Give Us Your Tired, Your Poor, Your Professional Subjects:

The Last Quartile of Phase 3 Enrollment

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DISCLOSURES

DR. SHIOVITZ HAS RECEIVED RESEARCH GRANT SUPPORT FROM:

Actavis, Alkermes, Allergan, Amgen, Arena, Astellas, Astra-Zeneca, Avanir, Axsome, Bayer, Biohaven, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Chiesi, Corcept, Eisai, Elan, Epix, Forest, Genentech/Roche, Glaxo SmithKline, Janssen, Johnson & Johnson, Eli Lilly, Lundbeck, Merck, Neurim, Novartis, Novo-Nordisk, Otsuka, Pfizer, Praecis, Sage, Sanofi-aventis, Shire, Sunovion, Synosia, Takeda

POTENTIAL CONFLICT OF INTEREST

Dr. Shiovitz is an owner of the CTSdatabase subject registry.

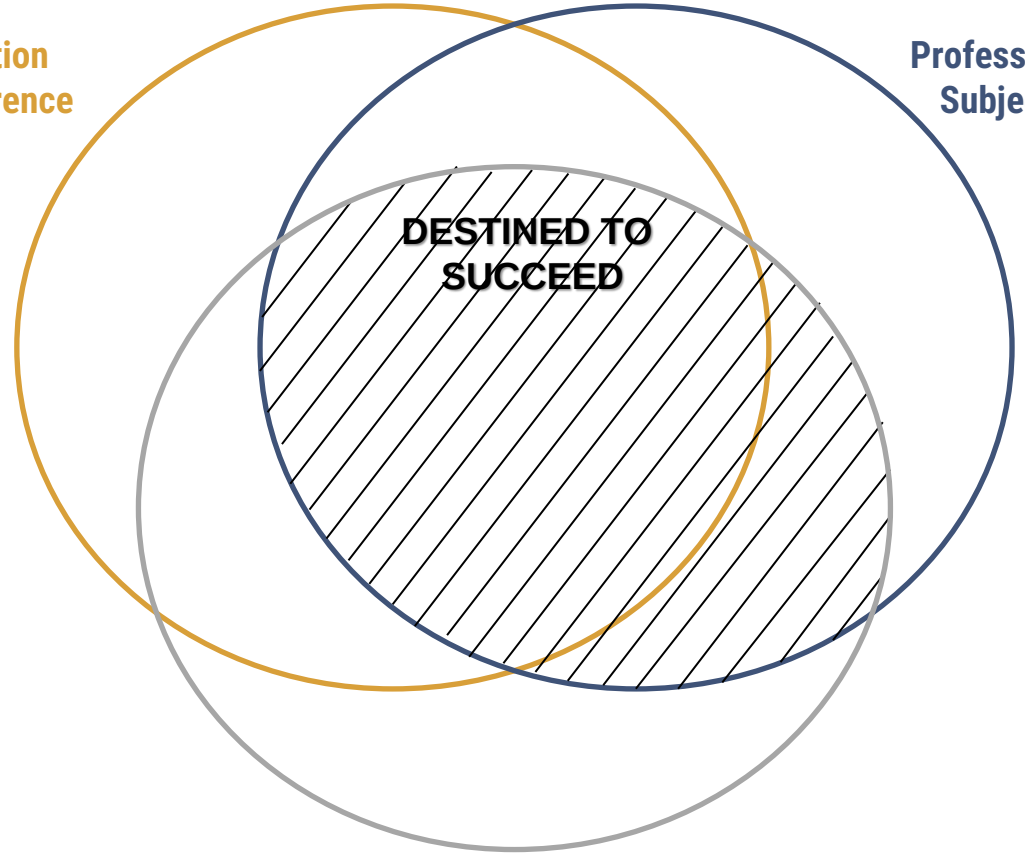
Inappropriate Subjects

- Duplicate subjects participate in multiple studies concurrently or within an exclusionary timeframe. Motives vary.
- Professional subjects: primary goal to collect stipends. Usually protocol or medication non-adherent, deceptive about exclusionary conditions or whether they have the disease/severity.
- Other protocol violators: e.g. Days since last study, excluded indication
- Can adversely affect safety in Ph. 1, efficacy and safety signals in Ph. 2-4.

