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Special Article

The impact of recent approvals on future alzheimer's disease clinical development: Statistical considerations for combination trials

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ABSTRACT

Background: A new era of Alzheimer's disease (AD) research is beginning with multiple approved anti-amyloid monoclonal antibodies (mABs). These drugs are currently not widely used, but may be soon, especially at clinical trial sites. Putative disease-modifying therapies (DMTs) may alter the progression rate, potentially reducing our ability to detect effects on top of mABs. Co-administration of amyloid-targeted agents may diminish benefit (antagonism, due to the overlapping mechanism of action); alternatively, complementary treatment mechanisms may increase benefit (synergy).
Method: We consider several clinical trial design scenarios: a 2-arm trial added-on to a mAB, a 2-arm combination compared to double placebo, and a 4-arm full factorial trial. We calculate the required sample sizes for the shortest practical study for secondary prevention (prevention of AD clinical diagnosis in biomarker positive individuals, 2-year study), early AD (18-months), and mild-to-moderate AD (1-year). We consider additivity, antagonism, and synergy.
Result: The expected interaction between investigational and mAB treatment can have a large effect on power and study design. Antagonistic treatment effects often require double the sample size of synergistic effects. The 4-arm scenario required ~10-fold increase compared to a 2-arm combination study.
Conclusion: Studies evaluating investigational therapies as add-on to mABs are complex, and their cost will depend on the interaction between treatments. An inescapable fact in add-on trials is the slower progression of the control arm; and it is difficult to further slow already slow progression. Treatments that are likely to work better with amyloid removal will be easier to study due to their complementary MOA. Symptomatic treatments may require fewer additional subjects than disease-modifying treatments since they are less affected by the presence or absence of mABs.

1. Introduction

1.1. Research setting

The disease modifying treatments (DMTs) lecanemab and donanemab have received full approval from FDA in June 2023 and July 2024 for the treatment of early Alzheimer's disease; and are covered by Medicare and Medicaid for eligible patients. Subsequently, they are now receiving regulatory authorization in ex-US regions, albeit at a slow pace. These treatments usher in a new era for the AD field, with widespread ramifications, including for the design of investigational drug trials.

1.2. Development of combination therapy is urgently needed in AD

AD is a complex disease, likely with more than one pathogenetic mechanism contributing to the onset and progression of the disease [1–3]. Treatment is further complicated by the frequent presence of co-pathologies, such as alpha-synuclein and TDP-43, alongside amyloid and tau pathology. Given this heterogeneity, therapies that target more than one underlying mechanism may be necessary to achieve significant clinical benefit, and combination treatment is a straight-forward approach to target multiple mechanisms.

For example, the approved mABs treatments reduce amyloid burden markedly in the brain, to sub-pathogenic levels in many patients;

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however, this results in only moderate average slowing of cognitive decline[4,5]. Other than amyloid beta accumulation, possible pathogenic mechanisms of AD include p-Tau aggregation and neurotoxicity, nueroinflammation[6], synaptic dysfunction and demyelination, mitochondrial dysfunction, lysosomal dysfunction, lipid abnormalities, insulin resistance [7,8], and more [1–3].

Combination treatments have been at the heart of key medical breakthroughs in the treatment of cancer[9,10] and AIDS[11,12], and about 25 % oncology trials are combination therapy trials[13]. Combination therapies are also commonly used in other complex diseases, including cardiovascular disease[14], pulmonary disease, and autoimmune diseases. Given the complexity of AD, it would not be surprising if therapies that combine drugs with different MOAs may be more efficacious than a single drug that works on a single mechanism. Beyond increased efficacy, combination therapy may offer additional advantages over monotherapy, such as reduced required dosages with maintained efficacy, lower toxicity, fewer side effects, and decreased risk of drug resistance[15].

1.3. *Design options (Combination trial and add-on trial)*

Combination therapy is when both treatments are included and provided as part of the study. Add on therapy is when patients come to the study already taking some medication that is not the main focus of the study.

When acetylcholinesterase inhibitors (ChEi) were the only available treatments for AD and later when memantine was also available, some AD treatment trials were designed as an add-on to standard of care (ChEi, memantine, both or neither),These add-on trials required the use of existing treatments[16], with examples trails like memantine and ChEi, ginkgo biloba extract EGb 761 and donepezil[17], multivitamin (B_6, B_{16}, and folic acid) and ChEi [18].

For these add-on trials, treatment effects were assessed in two arms, ChEi + investigational therapy and ChEi + placebo. Different designs have been used for investigational drug add-on trials, including 2-arm, 3-arm, and 4-arm designs. A simple 2-arm design allows the approved treatment as a background treatment, which must be stabilized prior to the randomization to add-on either placebo or the investigational drug. Stabilization periods of 2–6 months have typically been used [19–23].

