# Predicting Screen Failure Rates of Human Abuse Potential Studies

PRA HEALTH SCIENCES

Ashwin Rai[1], Erik Hansen[2], Kevin Rooney[1], Ryan Turncliff[2], Lynn Webster[2]
[1]PRA Health Sciences, Lenexa, KS, USA; [2]PRA Health Science, Salt Lake City, UT, USA;

## BACKGROUND

- Human Abuse Potential (HAP) studies are required for New Drug Approvals of all drugs that have a potential psychoactive effect. The steps of conducting a HAP study include, screening, drug discrimination, testing and discharge.

- The Study duration and cost are largely influenced by the screening Inclusion and Exclusion criteria, which includes setting an acceptable range of laboratory analytes. There is tremendous variability in what is an acceptable range of laboratory screening criteria by sponsors. This variability makes it difficult to predict study cost and duration of the study.

- It is crucial for research sites to accurately predict cost and duration of a study to ensure there are sufficient resources available for the study as well as to meet sponsor time line and cost consideration. The aim of this study was to evaluate the ability to accurately predict screen success rate and cost based upon sophisticated algorithms using historical data from previous HAP studies.
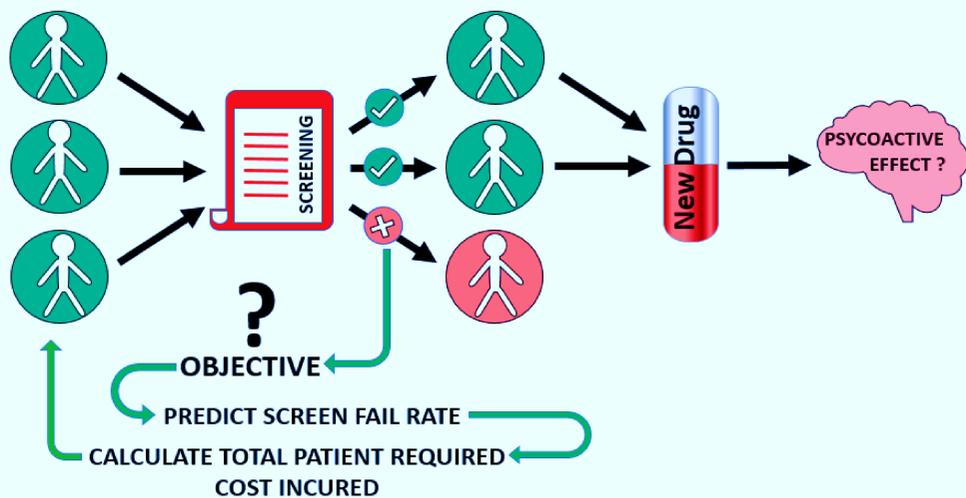


## METHODS

- Lab Data from 15 HAP studies (2629 subjects) and 8 HAP studies (940 subjects )were used to create a training and test data set, respectively.

- Multivariate Cumulative Distribution Function (MVCDF) was applied on training data set and a Screen Success Rate (SSR) predictor system that could predict the screen success rate was developed using python.

- MVCDF and Minimization algorithms was applied on training data set to build a Inclusion and Exclusion criteria (IEC) recommendation system. The IEC recommendation system recommends minimum analytes range that has high probability to achieve a desired screen success rate.

- IEC recommendation system is used only to improve the SSR for the sponsor provided criteria or get an idea on the analyte ranges required to achieve a desired SSR. For a predicted SSR of 79.6% to a given sponsored criteria, IEC recommendation system recommended analytes range that is different from the sponsor provided criteria (see below Density Plots)
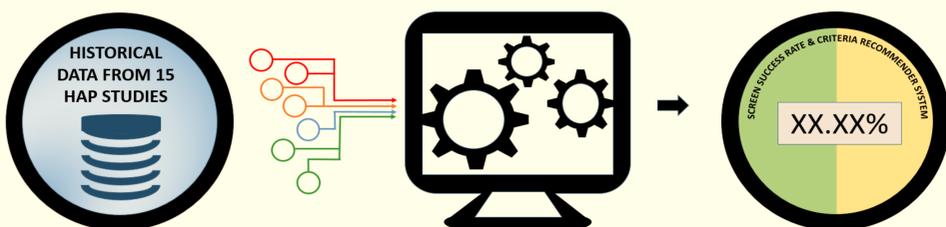


$$f(x) = \frac{1}{\sqrt{(2\pi)^{\frac{n}{2}}|\Sigma|}} \exp(-\frac{1}{2}(x-\mu)^T \Sigma^{-1}(x-\mu))$$

$$Where \; \mu \in R^n, \sum \in R^{n*n} \; covariance \; matrix$$

$$MVCDF = \int_{y_1}^{x_1}\int_{y_2}^{x_2}\int_{y_3}^{x_3}\int_{y_4}^{x_4}\int_{y_5}^{x_5}\int_{y_6}^{x_6} f(x) \; dx_6 dx_5 dx_4 dx_3 dx_2 dx_1$$
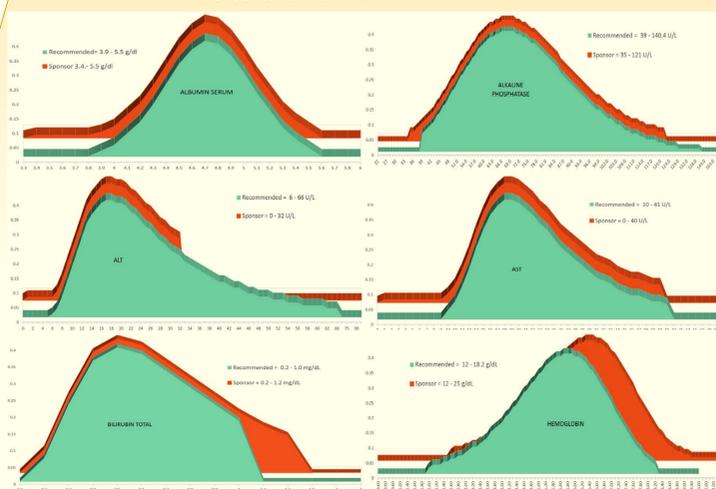
## RESULTS

- The SSR predictor system was tested using the Test dataset consisting of 8 HAP studies utilizing the sponsors Inclusion and Exclusion criteria. The system predicted screen rate of 79.6% compared to the actual screening success rate with an error of -6.0% to 3.2%.

