

Don't Change the Subject!

The Changing Nature of Screened Subjects During Phase 3 Clinical Trials

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ABSTRACT

Introduction: Clinical trial recruitment and enrollment are affected by a number of factors, such as use of recruitment vendors, the use of sites known to the sponsor and subjects known to the site early in the recruitment process, and addition of sites and pressure to increase enrollment later in the study. Previous reports describe placebo response increasing later in enrollment; we seek to understand more about how subjects enrolled early in a clinical trial might differ from those enrolled later in the same study. Our registry, which seeks to track and eliminate duplicate and professional subjects in clinical trials, has collected data on over 40,000 subjects screened or prescreened for clinical trials, especially for Phase 2-4 studies of CNS indications.

Methods: We looked at pooled study data for all subjects screened for Phase 3 studies that have used CTSdatabase and are completed or at least 75% enrolled (n = 4352). Only *actionable* matches that occurred at unique sites were included in the analysis. Actionable matches are exclusionary per protocol and include concurrent enrollment, participation in another study less than the number of days required by I/E criteria or previously enrolled in a study for a prohibited indication (e.g. Bipolar in an ADHD study). For each study, total subjects screened were divided into four equal quartiles based on enrollment and the results were pooled for analysis. Study indications included Schizophrenia (n=2), Binge Eating Disorder (BED, n=1) and Adult ADHD (n=2).

Results: 103 Actionable Matches were found among 4227 subjects screened through December 29, 2017. The overall percentage of actionable matches in these studies was 2.4%. When investigated by quartile, the percentages of excluded subjects were different: 1.6%, 2.1%, 3.2% and 2.8% in quartiles 1-4, respectively. There were fewer subjects excluded (inappropriate subjects who are likely duplicate and/or professional) in the 1st quartile and a greater number in the 3rd quartile of enrollment. The percentage of exclusionary matches in the second half of enrollment (3.0% in quartiles 3+4) was significantly higher than in the first half (1.8% in quartiles 1+2), p = .012.

Conclusions: Subjects excluded from studies by a registry are a marker for inappropriate or professional subjects. Our data support a hypothesis that subjects enrolled later in Phase 3 studies are more likely to be study-inappropriate. These findings should be investigated further in larger samples and for other indications. Correlation with recruitment data and PK data would be helpful to determine if rates of these inappropriate subjects correlate with enrollment efforts or rates of nonadherence. In addition, Phase 3 data on inappropriate subjects could be compared to Phase 2 data. If the type of subjects enrolled later in Phase 3 trials differ from those entered in successful Phase 2 studies, and they are not accounted for, they may contribute to study failure.

BACKGROUND & METHODS:

Introduction: Clinical trial recruitment and enrollment are affected by a number of factors, such as use of recruitment vendors, the use of sites known to the sponsor and subjects known to the site early in the recruitment process, and addition of sites and pressure to increase enrollment later in the study.¹ Previous reports describe placebo response increasing later in enrollment; we seek to understand more about how subjects enrolled early in a clinical trial might differ from those enrolled later in the same study.² Our registry, which seeks to track and eliminate duplicate and professional subjects in clinical trials, has collected data on over 40,152 subjects screened or prescreened for clinical trials, especially for Phase 2-4 studies of CNS indications.

Methods: We looked at pooled study data for all subjects screened for Phase 3 studies that have used CTSdatabase and are completed or at least 75% enrolled (n = 4352). Only *actionable* matches that occurred at unique sites were included in the analysis. Actionable Matches are exclusionary per protocol and include concurrent enrollment, participation in another study less than the number of days required by I/E criteria or previously enrolled in a study for a prohibited indication (eg. Bipolar in an ADHD study).

For each study, total subjects screened were divided into four equal quartiles based on enrollment and the results were pooled for analysis. Study indications included Schizophrenia (n=2), Binge Eating Disorder (BED, n=1) and Adult ADHD (n=2).