A variation of the simple add-on design is the controlled/sequential add-on design in which treatment naive participants are enrolled. All participants start the approved treatment at the start of the trial for a stabilization period, then the investigational treatment or placebo is added to the approved background treatment based on randomization [24]. Considering that the appropriate use recommendations for Donanemab suggested discontinuation of treatment based on amyloid clearance[25], a sequential add-on trial where the investigational treatment and placebo are administered right after mAB discontinuation could be considered in such a case.

Another variation is the *de-novo* add-on design that also enrolls treatment naive participants but participants are randomized to start both the approved treatment and the investigational treatment or

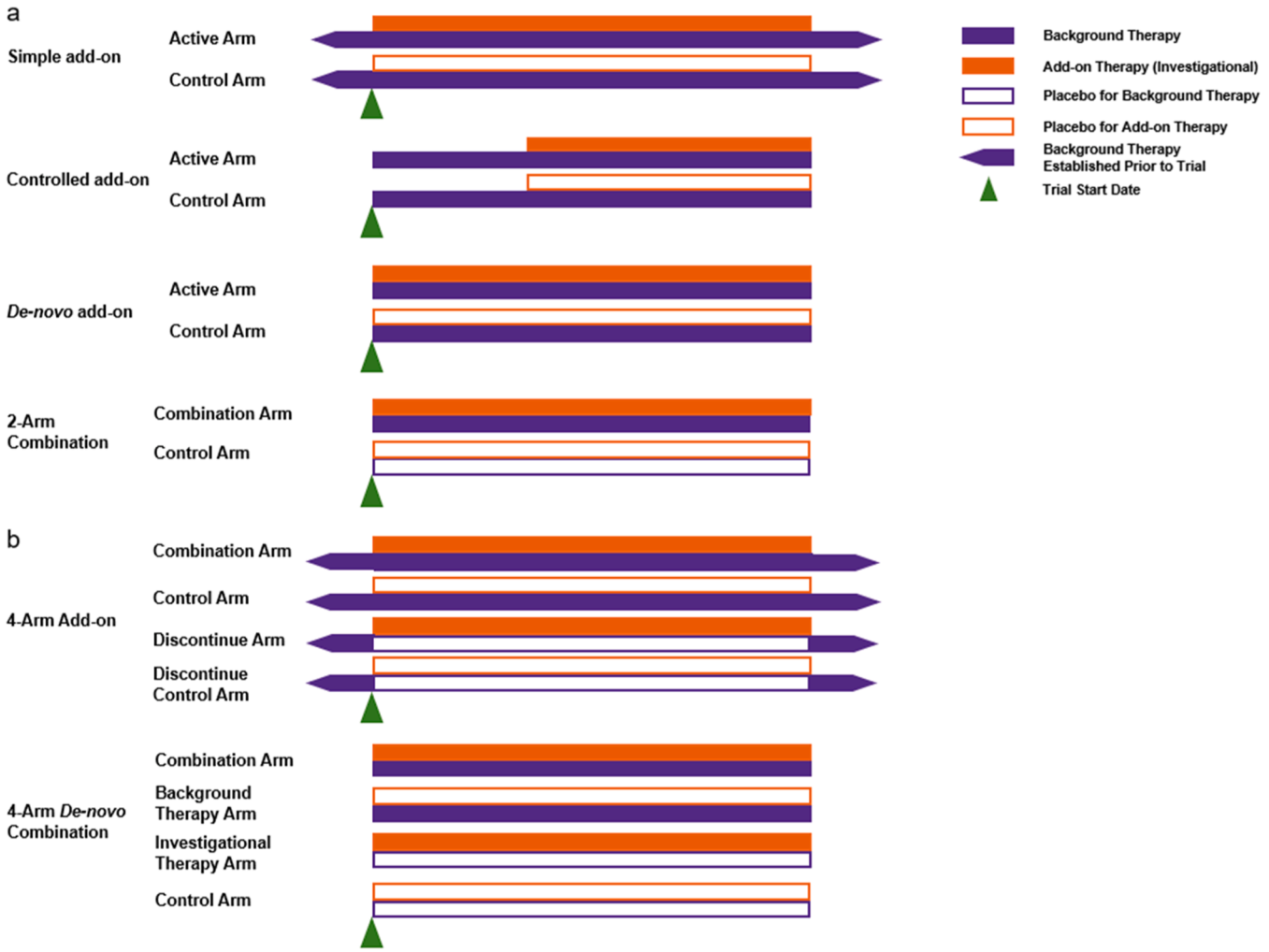

Fig. 1. Example clinical trial designs for add-on and combination trial. a, 2-arm designs; b, 4-arm designs.

placebo at the same time, immediately after randomization [26]. Other variations of these add-on designs include testing multiple doses of the investigational treatment [27,28]. Many other variations also exist and are not enumerated here.

