Understanding Subject Behaviors and Travel Habits in Preventable Inclusion and Exclusion Protocol Violations in CNS Clinical Trials by Using Verified Clinical Trials' Research Subject Database Registry

Authors: AnnMarie McDougall, PA; Bingnan Li; Kerri K Weingard, ANP; Mitchell D Efros, MD; Maria Demonte, DMD

Affiliations: *Verified Clinical Trials*

OBJECTIVE

- Prospectively determine the prevalence of and prevent inclusion/exclusion protocol violations (IEPVs) in central nervous system (CNS) clinical trials at United States (US) clinical research sites.
  - IEPVs are preventable inclusion and exclusion protocol deviations that can affect participant safety and data integrity.
  - IEPVs result from subject forgetfulness, deception or researchers' inability to reliably verify subject research history.
  - The prevalence of IEPVs has historically not been well understood because methods to collect the information were previously retrospective or unreliable.[1],[2]
  - We are interested in subjects behaviors and travel habits in IEPVs and try to give sponsors reasonable advice.

DESIGN

- CNS IEPV data was collected from a global research subject database registry (GRSDR) utilized at approximately 1,000 sites in the US (Verified Clinical Trials) from August 2016 through March 2019.
- **Number of IEPVs prevented** is defined as the number of IEPVs prevented among potential research subjects in CNS trials.
- **Number of screenings prevented** is defined as the number of subject verifications that resulted in IEPVs. Without a GRSDR, IEPVs would not have been identified or prevented; every verification would instead be an immediate screening of the potential research subject.
- **Travel distance** was collected when the subject tried to get screening. The longitude and latitude was collected into the database.
  - **Travel distance modeling** used mean travel distance of each subject and linear model to test whether there was an association between travel distance and the time of IEPV.

Inclusion/Exclusion Related Protocol Violations (IEPVs) Prevented by VCT at US Sites in CNS Studies
01 August 2016 through 31 March 2019

	All Potential IEPVs		Number of subjects generating these alerts
IEPV Description	**N**	**%**	
Washout period violation	138	27.7%	91
Prior IP exposure	61	12.2%	30
Re-screening attempt (same site)	51	10.2%	45
Exclusionary protocol in history	45	9.0%	39
Dual enrollment attempt	43	8.6%	42
Exclusionary compound in research history	33	6.6%	15
Dual screening attempt	31	6.2%	20
Exclusionary health condition in research history	30	6.0%	27
Re-screening attempt (different site)	25	5.0%	25
Subject age is not valid for study	18	3.6%	17
Subject already screening for same protocol at same location	14	2.8%	14
Re-enrollment attempt	8	1.6%	8
Biologic compound washout violation	1	0.2%	1
Total IEPVs	**498**	**-**	**374**