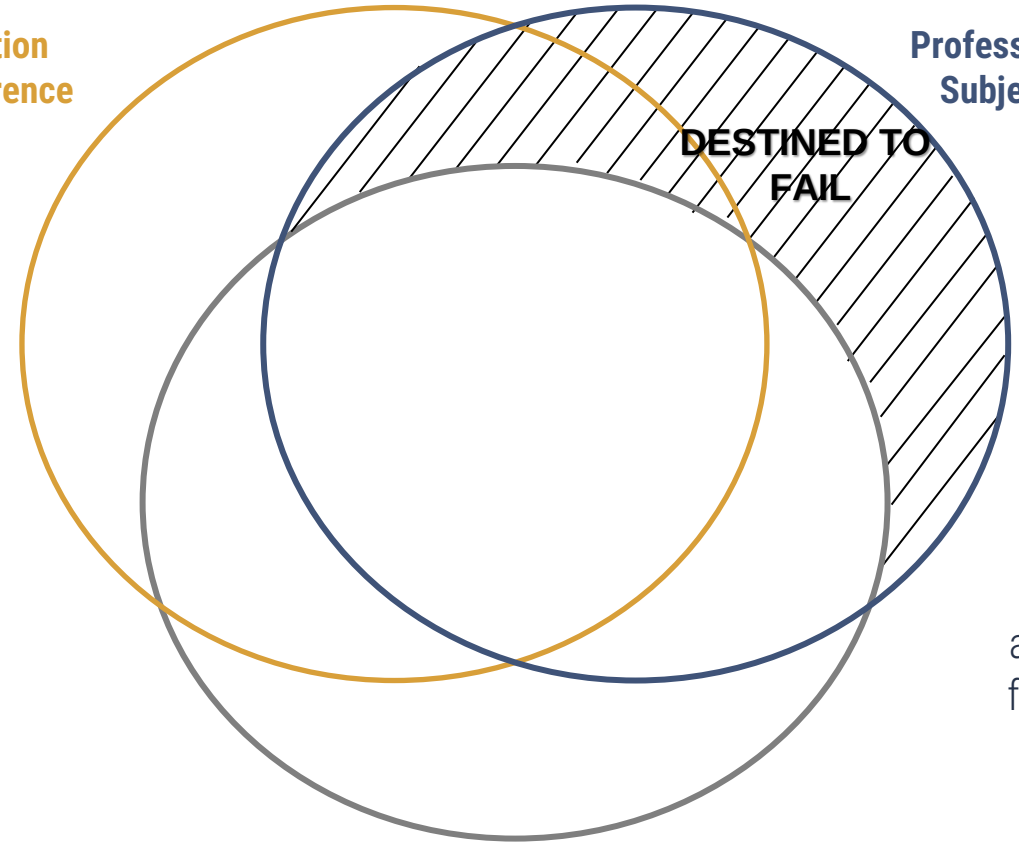
Case Example: MDD or GAD?

CJL, a 30 y.o. very depressed man enrolled in a DB, placebo-controlled study of recurrent MDD.
MADRS went from a 31 at BL to a 2 at end of study.

Subject was on placebo.
A year later he participated in a GAD study with initials JCL and denied any past h/o MDD.



Example:
Subject magnifies symptoms to meet I/E at screen, then responds truthfully during subsequent assessments
(From McCann DJ)



Example:
Subject feigning MDD sxs at screen and continues to feign sxs throughout study. (From McCann DJ)

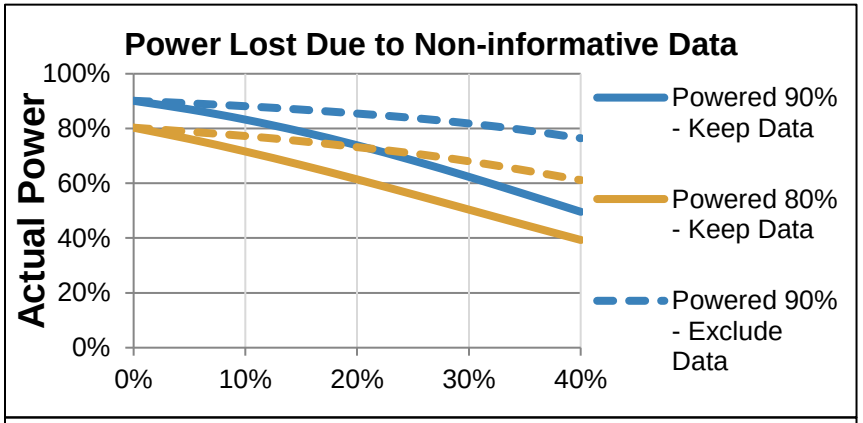
What if we simply exclude data from "bad" subjects?