Another option called the 2-arm combination design has a combination treatment arm and a double placebos arm. Examples of 2-arm designs are illustrated in Fig. 1a.

Common implementations of 4-arm add-on designs entail a two-by-two factorial arrangement of treatments: 1) investigational drug + placebo, 2) approved drug + placebo, 3) investigational drug + approved treatment, 4) placebo + placebo. As with the 2-arm design, participants could be de novo or stabilized on the background / approved treatment prior to randomization. The 4-arm design allows testing the following hypotheses: 1) investigational drug vs placebo; 2) investigational drug vs approved treatment, as either a superiority or non-inferiority test; 3) combination treatment vs approved treatment; 4) approved treatment vs placebo as a positive control to assess assay sensitivity; and 5) combination arm vs placebo, although this hypothesis is commonly of less scientific and regulatory interest. Examples of 4-arm designs are illustrated in Fig. 1b

Add-on trials can use 3-arm designs to either include the combination arm and the two single treatment arms[17] or the combination arm, background only arm, and the double placebo arm[29,30]. In the double placebo arm, one placebo matches the investigational treatment, and the other placebo matches the approved treatment.

The choice of design is driven by trial objectives and regulatory considerations. However, these design choices can have major implications on trial size and feasibility. For example, the two-by-two factorial, 4-arm design can provide the most information regarding the various treatment combinations, but at the cost of a larger trial.

The recent approvals of anti-amyloid mABs in AD motivates consideration of trial designs to investigate combination treatments that include an approved mAB treatment and an investigational treatment. The primary aim of this investigation is to assess the sample sizes required and summarize other design considerations for combination trials.

2. Methods

The sample size implications of three combination trial designs (2-arm add-on, 2-arm combination, and 4-arm combination) were investigated across scenarios defined by three disease stages (AD prevention, early AD, and mild-to-moderate AD). Three general types of combination drug effects were investigated: additive, synergistic, and antagonistic.

2.1. Placebo mean to standard deviation ratio (MSDR) for clinical outcomes in different stages

The progression rate and the most prevalent symptoms vary throughout the course of AD [31–33]. The mean to standard deviation ratio (MSDR) is a metric that provides a standardized method to compare magnitude of disease progression across outcomes within a trial and between trials. Mathematically, the MSDR is the mean change from baseline divided by the standard deviation in change from baseline. MSDR is most often applied to the control arm of a trial as an assessment of how much progression the investigational drug has the opportunity to prevent.

Consistent with this, we assumed different primary outcomes for populations at different AD stages. These selections were based on outcomes optimized for the specific populations, even if there has not been universal acceptance of these outcomes by regulators. In practice, slow adoption by regulators of optimized outcomes will lead to larger sample sizes or greater type II error, but for pivotal trials, traditional outcomes may be necessary. For the prevention population (participants have confirmed AD pathology but on clinical diagnosis), the Alzheimer's Prevention Initiative Preclinical Composite Cognitive test (APCC), an optimal composite cognitive test score comprised of seven cognitive tests/subtests is chosen, with an MSDR = 0.34 for 2-year studies [34]. For the early AD population, ADCOMS, a composite clinical outcome for prodromal Alzheimer's disease trials, is chosen, with an estimated MSDR of 0.55 for 18-month trials [35]. For the mild to moderate AD population, the combined MSDR of the Alzheimer's Disease Assessment Scale (ADAS-cog), the Mini-Mental State Examination (MMSE), and Clinical Dementia Rating Sum of Boxes (CDR-SB) is 0.67 for 1-year studies [36].

2.2. Scenarios for treatment interaction

The combined effect of two treatments can be additive, synergistic, or antagonistic, when the effect of the combination is equal to, greater than, or less than the sum of the effects of the individual drugs, respectively.

Table 1 summarizes the % slowing of disease progression for each of the 3 types of combination effects in each of the 3 designs, assuming the investigational treatment and the mAB treatment both have 100 % of the reference effect size (though the actual reference effect size may be large or small), and the synergistic and the antagonistic effects are 30 % higher or lower. The standardized treatment effect (Cohen's D) is equal to the MSDR in the control arm multiplied by the % slowing of the investigational treatment. For example, if MSDR = 0.55 and % slowing = 40 % (similar to the population and slowing of anti-amyloid mAB trials), the Cohen's $D = 0.55 \times 0.40 = 0.22$; if the MSDR = 0.34 and % slowing = 60 % (which may not be unreasonable for a prevention trial), Cohens $D = 0.204$.

The Cohen's D for the various combination arms in each scenario are summarized in Fig. 2. These effect sizes were used to determine power and sample size based on the *t*-test for the treatment contrast at the endpoint visit.

3. Results

3.1. General considerations

Detailed results for each of the three clinical trial scenarios (prevention, early AD, mild-moderate AD) are presented in the following respective subsections. General results that apply to all scenarios are summarized here.

