Target the Right Drug to the Right Patient at the Right Dose with Streaming Data

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INTRODUCTION:

"The top ten highest-grossing drugs in the United States help between 1 in 25 and 1 in 4 of the people who take them."[1] Such poor targeting increases the risk of side effects and increases costs. "Around nine out of every ten drug candidates fail to win approval, with huge implications for the overall cost of drug development."[2] Many failures result from poor targeting.

Streaming data, adequately processed, provide orders of magnitude more information than usual to target the right drug to the right patient at the right dose. Many recording and dispensing devices—embedded, wearable, home-based, hospital-based—and electronic diaries are providing a deluge of streaming multivariate time series data. Smartphones are becoming tools for self-care and medicine.

[1] https://www.nature.com/news/personalized-medicine-time-for-one-person-trials-1.17411
[2] https://www.pharmaceutical-technology.com/features/featurecounting-the-cost-of-failure-in-drug-development-5813046/

OBJECTIVES:

1. Demonstrate a Single-Patient, Randomized Controlled Trial (RCT) based on streaming data.
2. Describe why it often is best to conduct RCTs for groups as a series of Single-Patient RCTs.

RCT DESIGN & DATA:

Figure 1 uses mock data to illustrate a Single-Patient RCT designed to evaluate the safety and effectiveness of an analgesic for chronic pain. Five total daily doses, including placebo, were randomized and masked weekly and dispensed and monitored for each of 35 days. Figure 1 includes daily ratings for six response variables used to evaluate safety and effectiveness, including common harmful side effects of opioids.

DATA PROCESSING:

Figure 1 data were processed with DataSpeaks' software using an operationally defined scoring protocol. DataSpeaks' software embodies the proprietary Science of Individuality Measurement Algorithm (SIMA). SIMA applies to streaming data, illustrated in Figure 1, to quantify evidence for interactions over time. One application of SIMA, demonstrated here, is to quantify evidence for safety (harms) and effectiveness (benefits) of time-dependent treatments regarding time-dependent response variables.

DISCUSSION OF RESULTS:

Figure 2 shows the Personal Benefit & Harm Profile for the data in Figure 1. Benefit & Harm Scores are in standard deviation units, which are called Bagnes when computed with SIMA. Each Benefit & Harm Score in Figure 2 is standardized regarding all scores that are possible given Figure 1 data in combination with an operationally defined SIMA scoring protocol.

The probability of obtaining each Benefit & Harm Score in Figure 2 by random chance is < .001. The horizontal dashed line for each response variable in Figure 1 is the cut-point level. These cut-points identify response variable levels that provide the most evidence of benefit or harm when the drug is considered to be present above the cut-point level and absent below the cut point. Importance Weights, shown in Figure 2, quantify clinical significance and personal preferences regarding the response variables for the Figure 1 patient. Pain interference with work and daily activities was most important to this patient. Manageable analgesic side effects at low and moderate levels were of lesser importance.

The Overall Benefit & Harm Score, computed with evidence from the total of 245 repeated measurements in Figure 1 and the Importance Weights, is 3.72. The probability of obtaining this Overall Benefit & Harm Score by random chance also is < .001. Overall Benefit & Harm Scores enable comprehensive evaluations of the safety and effectiveness of time-dependent treatments regarding time-dependent response variables starting at the level of each patient.

DRILL-DOWN CAPABILITIES:

SIMA makes it possible to drill down from Overall Benefit & Harm Scores to help provide the detailed information needed for better targeting. Figure 3 shows Benefit & Harm Scores as nonlinear functions of dose for each of the six response variables and Overall Benefit & Harm Scores across all six of the differentially weighted response variables. The PERSONAL OPTIMAL SAFE AND EFFECTIVE DOSE for this patient, given the data in Figure 1, is 20. Harms outweigh benefits at dose 40 for this patient.

Figure 3: Benefit & Harm Scores as Functions of Dose
Treatment effects typically are delayed as because drug absorption and distribution take time. Figure 4 shows Benefit & Harm Scores as a function of delay of response in days for each of the six response variables.

Figure 4: Benefit & Harm Scores as Functions of Delay of Response
Treatment effects typically persist as because metabolism and excretion also take time. Figure 5 shows Benefit & Harm Scores as functions of persistence.