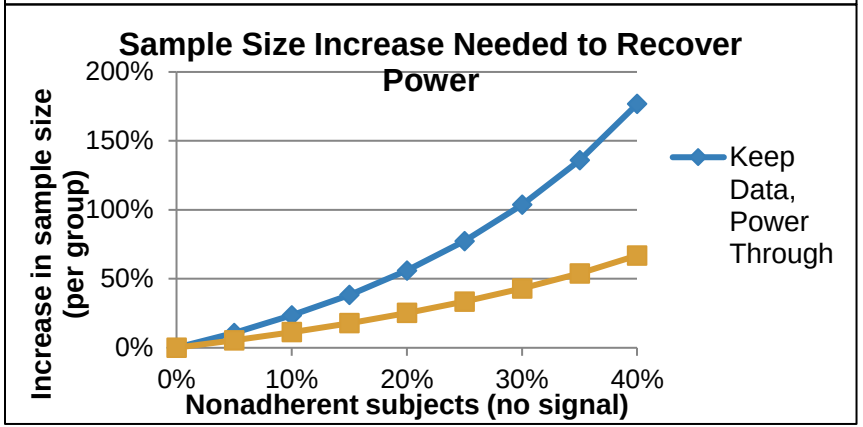
- Lose the benefit of a larger N, but remaining subjects exhibit "true" Δ
- Power is improved, even without replacing the missing data

What if we remove "bad" subjects and replace them to recover original sample size?

- Strategy is more efficient than "powering through" with bad data

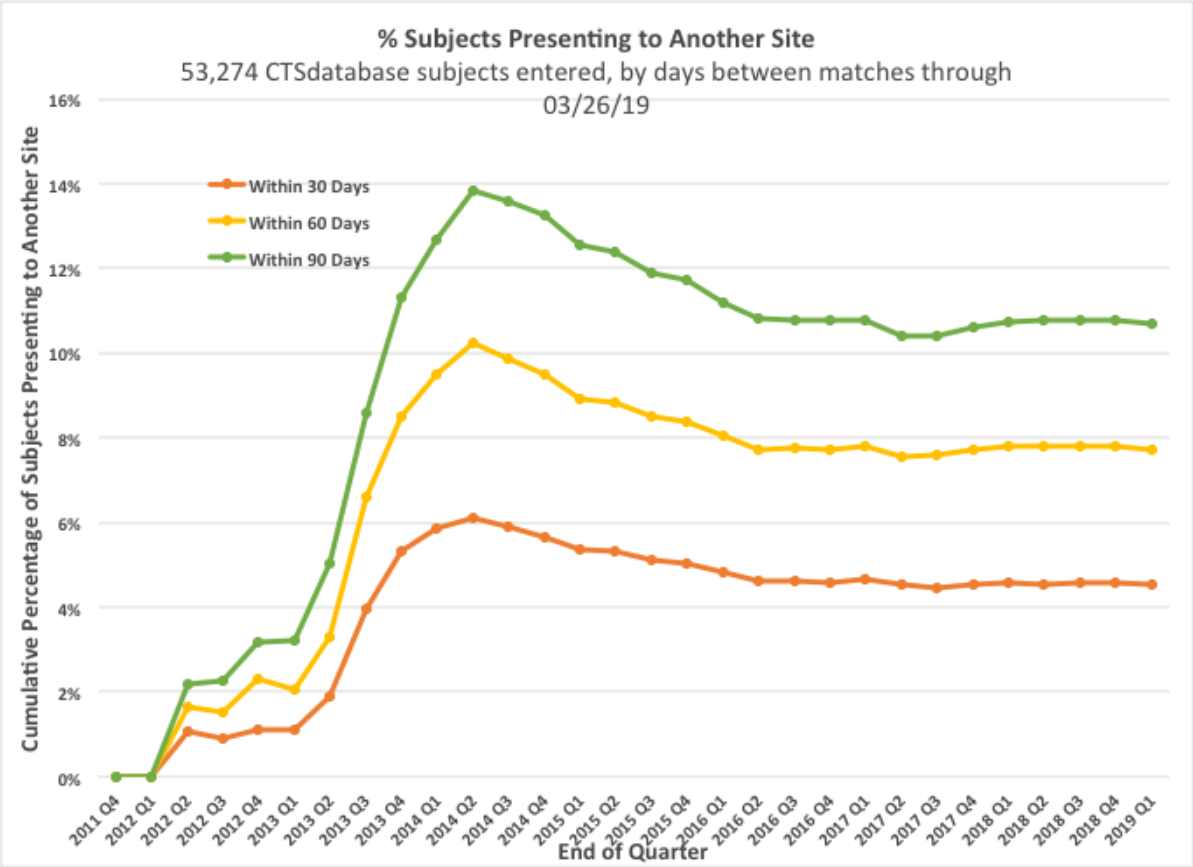
*from Shiovitz TM, Bain EE, McCann DJ et al, JClinPharmacol 2016, 56(9) 1151-1164



