Patient Selection for CNS Clinical Trials: Findings from Eligibility Review Database and Focusing on Complicated Alzheimer Disease Trials

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Introduction

Quality patient selection is one of the most critical elements of a successful clinical trial. A growing body of evidence suggests that high CNS trial failure rates are partly attributable to inappropriate patient selection (Sacks et al., 2014). Investigators, while clearly dedicated to quality and compliance, interpret protocol criteria differently and have varying levels of tolerance for risk. Astute clinical judgment is the most important quality driver; however, in CNS trials with no biomarkers and a heavy judgment burden, quality, patient safety, and internal validity are at particular risk. The variability in clinical judgment may be even more significant in international studies involving sites with different diagnostic and rating approaches. In this data analysis of central eligibility review findings from a large dataset across dozens of indications, we also focus on Alzheimer Disease (AD) trials, where judgment burden is particularly heavy. The level of complexity is magnified in AD trials due to the older age of most subjects and their many comorbid medical and psychiatric conditions. Variability in clinical phenotypes of AD, as well as variability in clinical endpoints, are believed to have hampered efforts to find effective treatments for AD (Bateman et al., 2016). Subjectivity when interpreting the data naturally translates to compromised internal validity and potentially decreased power in AD clinical trials in the absence of careful oversight of incoming subjects (Jiang et al., 2010).

The purpose of the current study was to describe a centralized eligibility review process utilized in CNS trials that is both operationally feasible and acceptable to Investigators when conducted collaboratively and leaving final eligibility decisions in the hands of the treating physicians. Sub-analyses of eligibility review findings in AD trials were conducted to determine relevant differences specific to this patient population.

Methods

A central team of physicians and doctoral-level clinical scientists collected key screening diagnostic and medical data just after the Screening visit, then reviewed each subject in group format. Resulting eligibility concerns and questions were thereafter discussed with sites, leaving final decisions on randomization in the hands of the Investigators. In the majority of cases, Investigators were able to provide additional clinical history that supported subject eligibility; however, in those cases where Investigators agreed the subject was unsuitable, the site screen failed the subject. The full process and dialogue took place within the screening period so that patients ultimately deemed ineligible were not enrolled.

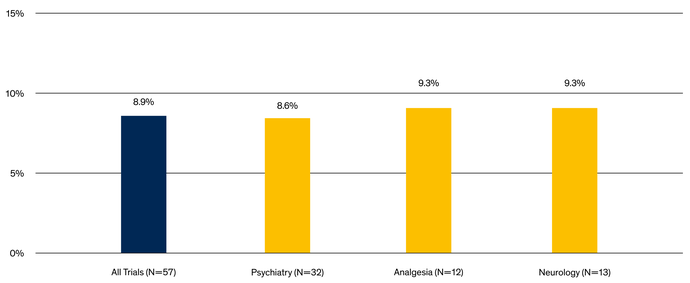
All elements of discussion and screen failures following this review were tracked and evaluated for trends and patterns.

Descriptive statistics were utilized to characterize findings overall, by therapeutic area, by trial indication, by country, by type of site, and by reason for ineligibility. Proportions/percentages were transformed for parametric statistical testing. All analyses were undertaken in exploratory fashion, without a priori hypotheses; alpha was set at .05

Results

- As of May 2017, a total of 29,240 subjects had been reviewed for eligibility by a central medical/clinical team, covering 57 trials in 48 countries over a 7-year period, 32 in psychiatric indications, 12 in analgesia, and 13 in neurology.
- Although the submitting Investigators considered all subjects to be eligible, the review team identified 2,601 subjects (8.9%) who did not meet eligibility criteria and were ultimately considered unsuitable to enter the trials following collaborative discussions between the central review team and Investigators (see Figure 1).

Figure 1: Rate of Ineligible Subjects Following Centralized Eligibility Review (N Reviewed = 29,240 Subjects)



Rate of Ineligible Subjects by Therapeutic Area and Trial Indication

- The rate of unsuitable subjects following consultation with the central review team did not differ significantly between therapeutic area: 8.6% of subjects reviewed were considered ineligible in psychiatry trials, 9.3% in analgesia trials, and 9.3% in neurology trials [F(2,54)=0.34, p=.72] (see Figure 1 and Table 1).
- The rate of findings also did not differ significantly between specific indications [F(10,46)=1.98, p=.06] (see Table 1).
- However, further examination showed that the rate of ineligible subjects was highly dependent on individual trial, where this metric ranged from 0% to 29% in psychiatry trials, 2% to 19% in analgesia trials, and 0% to 31% in neurology trials (see Table 1).

References

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Disclosures

All authors are employees of INC Research/inVentiv Health, the Contract Research Organization responsible for execution of all trials included in this analysis.