Within scenarios, the effect size for a synergistic treatment effect is always > additive effect, which is always > than the antagonistic effect. Therefore, within every scenario the synergistic effect always has the highest power for a given sample size and the smallest sample size for a

Table 1
Interactions between Investigational treatment and background anti-amyloid mAB.

Scenarios		Effect size (relative to reference)*
Add-on trial (Combination Treatment vs background therapy)	Additive with background therapy	100 %
	Synergistic with background therapy	130 %
	Antagonistic with background therapy	70 %
2-Arm Combination trial (Combination Treatment vs Double Placebo)	Additive	200 %
	Synergistic additive	230 %
	Antagonistic additive	170 %
4-Arm Combination trial (Combination Treatment vs Each Component)	Additive	100 %
	Synergistic additive	130 %
	Antagonistic additive	70 %

* Here we assume each treatment has 100% of an anti-amyloid mAB or other approved treatments (when available), and the synergistic and the antagonistic effects are 30% higher or 30% lower (relative to the mAB or base treatment).

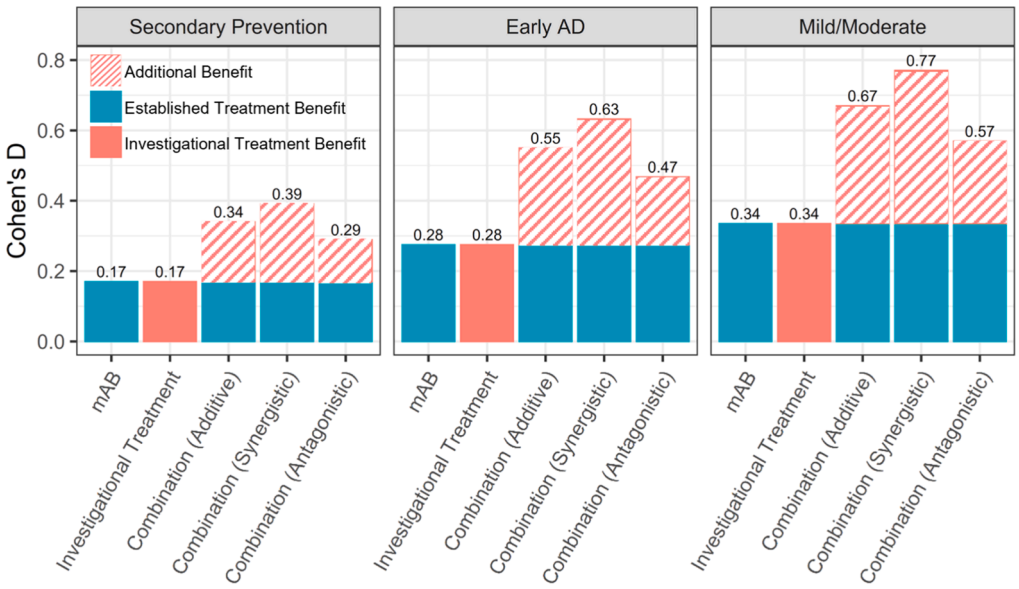

Fig. 2. Demonstration of Cohen's d effect size clinical trial designs with single investigational treatment, add-on investigational treatment to mABs, and 4-arm combination trials in AD populations.

given power.

Commensurate with the MSDRs, within each type of combination drug effect (additive, synergistic, antagonistic), power was greater and sample size lower for mild-moderate AD than for early AD, and early AD had greater power and smaller sample size than prevention.

3.2. Prevention population

Results are summarized below for the prevention trial scenarios (2-year treatment duration and MSDR = 0.34). Table 2 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 3 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing relative to placebo) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect in 4-arm combination trials, assuming 80 % power.

Table 2
Sample size calculation for 2-arm combination, 2-arm add-on, and 4-arm combination trial designs in AD prevention population for 2-year studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	545	1090	22.2 %
Synergistic: + 30 %	323	646	34.2 %
Antagonistic: - 30 %	1111	2222	13.1 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	137	274	66.7 %
Synergistic: Additive + 30 %	104	208	78.5 %
Antagonistic: additive - 30 %	190	380	52.9 %
4-Arm Combination Trial (All 4 comparisons – Combination vs each, each vs Placebo)			
Additive	882	3528	<1 %
Synergistic: Additive + 30 %	741	2964	1 %
Antagonistic: additive - 30 %	1477	5908	<1 %

Assuming a 50 % effect size on disease progression slowing for 2-year studies. The last column assumes 100 completers per arm.

3.3. Early AD population

Results are summarized below for the early AD trial scenarios (18-month treatment duration and MSDR = 0.55). Table 3 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 4 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect (percent slowing) in 4-arm combination trials, assuming 80 % power.