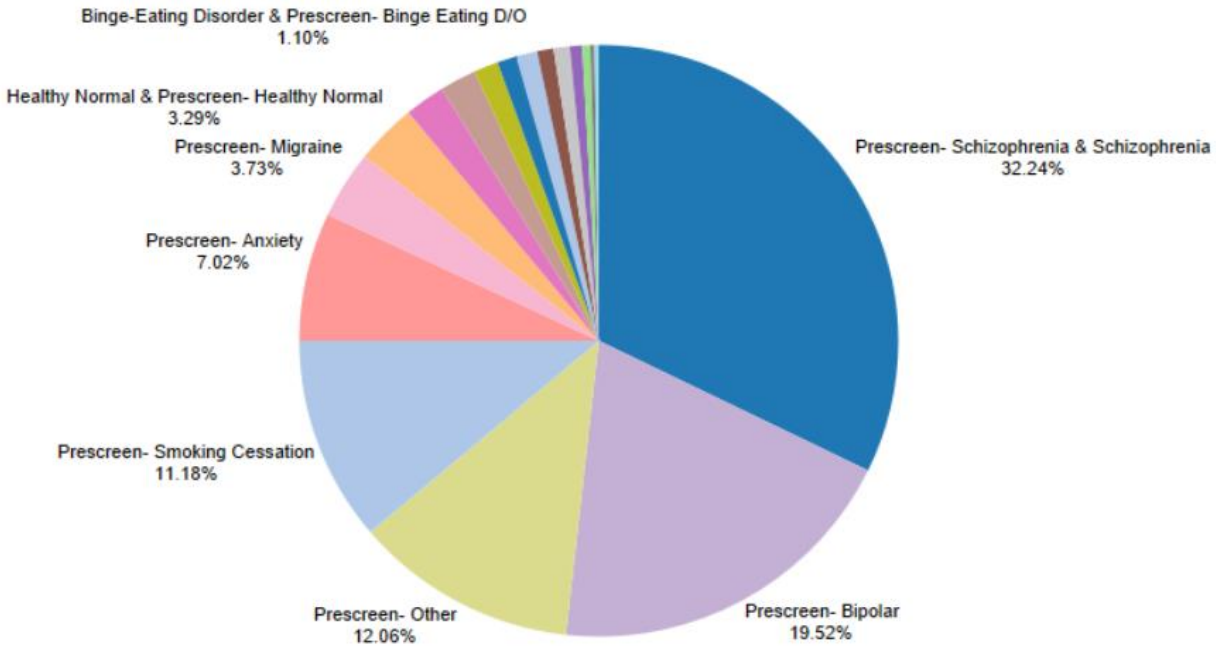


A 42-year-old screening for a schizophrenia study was found to be concurrently participating in another study. He had denied any previous study participation, but laughed and said "you caught me" when confronted. CTSdatabase found he had screened or prescreened at a minimum of 7 different sites (duplicating 3x) in the last 12 mos.

He admitted taking IP "only when it makes my head feel clearer" while reporting 100% compliance by pill count.