- **There were 498 IEPVs with in 10,092 screening, with up to 4.92% percentage**

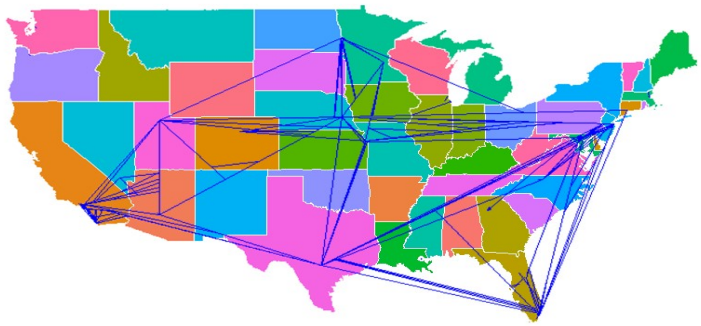

Figure1. All travel violation generated visualization in the United States

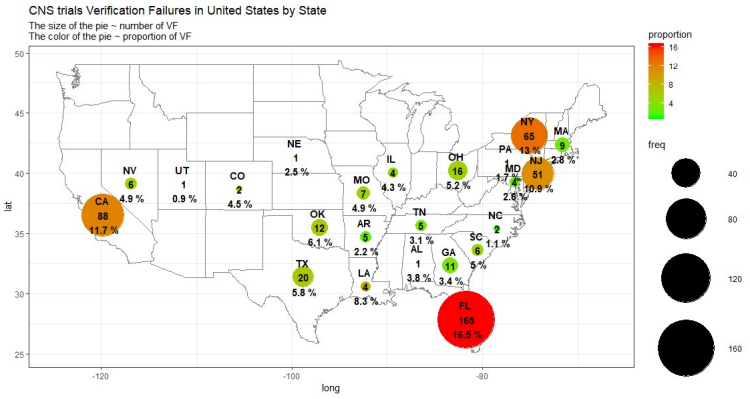

Figure2. National map of number and proportion of IEPVs in CNS trials

Modeling

We assume the model to be: $VF(once\ vs\ multiple\ times) = \beta_0 + \beta_1 * mean\_travel\_distance + \varepsilon$

- The null and alternative hypothesis are:

H_0 = There is no significant association between IEPV times and mean travel distance under the significance level of 0.05

H_a = There is significant association between IEPV times and mean travel distance under the significance level of 0.05

- Outcome: Verification times. Subjects have at least one verification failure. There are two categories in the outcome: 1 verification failure or multiple verification failures.
- Predictor: Mean travel distance. We took the mean travel distance by subjects in order to avoid the correlation of travel distance within the same subject.
- Modeling method: Used Generalized Linear Model (GLM) to fit the model.
- All the modeling was conducted under R version 3.5.0

RESULTS

- **498 (4.93%) potential IEPVs identified and prevented** in CNS studies from August 2016 through March 2019
  - 27.7% of the IEPVs were washout period truncations
  - 18.0% of the IEPVs were re-screening/re-enrollment attempts
  - 12.2% of the IEPVs were Prior IP exposure
  - 8.6% of the IEPVs were dual enrollment attempts
  - 6.2% of the IEPVs were dual screening attempts
- The result of the model showed that **the p-value of mean travel distance is 0.103**. Thus, we fail to reject the null hypothesis and there is no significant association between IEPV times and mean travel distance for different CNS subjects.
- From Figure1 we can see that subjects that caused IEPVs often traveled a lot through out the United States, with short travel distance as well as long travel distance.
- From Figure 1 and Figure 2 we can see that the highest concentration of travel and IEPVs occurred in New York, New Jersey, Florida and California. These states contain the largest concentration of research site locations in the United States.
- We have found that mean travel distance is significantly associated with the IEPV times in all clinical trials.

CONCLUSIONS

- Prospective identification of IEPVs is an important way to understand the scope of and prevent this problem in CNS trials.
- Without a GRSDR, these 498 IEPVs would not have been identified and prevented.
- Preventing subjects with IEPVs from screening for trials can result in significant savings in terms of screening and enrollment costs
- In CNS studies, travel distance is not associated with the times of IEPVs. However in all study conditions, travel distance is significantly associated with IEPV times.
- We argue that all sponsors should use a GRSDR at their CNS research sites to protect clinical trial participant safety and data integrity.
- We argue that all CNS clinical trials should be protected by a GRSDR to ensure participant safety and data integrity.

REFERENCES

- [1] DiFrancesco R., Rosenkranz, S. L., Craft J., Morse, G. D. (2006). Tutorial reduces protocol deviations in multicenter ACTG trials with pharmacology endpoints. *HIV Clinical Trials*, *7*(4) pp. 203-209. doi: 10.1310/hct0704-203
- [2] Sweetman, E. A., Doig, G. S. (2011). Failure to report protocol violations in clinical trials: a threat to internal validity?. *Trials*, *12* pp. 214-221 doi: 10.1186/1745-6215-12-214

DISCLOSURES

- All presenters/authors work for Verified Clinical Trials, the global research subject database registry (GRSDR) utilized in this analysis.