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Table 1: Rate, Confidence Interval, and Range of Ineligible Subjects: Overall, by Therapeutic Area, and by Trial Indication

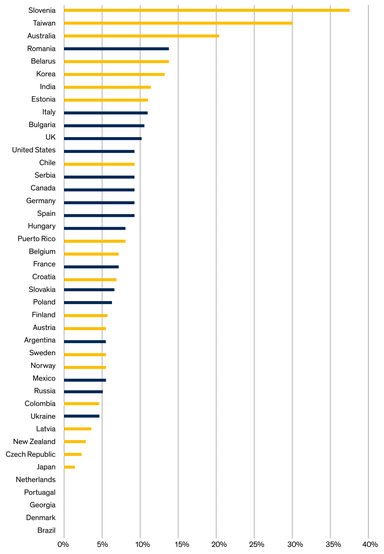
	Overall rate of findings (%)	95% Confidence Interval	Range of findings in all trials (%)
All trials	8.9%	8.6% - 9.2%	0% - 31%
Psychiatry	8.6%	8.2% - 9.1%	0% - 29%
Analgesia	9.3%	8.7% - 9.9%	2% - 19%
Neurology	9.3%	8.4% - 10.2%	0% - 31%
Major depressive disorder	8.9%	8.4% - 9.5%	0% - 17%
Schizophrenia	7.5%	6.7% - 8.4%	3% - 29%
Attention-deficit/hyperactivity disorder	9.3%	8.1% - 10.6%	3% - 23%
Bipolar disorder	8.6%	7.0% - 10.7%	9%
Other psychiatry	8.6%	6.6% - 11.2%	7% - 13%
Fibromyalgia	9.1%	8.3% - 10.1%	2% - 12%
Neuropathic pain	14.9%	12.9% - 17.2%	10% - 19%
Non-neuropathic pain	7.7%	6.8% - 8.7%	6% - 10%
Alzheimer disease	16.1%	14.0% - 18.7%	12% - 18%
Sleep disorders	4.9%	3.9% - 6.1%	3% - 6%
Multiple sclerosis	11.0%	8.9% - 13.5%	11% - 31%
Pooled other neurology	4.8%	3.9% - 7.3%	0% - 7%

Note that Figure 1 and Table 1 do not include an additional 6 trials which had not yet reached 10 subjects reviewed at the time of this publication.

Rates of Ineligible Subjects by Country

- Figure 2 presents the overall rate of ineligible subjects by country.
- Countries with more than 100 subjects reviewed (depicted in blue) tended to converge around the overall global rate (i.e., 8.9%), while countries with fewer than 100 reviews (depicted in yellow) were more variable to both extremes.
- Six countries with fewer than 10 subjects reviewed were excluded in support of data stability and interpretability.

Figure 2: Country-Level Rate of Ineligible Subjects after Centralized Eligibility Review (N Reviewed = 29,558 Subjects)



Rate of Ineligible Subjects by Type of Site

- The rate of subjects deemed ineligible following consultation with the central review team did not differ significantly between purely academic research centers and private research centers [X2 (1) = 0.76, p = 0.38].
- Note that data from the United States only were included given the limited number of purely academic centers utilized outside of the United States.

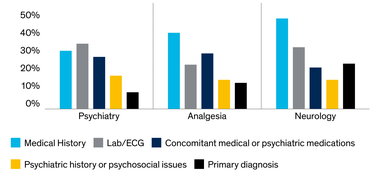
Table 2: Rate of Ineligible Subjects by Type of Site

	Private Center	Academic Center	p Value
Sites	548	76	
N Reviewed	8569	438	
Rate of Eligibility Findings	10.3%	11.6%	p = 0.38

Reasons for Ineligibility as a Result of Centralized Eligibility Review

- Reasons subjects were considered ineligible were broad (some for more than one reason).
- Across all trials, 35% were ineligible for reasons related to medical history, 32% for exclusionary laboratory or ECG findings, 26% for concomitant medical or psychiatric medications, 16% for psychiatric history or psychosocial reasons, and 12% due to findings related to primary diagnostic validity.
- Figure 3 shows reasons for ineligibility by therapeutic area.

Figure 3: Distribution of Centralized Eligibility Review Reasons for Ineligibility by Therapeutic Area (N Reviewed = 29,240; N Considered Ineligible = 2,601)



Patient Selection in AD Trials

AD Clinical Trials Sub-Analyses

- Quality patient selection is particularly challenging in AD trials as evident in Table 1, revealing that AD trials demonstrate the highest overall rate of subjects considered ineligible following consultation with the central review team.
- The rate of 16.1% of subjects deemed ineligible in AD trials was significantly higher compared to all other indications combined (i.e., 8.9%) [X2(1)=73.76; p<.001].
- The average age of subjects with AD who were ultimately deemed unsuitable for the trials was 77.3 years (SD=8.0), and the average Mini-Mental Status Examination (MMSE) score at screening for this group was 15.1 (SD=5.6). 67% were women.
- Although differences were small, subjects who were deemed unsuitable were significantly older [t(1239)=3.18, p=.002], had significantly lower MMSE scores at screening [t(1232)=-4.07, p<.001], and were more likely to be women [X2(1)=3.90; p=.05] compared to the subjects who were randomized into the clinical trials (see Table 3).
- The number of inclusion and exclusion criteria employed in the AD trials was significantly higher compared to all other indications (i.e., 42.3 vs. 34.3; U=58; p=.03).

