# Using Verified Clinical Trials' Database Registry to Determine the Prevalence of and Prevent Inclusion/Exclusion Related Protocol Violations in Early Phase Clinical Trials

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## OBJECTIVE

- Prospectively determine the prevalence of and prevent inclusion/exclusion related protocol violations (IEPVs) in early phase trials at United States (US) Clinical Pharmacology Units (CPUs) using a global research subject database registry (GRSDR).
  - IEPVs are preventable 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]
  - Prospective prevention of IEPVs provides cost savings to both sponsors and sites.[3]

## DESIGN

- Early phase IEPV data was collected from Verified Clinical Trials, a GRSDR utilized at approximately 1,000 sites in the US from Jan 2016 through Dec 2018.
  - Subject partial identifiers, with or without biometrics, were entered into the database after execution of the site-associated IRB approved consent form.
  - IEPVs were identified after entries were authenticated and compared with the subject's research history via proprietary algorithm.
- **Number of IEPVs prevented** is defined as the number of IEPVs prevented among potential research subjects in Phase I trials across all therapeutic areas.
- **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.
- **Number of health condition crossover (HCC)** is defined as number participation in trials with different health conditions. HCC information between healthy volunteer trials and trials with disease conditions is collected; Number of washout violations, dual enrollment violations and exclusionary protocol violations associated with HCC are also summarized. The association between having IEPVs and having HCC is investigated.
- GPS Location for all verifications are collected in VCT system during verifications; The distribution of all IEPVs prevented by states in the US is summarized in a US map.
- Travel distances are calculated via GPS location associated with each verification. Summary statistics on subjects' travel distance are provided. The association between having IEPVs and travel across verifications is also investigated.
- Analysis was conducted using R version 3.5.0

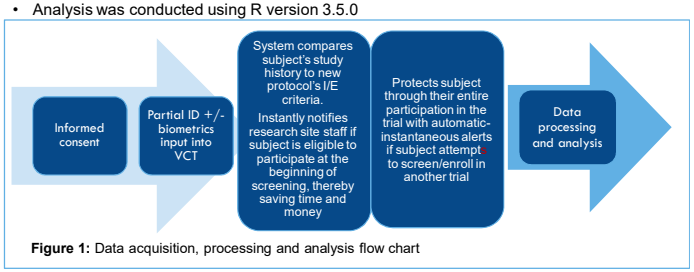


**Figure 1:** Data acquisition, processing and analysis flow chart

## RESULTS

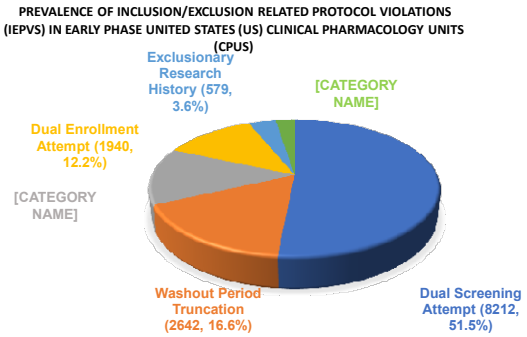


**Figure 2:** Distribution of IEPVs prevented in early phase trials in the United States by violation category (Jan 2016 through Dec 2018). A total of 15932 IEPVs identified and prevented.

| Health Condition From | Health Condition To | Number of Crossover Attempts | Number of Washout Violations Prevented | Number of Dual Enrollment Attempts Prevented | Number of Exclusionary Protocols Prevented |
|---|---|---|---|---|---|
| Healthy | Diseased | 1967 | 37 | 33 | 17 |
| Diseased | Healthy | 1758 | 56 | 37 | 2 |
| | Total | 3725 | 93 | 70 | 19 |

**Table 1:** Number of HCC attempts and related IEPVs prevented in early phase trials in the United States (Jan 2016 through Dec 2018).

**•Violations Analysis**
- **15932 (11.04%) potential IEPVs identified and prevented** out of 144342 VCT entries in early phase studies from Jan 2016 through Dec 2018
- **10250 (7.1%) inappropriate screenings were prevented** in early phase trials from Jan 2016 through Dec 2018
- Distribution of different types of IEPVs are shown in the pie chart in **Figure 2**.
- Early phase IEPVs identified and prevented in the United States by states is shown in the map is **Figure 3:** KS has the highest number of IEPVs prevented; NY and NJ has the highest proportion of IEPVs across all early phase screenings.

**•Travel Analysis**
- Subjects traveled a mean distance of 145.8 miles, median of 8 miles and maximum of 2492 miles.
- Per $\chi^2$-test conducted, there is a significant association between having IEPVs and having travel attempts.

**•Health Condition Crossover (HCC) Analysis**
- Per $\chi^2$-test conducted, there is a significant association between having IEPVs and having HCC.
- Number of HCC attempts and related IEPVs prevented in early phase trials in the United States (Jan 2016 through Dec 2018) is shown in **Table 1**.

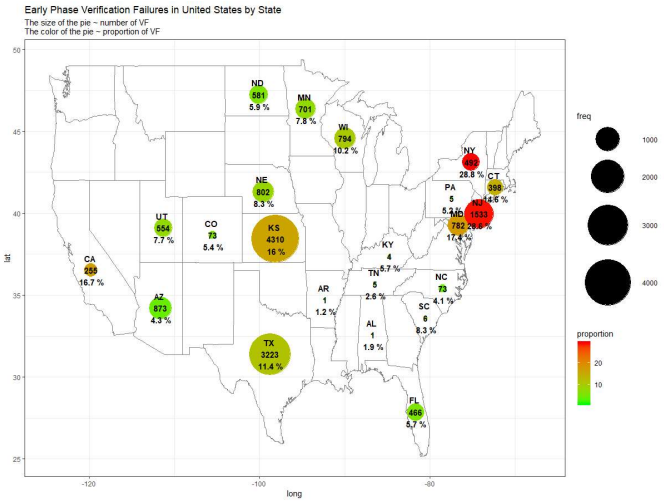


**Figure 3:** Distribution of IEPVs prevented in early phase trials in the United States by state (Jan 2016 through Dec 2018).

## CONCLUSIONS

- Prospective identification of IEPVs is an important way to understand the scope of and prevent this problem in Phase I clinical trials.
- Without a GRSDR, these 15932 IEPVs would not have been identified and prevented.
- Travel analysis concludes that subjects travel between sites are more likely to have IEPVs.
- HCC analysis concludes that subjects having HCC are more likely to have IEPVs.
- We argue that all sponsors should use a GRSDR at their early phase research sites to protect the clinical trial participants safety and improve data integrity.
- We argue that all early phase 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
- [3] Wang Y, Zhang Y (2018). Understanding the prevalence of inclusion/exclusion related protocol violations in CNS clinical trials by using Verified Clinical Trials' research subject database registry

## DISCLOSURES

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