3.4. Mild-moderate AD population

Results are summarized below for the mild-moderate AD trial scenarios (12-month treatment duration and MSDR = 0.67). Table 4 summarizes the number of patients needed for each arm in the trial and the total for the trial under specific conditions. Fig. 5 depicts sample sizes required across a range of effect sizes as described by % slowing.

A, Sample size (per group) vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 80 % power. B, Power vs treatment effect (percent slowing) in single group or add-on trial designs, assuming 100 completers per group. C, Sample size (per group) vs treatment effect (percent slowing)

4. Discussion

In this analysis, we investigated trial design options when combining an investigational treatment with a standard treatment. The specific findings of this study apply to the scenarios investigated; however, the basic approach can be extended and generalized, for example, to any mechanism of action for background and investigational treatments. The concepts of synergy, additivity, and antagonism apply universally to combination treatments even though the type and magnitude of combination effect will vary.

Among the 2-arm combination, 2-arm add-on, and 4-arm combination trial designs, 2-arm combination trials had the greatest power and required the smallest sample sizes under the conditions assumed here. This finding was consistent across all AD populations investigated. These

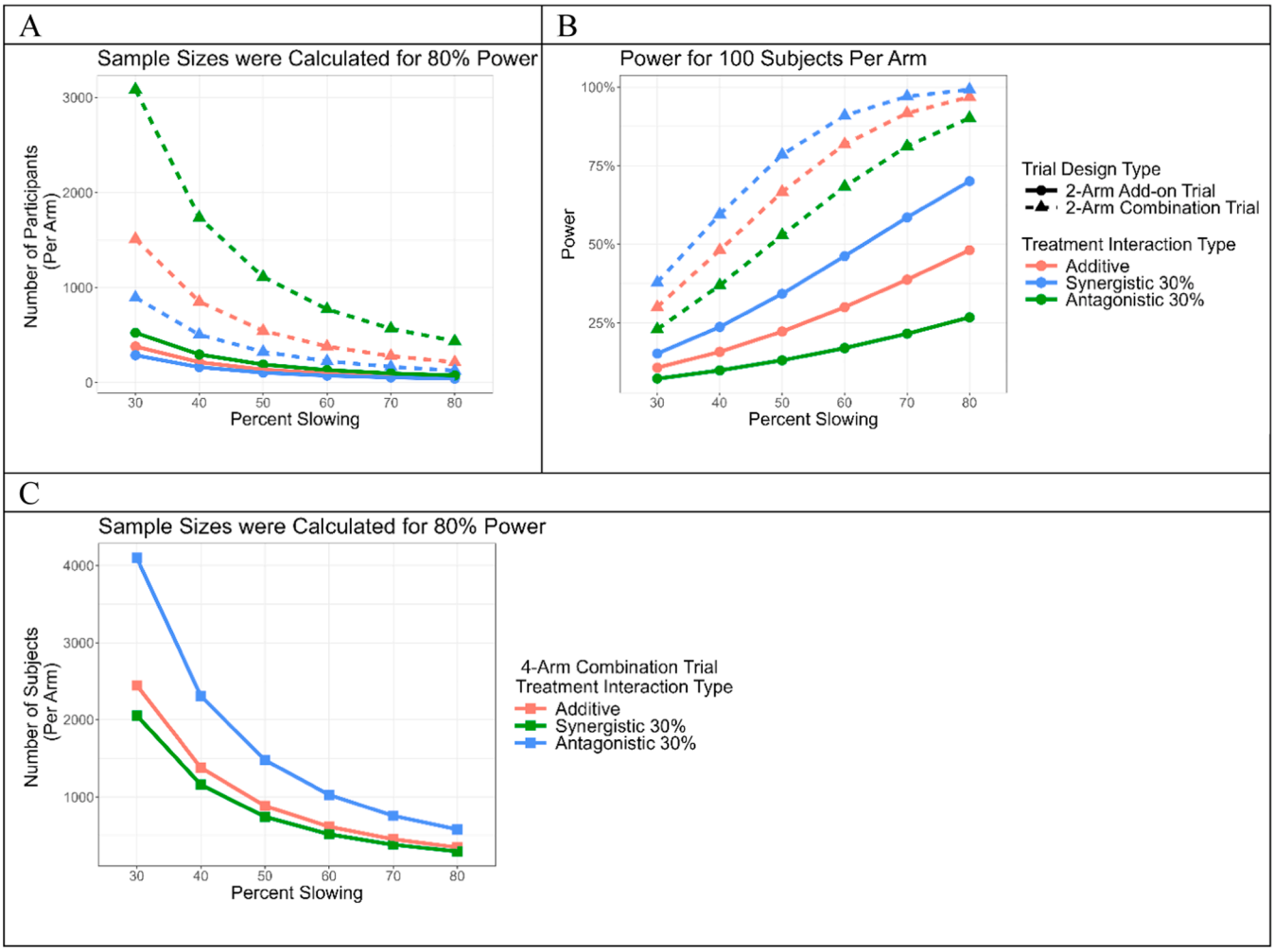

Fig. 3. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in AD prevention population.

