Navigating the Complexities of Alzheimer's Clinical Trials: Studies and the The Perils of Small Molecule Risk of Fraudulent Practices

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The AD community must take a unified aggressive stance against fraudulent practices to safeguard AD research integrity, protect and benefit vulnerable populations, and accelerate development of effective therapeutics.

INTRODUCTION

Companies recently identified clinical study sites engaging in fraudulent practices, reducing success in Alzheimer's disease (AD) clinical trials. Successful trials are reliable despite possible victimization by these practices because these sites introduce a negative bias meaning that effects may be larger than estimated in a clinical trial, however safety concerns may be underestimated. Ease of simulating Alzheimer's diagnosis documentation (based on clinical or blood markers) and clinical outcome data, coupled with inadequate oversight by Contract Research Organizations (CROs), facilitates deceptive practices.

Fraudulent practices at sites and with patients ("professional patients") often go hand-in-hand and flourished during COVID. These must be aggressively addressed in the post-COVID environment. Requiring and scrutinizing PET scans increases the chance of detecting fraud. Alarmingly, sites most prone to deceitful practices include predominantly underrepresented populations, thwarting inclusion efforts.

METHODS

We reviewed completed and ongoing studies to estimate the percentage of potentially fraudulent sites. We developed medical audit methods, based on extensive AD neurology experience to identify issues invisible in regulatory audits. Traditional rater training, data review, data management and statistical analysis methods fail to identify these issues. We use expected enrollment and true effect size to estimate potential bias and added variability introduced by these sites. We propose methods for detecting fraud based on clinical and operational data.

RESULTS

It is possible that many promising AD treatments have failed due to compromised clinical trial integrity rather than lack of efficacy or safety concerns. Certain areas require more oversight to mitigate risks. Operational, enrollment and rater oversight are all critical.

Figure 1 Mitigation of Key Risk Indicators to prevent the common vulnerabilities for fraudulent activities in Alzheimer Clinical Trials

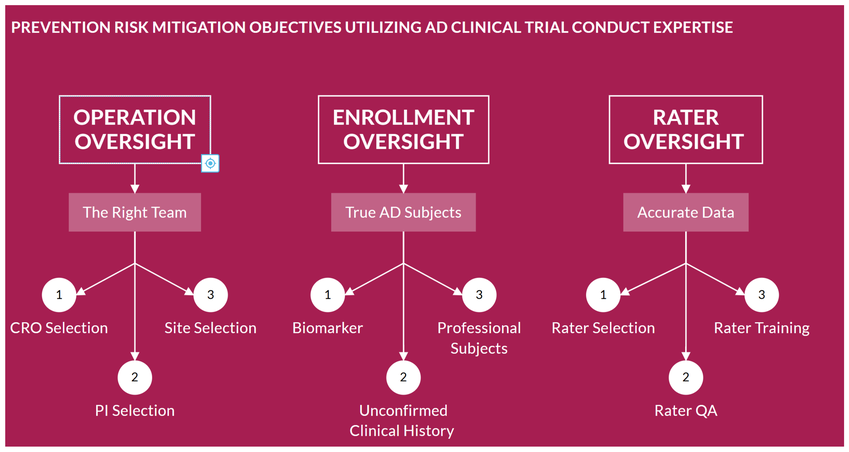
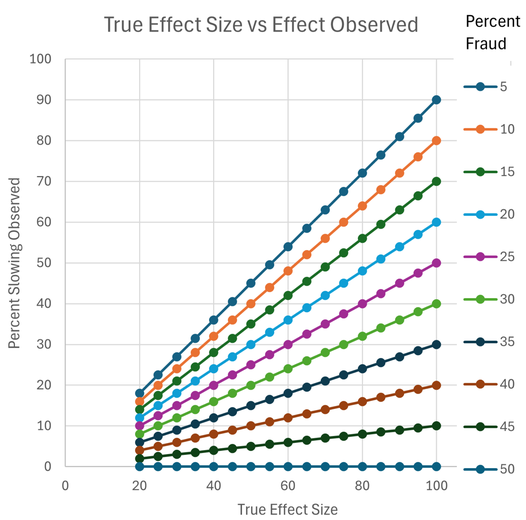
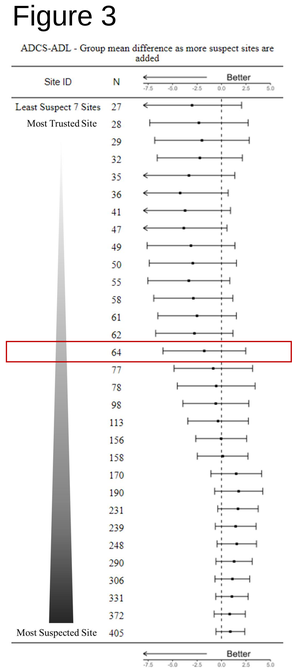