% Subjects Presenting to Another Site
53,274 CTSdatabase subjects entered, by days between matches through 03/26/19
Cumulative Percentage of Subjects Presenting to Another Site
16%
14%
12%
10%
8%
6%
4%
2%
0%
Within 30 Days
Within 60 Days
Within 90 Days
2011 Q4
2012 Q1
2012 Q2
2012 Q3
2012 Q4
2013 Q1
2013 Q2
2013 Q3
2013 Q4
2014 Q1
2014 Q2
2014 Q3
2014 Q4
2015 Q1
2015 Q2
2015 Q3
2015 Q4
2016 Q1
2016 Q2
2016 Q3
2016 Q4
2017 Q1
2017 Q2
2017 Q3
2017 Q4
2018 Q1
2018 Q2
2018 Q3
2018 Q4
2019 Q1
End of Quarter

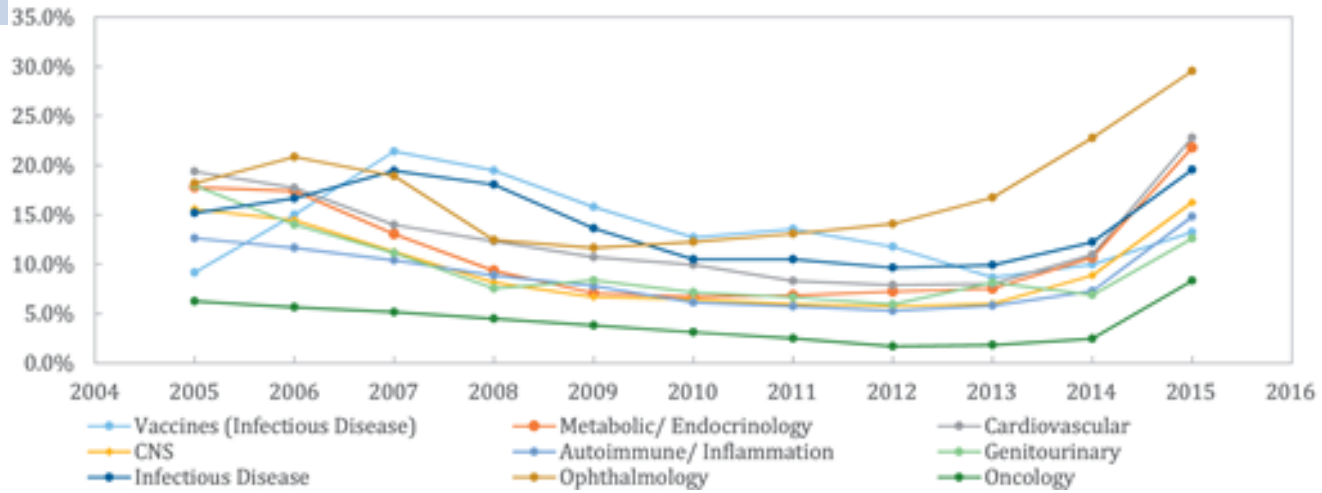
Depression Cross Indications
(25.7% of Depression Matches)