Table 3
Sample size calculation for 2-arm combination, 2-arm add-on, and 4-arm combination trial designs in early AD population for 18-month studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	209	418	49.0 %
Synergistic: + 30 %	124	248	71.1 %
Antagonistic: - 30 %	425	850	27.2 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	53	106	97.2 %
Synergistic: Additive + 30 %	41	82	99.4 %
Antagonistic: additive - 30 %	73	146	90.8 %
4-Arm Combination Trial			
Additive	338	1352	5.8 %
Synergistic: Additive + 30 %	284	1136	12.1 %
Antagonistic: additive - 30 %	565	2260	1.8 %

Assuming a 50 % effect size on disease progression slowing for 1.5-year studies. The last column assuming 100 completers per arm.

results should be unsurprising given that 2-arm combination trials compare the combined effect of two treatments to placebo, creating the greatest expected difference in effect between treatment arms, and 4-arm combination trials have the smallest expected difference in effect size between arms and the most number of arms; however, these are important concepts for development programs to consider when determining the direction of development. For instance, there may be scenarios where a 4-arm combination trial is the most efficient design to address the current needs of a development program, but preference should usually be given to smaller more focused trials, when possible.

2-arm add-on studies should be considered for an investigational treatment in an environment where approved treatment is becoming common. 2-arm combination trials are suitable for treatments with low risk of side effects, and when drugs are being considered for alternative indications. Scenarios to consider four-arm studies include when multiple questions are necessary to move development forward, especially when treatment interactions are likely both with respect to efficacy and safety.

By definition, a synergistic effect yields larger effect sizes than an additive effect, which is larger than an antagonistic effect. In the scenarios investigated here, power and sample size varied markedly by type of treatment interaction. An antagonistic effect (additive effect – 30 %) resulted in up to double the sample size for the same power compared with an additive effect. The difference in sample size between antagonistic and synergistic scenarios was as much as 3–4-fold increase.

These sample size implications highlight the importance of understanding if, and if so how the investigation drug interacts with the standard / background therapy. Therefore, as much information as is feasible should be leveraged from pre-clinical and early phase clinical