Figure 2 Increased percentage of fraud data diminishes true treatment effect*



*We don't know why, but effects at fraudulent sites were sometimes positive for placebo

Figure 3



In studies not requiring PET scans, ***approximately 10% of sites may be fraudulent, corresponding to a higher proportion of enrolled subjects (~20-50%).*** These sites can reduce observed effect size by 40% (estimated bias) at best and can completely cancel out a true treatment effect at worst, Figure 2. We estimate variability increases by 35-100%, reducing our ability to observe significance. Algorithms to identify potential problematic study sites and individuals, and methods for site inspections to investigate issues will be shared confidentially, but not broadly, to prevent sites from circumventing our algorithms.

Figure 3-5 Efficacy diminishing effect of fraudulent sites, 3 real-world case studies. Top row of the plot is the effect from the least suspected sites. Below that, data from study sites were added one by one in each row from the most trusted to the most suspected (algorithm ranked) to see how suspected sites shifted the result from beneficial to no different. The last row is the effect with all sites included.

Figure 4

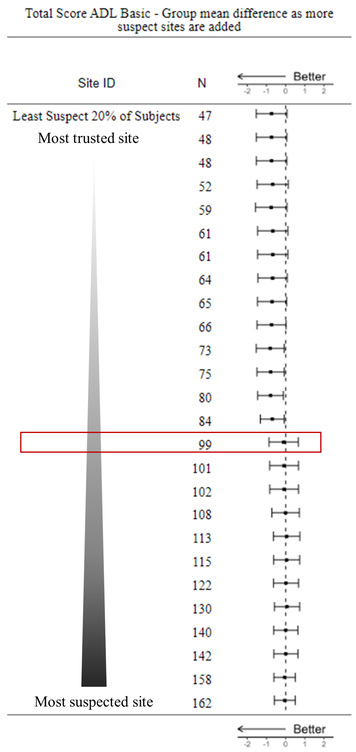
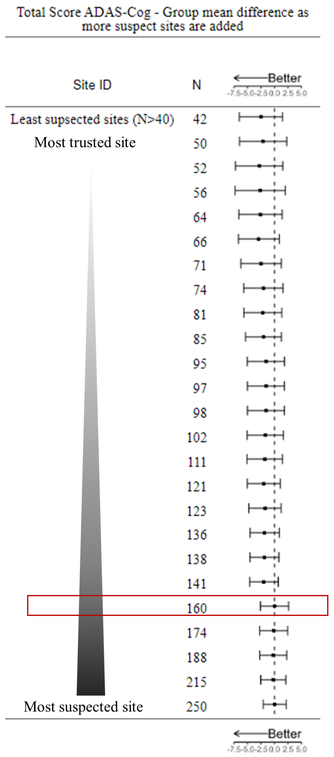


Figure 5



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ALZHEIMER'S ASSOCIATION AAIC 24 Alzheimer's Association International Conference

CONCLUSIONS

Fraudulent practices at Alzheimer's disease clinical sites have caused serious problems for many companies in this space. We are seeking to spread awareness of this issue and rally the community to actively work against these practices. AD clinical trials affected by even a minority of fraudulent sites may have underestimated treatment effects. We have developed a toolbox for combating these issues. It includes best practices for enhanced CRO oversight, incorporation of medical expertise in audits, and identification of problems based on targeted, blinded statistical algorithms. We freely share it with qualified researchers. Awareness of and taking an aggressive stance as a community against these fraudulent practices can safeguard AD research integrity, protect and benefit vulnerable populations, and accelerate development of effective therapeutics.