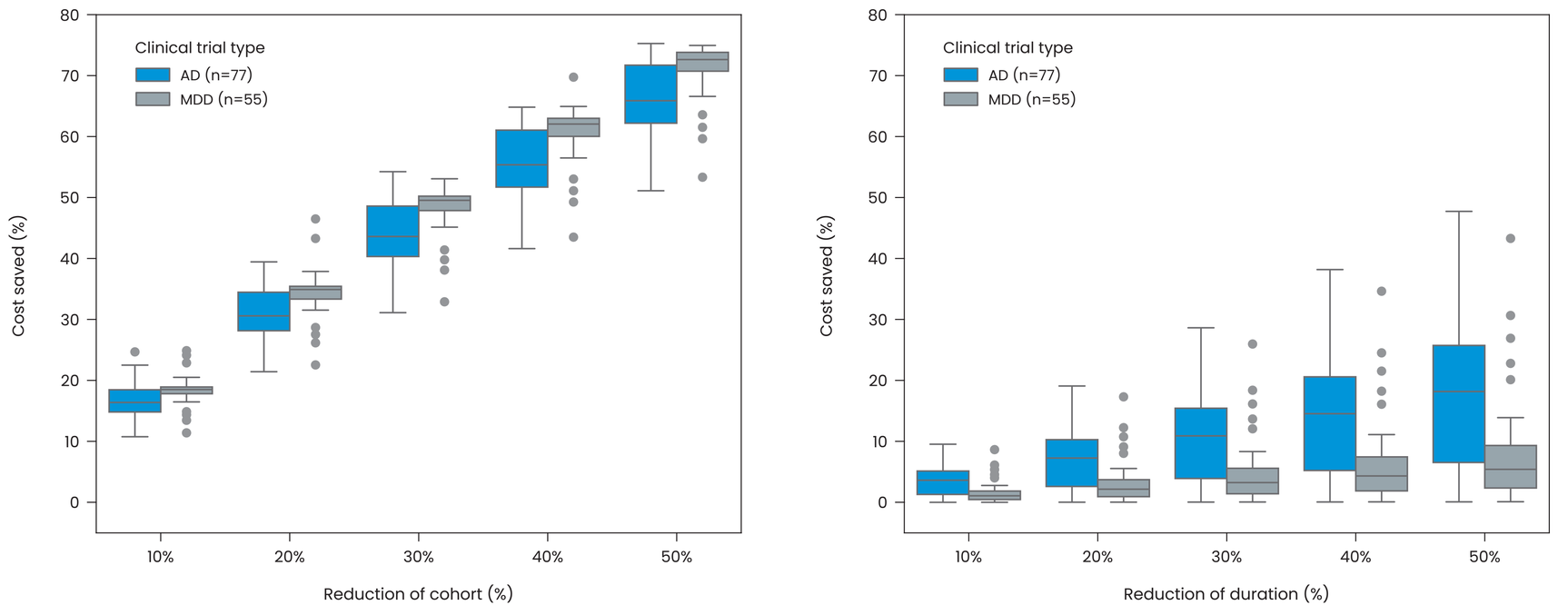

Figure 2: Percentage costs saved given a reduction in the cohort size (left) or in the duration of participation (right). Reducing the cohort size by 50% yields costs savings of 65.9% and 72.6% in AD and MDD trials, respectively. Line in box shows the median, box shows interquartile range (IQR), whiskers show the point at 1.5x IQR, outliers are those past the whiskers.