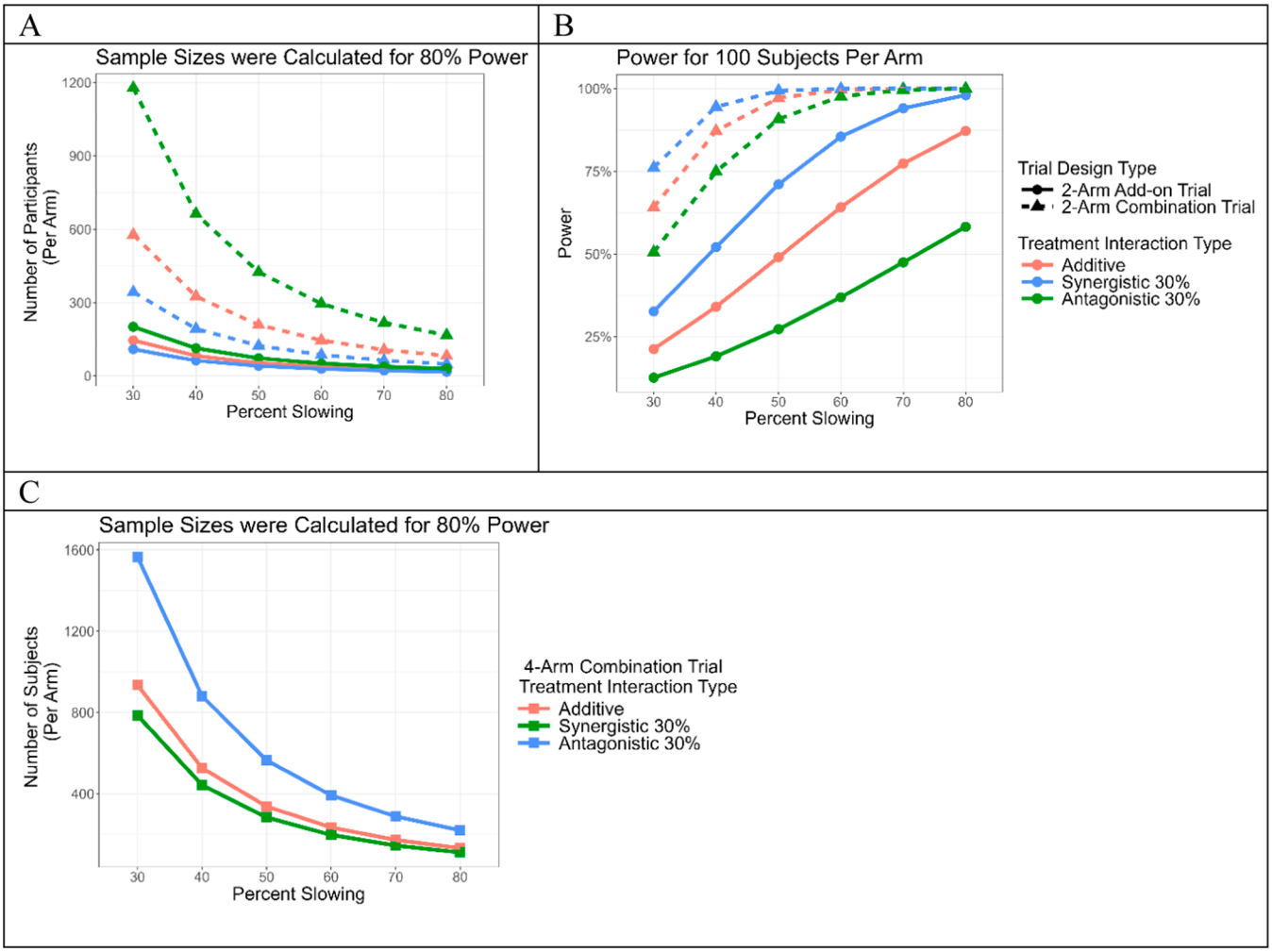

Fig. 4. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in early AD population.

Table 4
Sample size calculation for 2-arm add-on, 2-arm combination, and 4-arm combination trial designs in mild to moderate AD population for 1-year studies.

Scenario	N Per Group 80 % power	Total N 80 % power	Power with 100 per arm
2-Arm Add-on Trial			
Single Treatment is additive	141	282	65.4 %
Synergistic: + 30 %	84	168	86.5 %
Antagonistic: - 30 %	287	574	37.8 %
2-Arm Combination Trial (Combination Treatment vs Placebo)			
Additive Treatments	36	72	99.7 %
Synergistic: Additive + 30 %	28	56	>99.9 %
Antagonistic: additive - 30 %	50	100	98.0 %
4-Arm Combination Trial			
Additive	228	912	18.3 %
Synergistic: Additive + 30 %	192	768	32.1 %
Antagonistic: additive - 30 %	381	1524	6.1 %

Assuming a 50 % effect size on disease progression slowing for 1-year studies. The last column assuming 100 completers per arm.

studies to anticipate either additive, synergistic, or antagonistic effects for the two treatments. In addition, studying a novel therapy alone in a phase 2/ proof of concept study provides critical information for study design. Although this investigation focused on efficacy considerations, the possible interaction of the two treatments in a combination is also critically important to safety.

Although sample size is a key consideration for combination trials, other operational issues are also important to consider. For example, with ≥ 2 active treatments, multiple placebos are needed to blind each active arm; inclusion and exclusion criteria and adverse event management and reporting must factor in both active arms.

The 4-arm combination trial allows testing multiple hypotheses simultaneously: 1) investigational drug vs placebo; 2) combination treatment vs standard treatment; 3) investigational drug vs standard treatment, either in a superiority or non-inferiority testing scheme; and 4) standard treatment vs placebo as a positive control to assess assay sensitivity of the trial. However, the total sample size required for such studies is formidable. Given the common scenario where many sites in a trial will enroll a small number of patients, many sites will not have patients randomized to every arm, creating a confounding of site with treatment, which can increase variability in the data, thereby diluting the treatment signal and leading to need for an even larger sample size. Studies requiring such large sample sizes may benefit from Bayesian or other adaptive sample size determination, but these designs should be discussed with regulators prior to use.