*Percentages representative of all cross-indication match records

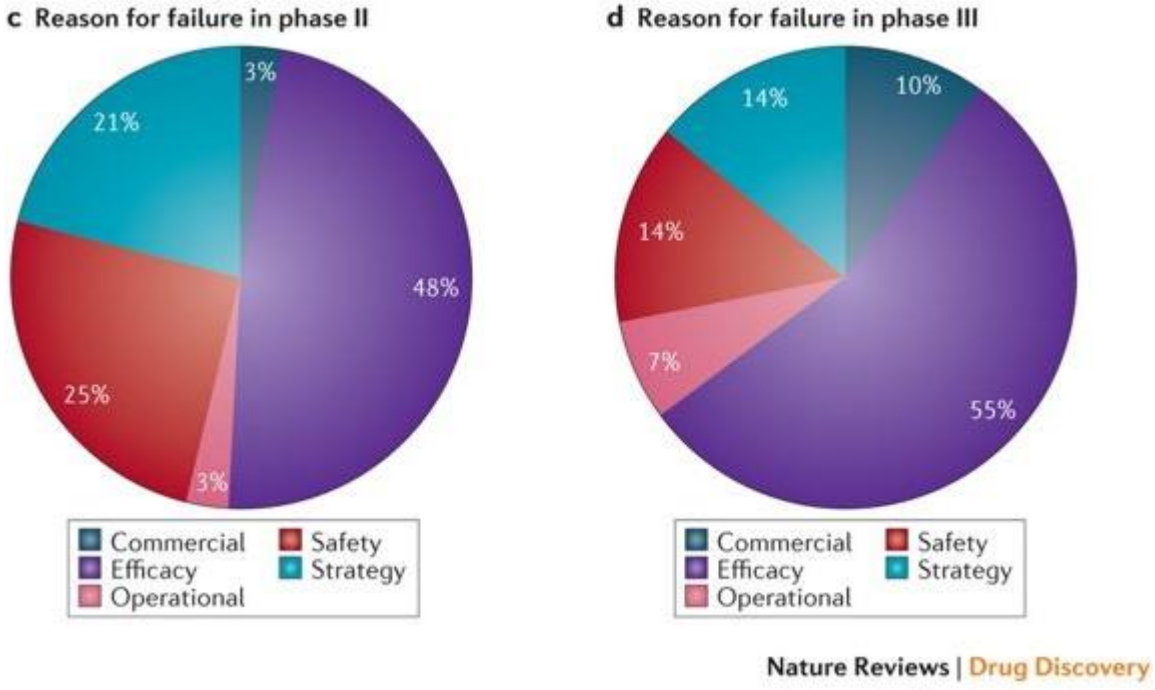
Estimation of clinical trial POS (Probability of success)

from Wong CH, Siah KW and Lo AW, Biostatistics (2019) 20, 2:273-286)



- Next to Oncology, CNS has the highest percentage of study failure.
- Trials that use biomarkers (BMs) in patient selection have almost twice the POS c/w trials w/o BMs
- Overall success rates for drug devel. programs decreased between 2005 and 2013; this decline may be reversing since 2013

Study Failure Reasons by Phase (from Harrison RK, Nature 15:817-18, Dec 2016)

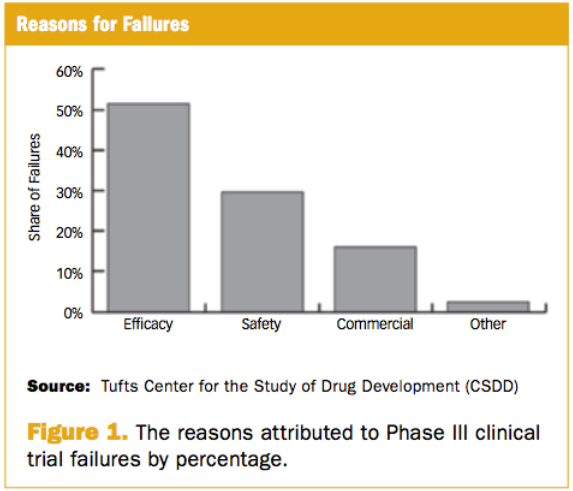


- Efficacy is (by far) the most common reason for failure.

Why do >50% of Phase 3 studies fail*?

* http://www.appliedclinicaltrialsonline.com/top-6-reasons-phase-iii-trial-failures?id=7

- Study Design, e.g. Δ patient definition, endpoint, etc.
- Dose Selection, e.g. inadequate dose finding in Ph 2
- Variability, e.g. larger study, more sites, rater bias
- Statistical Issues, e.g. sample size, missing data
- Execution, e.g. recruitment, nonadherence



Hypotheses

Subjects entering Phase 3 studies differ from those entering Phase 2 studies

Subjects entering later (i.e. in later quartiles of Phase 3 enrollment) differ from those entering early in Phase 3 studies.

METHODS

Pooled analysis of completed Phase 2 and 3 studies using CTSdatabase from beginning to end.

Twelve Studies: 5 Schizophrenia, 1 MDD, 2 BED, 2 ADHD, 2 FM

Total Phase 2 subjects: 2387

Total Phase 3 subjects: 4610

For each Phase 3 study, enrollment was divided by quartile. The data was then pooled by quartile of enrollment and examined for all subjects excluded by the db (as duplicate, professional or protocol inappropriate) in each quartile.

The *n* was small for some Phase 2 quartiles, so all Phase 2 were compared with Phase 3, and each quartile of Phase 3 enrollment were compared.