- The IEC recommendation system was tested using the Test Data Set for the desired screen success rate 60%. The actual screening rate of recommended criteria when compared to the desired SSR, resulted in a mean absolute error of 5%.

- The IEC recommendation system was tested using the Test Data Set for desired screen success rate ranging from 0.1 – 0.95%. The system resulted in mean absolute error ranging from 0.02% to 0.07% (see Error chart below)

### SCREEN SUCCESS RATE PREDICTOR SYSTEM

| | ACTUAL SCREEN SUCCESS RATE | PREDICTED SCREEN SUCCESS RATE | ERROR | ERROR RANGE |
|---|---|---|---|---|
| STUDY 1 | 81.5 % | | 1.9 % | |
| STUDY 2 | 75.3 % | | -4.3 % | |
| STUDY 3 | 81.8 % | | 2.2 % | |
| STUDY 4 | 79.1 % | 79.6 % | -0.5 % | ±6.0 % |
| STUDY 5 | 73.6 % | | -6.0 % | |
| STUDY 6 | 82.8 % | | 3.2 % | |
| STUDY 7 | 78.9 % | | -0.7 % | |
| STUDY 8 | 83.1 % | | 3.5 % | |

**SPONSOR PROVIDED CRITERIA IN**

HEMOGLOBIN : 12.0 – 25 g/dL
ALBUMIN SERUM : 3.4 – 5.5 g/dL
TOTAL BILIRUBIN : 0 ~ 1.2 mg/dL
ALKALINE PHOSPHATASE: 39 – 140.4 U/L
ALANINE AMINOTRANSFERASE: 0 – 32 U/L
ASPARTATE AMINOSTRANSFERASE : 0 – 40 U/L

**SSR OUT**

**79.6%**

**OR**
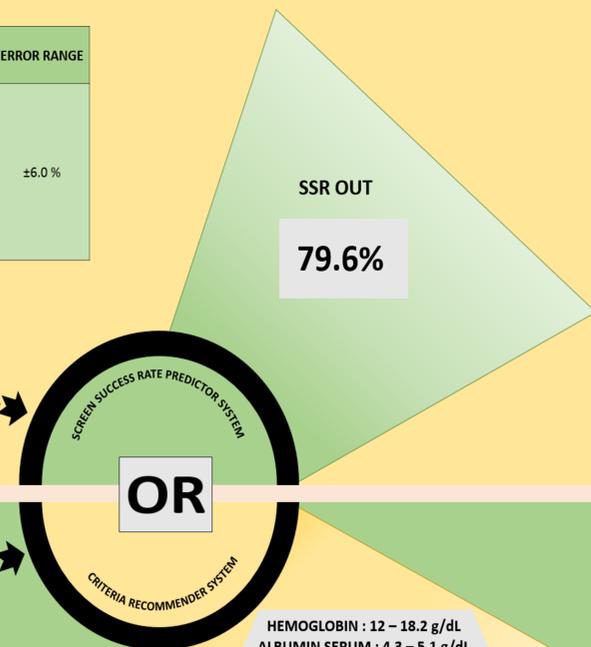
**DESIRED SCREEN SUCCESS RATE IN 60%**

| | DESIRED SCREEN SUCCESS RATE | ACTUAL SCREEN SUCCESS RATE | ERROR | MEAN ABSOLUTE ERROR |
|---|---|---|---|---|
| STUDY 1 | | 63.6 % | 3.6 % | |
| STUDY 2 | | 55.4 % | -4.6 % | |
| STUDY 3 | | 70.9 % | 10.9 % | |
| STUDY 4 | 60.0 % | 67.4 % | 7.4 % | 5 % |
| STUDY 5 | | 58.2 % | -1.8 % | |
| STUDY 6 | | 57.0 % | -3.0 % | |
| STUDY 7 | | 65.4 % | 5.4 % | |
| STUDY 8 | | 62.0 % | 2.0 % | |

HEMOGLOBIN : 12 – 18.2 g/dL
ALBUMIN SERUM : 4.3 – 5.1 g/dL
TOTAL BILIRUBIN : 0.2 – 0.9 mg/dL
ALKALINE PHOSPHATASE: 38 – 113 U/L
ALANINE AMINOTRANSFERASE: 6 – 66 U/L
ASPARTATE AMINOSTRANSFERASE : 11 – 34 U/L

**CRITERIA OUT**



Error Chart

### CRITERIA RECOMMENDER SYSTEM

## CONCLUSIONS

The screen success rate predicted by the SSR predictor system is used to estimate total patients that needs to be screened to achieve the desired target population and also calculate cost involved.

$$Y = Target\; patients\; required \; * \left(\frac{Target\; patients\; required}{predicted\; Screen\; Success\; rate}\right)$$

$$Cost = Y \; * \; \$/patient$$

$$Where \; Y = Total\; patients\; that\; need\; to\; be\; screened$$

The preliminary findings suggest the program developed to predict screen success rates and cost of a HAP study due to screening criteria is possible. It is likely this program will also be able to help determine the effect of inclusion and exclusion criteria on enrollment on all studies and not just HAP studies.