In inescapable fact of combination trials that use an approved

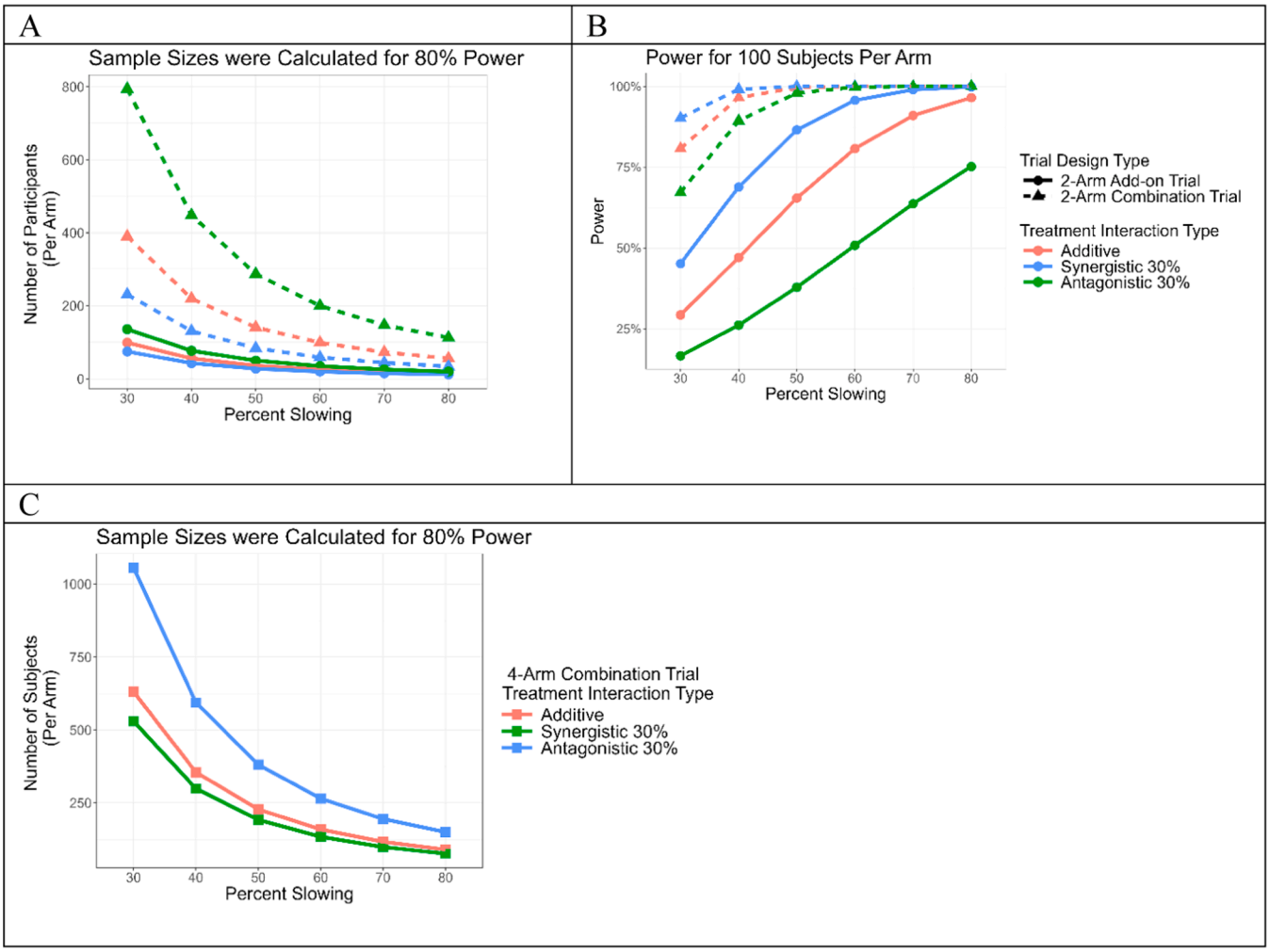

Fig. 5. Sample size requirements with different treatment effect sizes for 2-arm combination trials, 2-arm add-on trials, and 4-arm combination trials in moderate to mild AD population.

treatment as the control arm, the control arm will have less progression than a placebo arm and therefore sample sizes for a given level of power will be larger than with placebo control.

4.1. Considerations of treatment interaction in combination treatment

An important consideration for combination trials is the possible interaction between two treatments. As our results suggest, the effect size is greater with synergistic interaction and therefore easier to detect in the add-on or combination trials. Whereas antagonistic interaction makes it harder to detect an effect and requires a larger sample size. Factors influencing interactions of combination treatment include Mechanism of Action (MOA), pharmacokinetic, and pharmacodynamic. Oncology trials with combination treatment targeting the same pathway may result in antagonism or increased toxicity [37–39]. To inform assumptions in sample size determination, early phase pharmacokinetic and pharmacodynamic studies are recommended, since it may lend insight into the nature of the combination drug effect, for example, is drug absorption, distribution, and/or elimination of each drug influenced by the other; or are effects on pharmacodynamic biomarkers additive or synergistic. Further consideration should be given to the merits of evaluating novel investigational drugs as monotherapy to understand the effects of the individual agent on biomarkers and clinical outcome measures, thereby providing information to enable the design of later stage add-on or combination trials.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Suzanne Hendrix reports the APC fee for this publication was provided by Alzheimer's Drug Discovery Foundation. Suzanne Hendrix reports a relationship with Pentara Corporation that includes: employment and equity or stocks. Samuel P Dickson, Craig Mallinckrodt, Chenge Zhang reports a relationship with Pentara Corporation that includes: employment. Aaron H Burstein, Laura Nisenbaum, Howard M Fillit reports a relationship with Alzheimer's Drug Discovery Foundation that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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