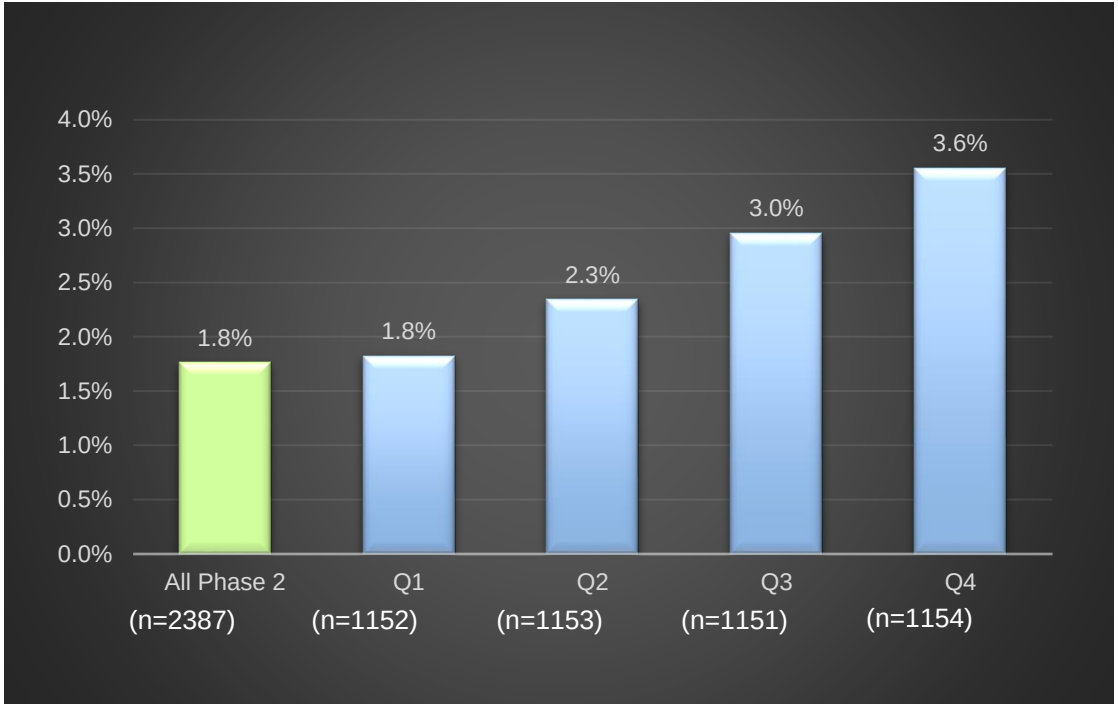
EXAMPLES OF EXCLUSIONARY MATCHES (1/2)

- A 47-year-old woman, while enrolled in a PTSD study, attempted twice to screen for the same BED study under different last four of SSN – this occurred across 3 different sites in Atlanta.
- A 51-year-old woman attempted to screen four times for the same schizophrenia study at different Southern California sites, sometimes changing her last initial.
- A 32-year-old man attempting to screen for a schizophrenia study in New Jersey was found to have been a year into an outpatient schizophrenia study in New York.

EXAMPLES OF EXCLUSIONARY MATCHES (2/2)

- A 62 year-old-woman presenting for a TRD study was on sertraline 200mg x 6 mos. with partial response, *denied* previous study participation. We found that she was in 2 MDD studies in the last 6 mos. and was due to return next week for another (all different sites).
- A 34-year-old male subject who screened for a schizophrenia study in S. FL, had recently completed a GAD study.

Percentage of Exclusionary Matches
Phase 2 vs. Phase 3 by Quartile of Enrollment



CONCLUSIONS

- Subjects entered into the latter part of Phase 3 studies may be different, i.e. more likely inappropriate/duplicate/professional, than in Phase 2 and Early Phase 3 studies.
- If confirmed, we have another reason why successful Phase 2 studies frequently lead to failed Phase 3 studies: The subjects are different.
- Further efforts could be then be taken (e.g. through sample size calculation and study design, use of subject registries, pharmacokinetic sampling and adherence technologies, care with timelines and recruitment) to mitigate the increased effects of inappropriate subjects on Phase 3 study outcomes.

Questions?