Smaller Cohorts Reduce Study Duration More than Shorter Protocols

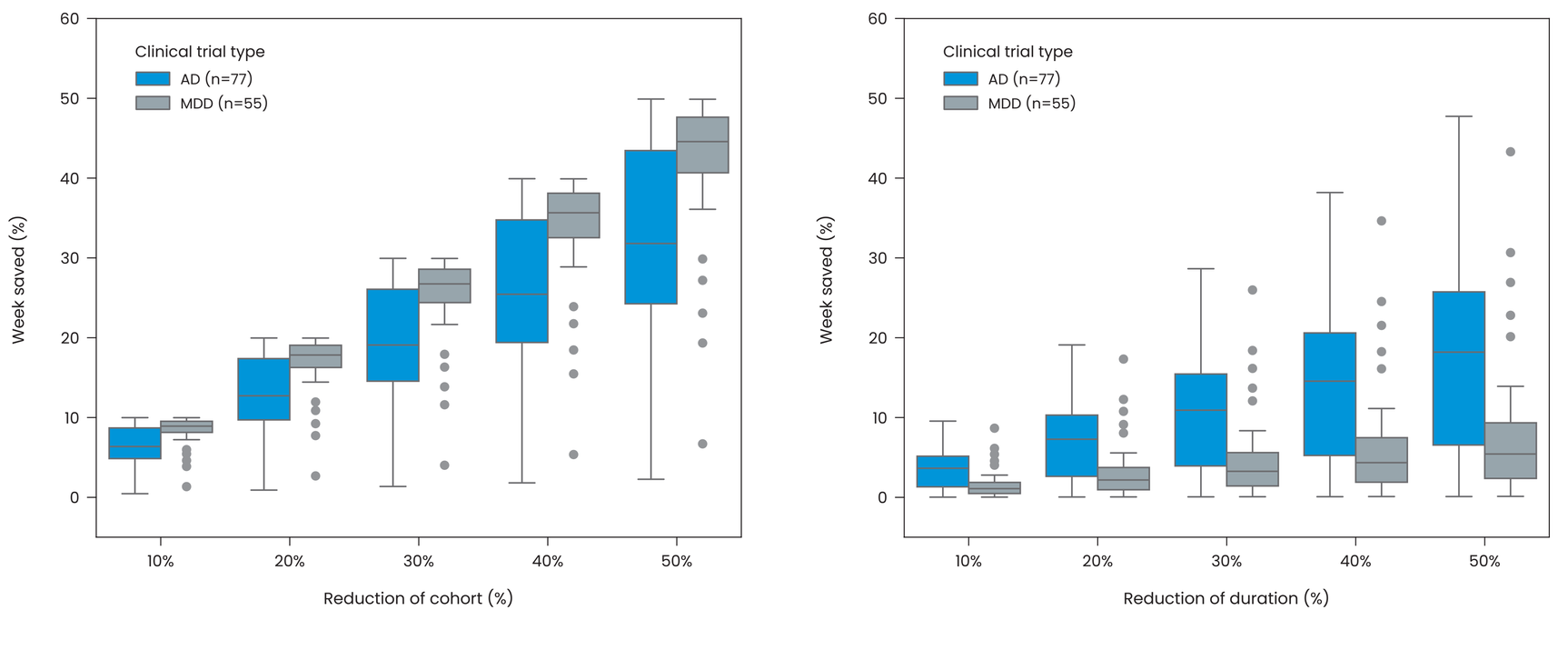

Figure 3: Percentage time saved given a reduction in the cohort size (left) or in the duration of participation (right). Reducing the cohort size by 50% yields time savings of 31.8% and 44.6% in AD and MDD trials, respectively. Line in box shows the median, box shows interquartile range (IQR), whiskers show the point at 1.5x IQR, outliers are those past the whiskers.

Conclusions

- Reducing cohort size saved more time and costs in 81% of recent MDD and AD clinical trials – all cases where the duration of study was dominated by recruitment rates, and the costs by cohort numbers
- In 19% of trials, study duration could be reduced by shortening the protocol (where the recruitment timeline was shorter than participation duration), but costs were still higher
- A combination of smaller cohorts and shorter participation may be possible, **but in most cases smaller cohorts have compounding benefits of reducing both recruitment timelines and total costs**
- Smaller cohorts reduce burden on patients in the trial, and bring forward decision-making forward – either by accelerating the benefits of a newly introduced therapy, or by freeing up resources to pursue other more promising candidate therapies

Disclosures: All authors are employees of, and hold equity in, Cumulus Neuroscience Ltd.

Study Limitations

- Here we assume that the study costs increase linearly, with uniform cost per patient per year. This may yield overestimates of costs and savings. Other approaches may be considered in future work, e.g. a cost basis based on patient numbers only, or driven by protocol duration
- Duration of participation is based on the Primary Endpoint, and considers all phase 2 trials. The cost structure may vary by study purpose (e.g. safety, mechanisms, efficacy) and importance of secondary endpoints

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