RESULTS

- **103 Actionable Matches were found among 4352 subjects screened through December 29, 2017. The overall percentage of Actionable Matches in these studies was 2.4%.**
- **When investigated by quartile, the percentages of excluded subjects were: 1.6%, 2.1%, 3.2% and 2.8% in quartiles 1-4, respectively.**
- **There were fewer study-inappropriate subjects (subjects who are likely duplicate/professional) excluded in the 1st quartile (p=0.096) and significantly more in the 3rd quartile (p=0.012) of enrollment.**
- **The percentage of exclusionary matches/inappropriate subjects in the second half of enrollment (3.0%) was significantly higher compared to the percentage found in the first half (1.8%). Comparing quartiles 1+2 vs. quartiles 3+4 showed statistical significance, p= 0.012.**

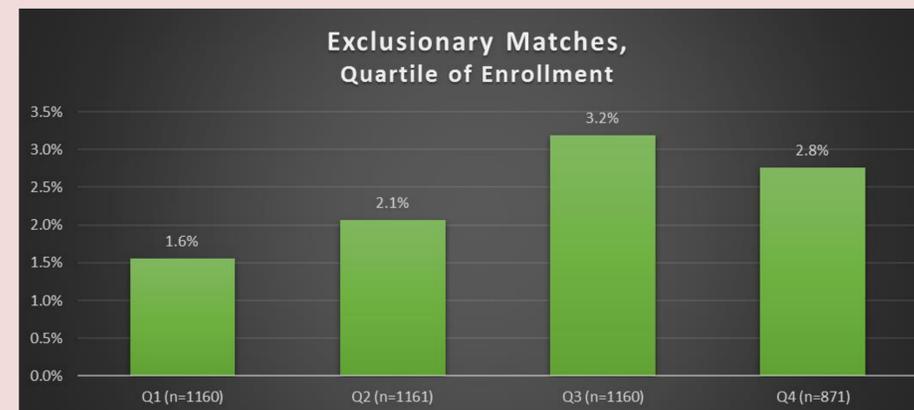


Figure 1. The 1st quartile had the lowest percentage and the 3rd and 4th quartiles had the highest percentage of excluded/inappropriate subjects.

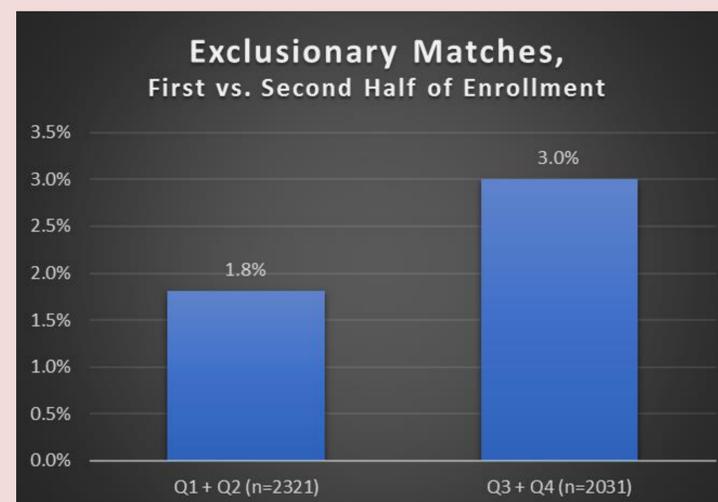


Figure 2. The second half of enrollment had a significantly higher percentage of excluded duplicate/inappropriate subjects (p=0.012)

DISCUSSION

- Deception by research subjects is a common occurrence. Duplicate and professional subjects may magnify inclusionary or deny exclusionary conditions and are often nonadherent.^{3,4}
- Subjects excluded from studies by a registry are a marker for inappropriate or professional subjects.
- Our data support a hypothesis that subjects enrolled later in Phase 3 studies are more likely to be study inappropriate.
- This may be due to “quantity over quality” factors such as pressure to maintain study timelines, increased recruitment pressures and the exhaustion of the pool of qualified participants at any given site.
- Phase 3 data on inappropriate and nonadherent subjects could be compared to Phase 2 data.
- If subjects enrolled later in Phase 3 trials differ from those entered in successful Phase 2 studies, and they are not accounted for, they may contribute to study failure.

CONCLUSIONS

- **Our data indicate that subjects enrolled later in Phase 3 studies may be more likely to be duplicate enrollers or excluded for not meeting other study criteria.**
- **Further studies could help determine if rates of these inappropriate subjects differ from Phase 2 studies or correlate with enrollment efforts or rates of nonadherence.**
- **If subjects enrolled later in Phase 3 trials differ from those entered in successful Phase 2 studies, they may contribute to study failure.**
- **These subjects may be accounted for through use of subject registries that track previous/concurrent study participation**

REFERENCES

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