Table 3: AD Subject Characteristics by Group

Primary Reason	Subject Finding	Protocol Relevance
Cardiovascular Disease Risk	Subject has hypertension, ischemic heart disease, coronary artery disease, intermittent claudication and hyperthyreosis	Exclusion criterion: Clinically significant cardiovascular disorders or uncontrolled cardiovascular disease
Dementia not due to AD	Subject has significant and progressing parkinsonian symptoms: Gait is slow. There is tremor in all extremities in rest.	Exclusion criterion: Subjects with dementia or other memory impairment not due to AD
Other Medical Condition	Labs indicated hypothyroidism is not controlled.	Exclusion criterion: Hypothyroidism that has not been stabilized by medications for at least 90 days
Exclusionary Lab Values	Fasting triglyceride level at screening was 401 mg/dL	Exclusion criterion: Fasting triglyceride > 2.5 × ULN

Reasons for Ineligibility of Subjects in AD trials

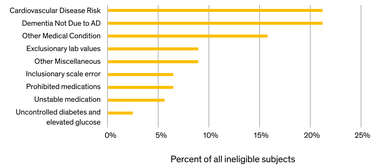
- To understand whether subjects submitted for centralized review were considered ineligible due to reasons that were simple protocol criteria misses (such as exceeding an explicit QTc threshold on ECG) or for reasons that were more complex, requiring consideration of multiple factors, a detailed examination of the reasons subjects were deemed unsuitable was conducted and examples are presented in Table 5.

Table 4: Examples of Reasons Subjects with AD were Deemed Ineligible by Clinical Category

	Ineligible Subjects	Randomized Subjects	p
Age (years)	77.3 (SD=8.0)	75.3 (SD=7.6)	.002
Gender (% women)	64.2%	59.4%	.220
MMSE score	15.1 (SD=5.6)	16.8 (SD=5.0)	<.001

- All findings would be considered protocol violations; however, under the process and data presented here, these subjects were never randomized into the trials and therefore did not cause protocol violations.
- A closer look at the primary reasons subjects were ultimately deemed unsuitable for the AD trials revealed several noteworthy clinical findings.
- As shown in Figure 4, cardiovascular disease risk and dementia not due to probable AD were the most common primary reasons subjects were deemed unsuitable (see Table 4 for representative examples of primary reasons for ineligibility).

Figure 4: Primary Reasons for Ineligibility in Subjects with AD (N Considered Ineligible = 177)



- There were no significant differences in primary reasons for ineligibility between North America and Europe [X2(8)=14.01; p=.08] or between subjects aged 80 and older and those less than 80 compared to subjects younger than 80 years old [X2(8)=13.45; p=.10].
- There also were significant differences in primary reasons for ineligibility in subjects aged 80 and older.

Improvement in Rates of Subjects Deemed Ineligible Over Time

- The rate of ineligible subjects was examined to determine whether sites showed improvement throughout the course of the enrollment period.
  - As shown in Figure 5, there is a slight slope of the line suggesting that sites improved overall, but the linear regression model was not statistically significant (R2 = 0.03, p=.26), largely due to an increase in the rate of subjects determined to be ineligible in the last 2 out of 3 months of the enrollment period.
  - If these last 3 months are removed from the regression analyses, time since the start of the enrollment period is a significant predictor of the rate of findings (R2 = 0.15, p=.02).
  - It is important to note that the higher rates of ineligible subjects found in months 37 and 38 depicted in the graph below is due to a combination of a low number of reviews, new sites screening their first subjects, and experienced sites hurrying to screen subjects before they are closed at the end of the study.

Figure 5: Rate of Findings Following Centralized Eligibility Review by Month of Enrollment

Conclusions

- CNS trials are highly susceptible to penetration by unqualified subjects with variables rates across indications, countries, and experience.
- The rate of ineligibility after consultation with a central review team is significantly higher in AD trials compared to all other indications.
- The most common reasons subjects in AD trials were deemed unsuitable were:
  - Cardiovascular disease risk,
  - Dementia not due to probable AD, and
  - other medical history.
- Sites show improvement over the course of the trial, with decreasing rates of subjects deemed unsuitable after centralized review; however, rates can increase significantly at the end of enrollment due to a variety of factors.
- High rates of AD patient selection error may shed some light on how protocol and patient complexity increases risk, and ways in which trial designers and managers can focus their efforts to protect trial quality and patient safety.
- Centralized eligibility review is feasible, globally scalable, and effective at preventing unqualified subjects, as defined by the protocol, from entering clinical trials. This process reduces unwanted heterogeneity in the study sample, which helps protect statistical assumptions and power and allows greater confidence in the interpretation of efficacy and safety data.

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