Figure 5: Benefit & Harm Scores as Functions of Persistence of Response
Together, Figures 4 and 5 show that beneficial effects on pain are rapid and do not persist. In contrast, harmful effects on constipation are somewhat delayed and persistent.

Data & Results

FIGURE 1: TREATMENT & HEALTH DATA FOR A SINGLE-PATIENT RCT

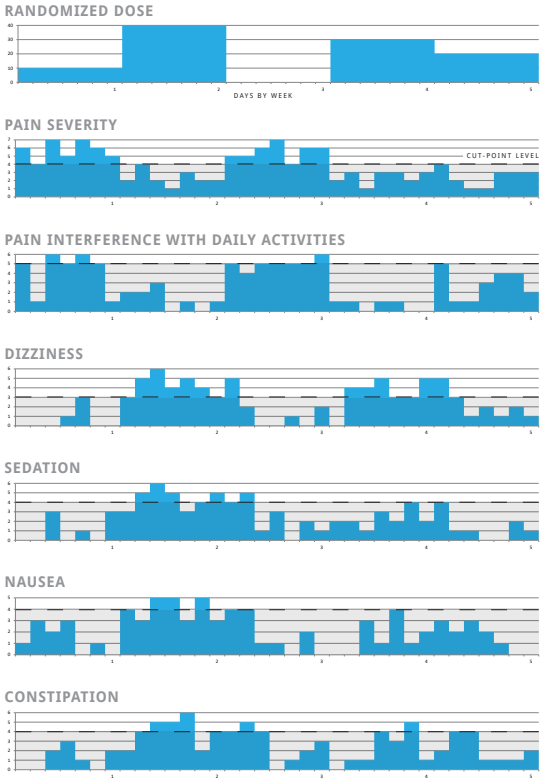


FIGURE 2: PERSONAL BENEFIT & HARM PROFILE

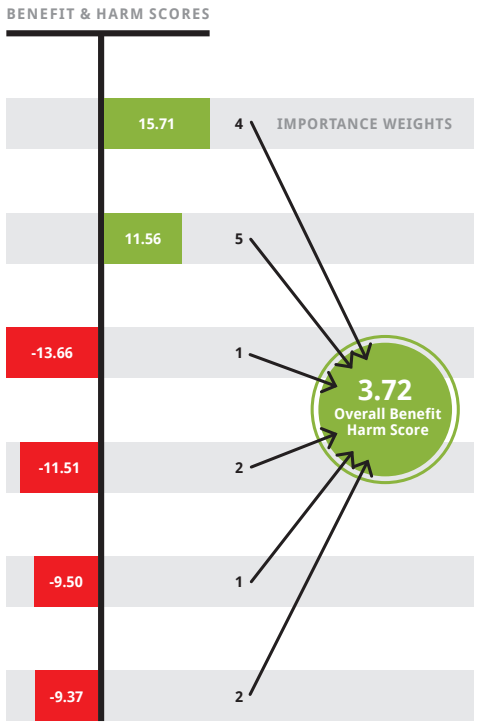


FIGURE 3: BENEFIT & HARM SCORES AS FUNCTIONS OF DOSE

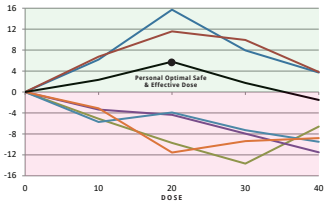


FIGURE 4: BENEFIT & HARM SCORES AS FUNCTIONS OF DELAY OF RESPONSE

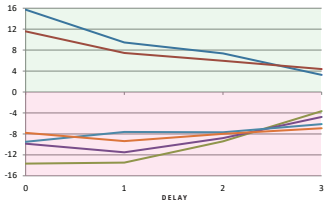
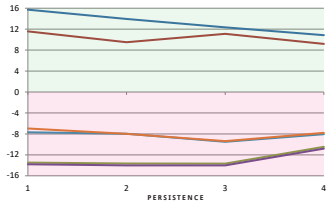


FIGURE 5: BENEFIT & HARM SCORES AS FUNCTIONS OF PERSISTENCE OF RESPONSE



FROM INDIVIDUALS TO GROUPS, SAMPLES & POPULATIONS:

Suppose 50 patients provided data, as shown in Figure 1. Test the null hypothesis of no overall safety and effectiveness with a single group, two-tailed t-test on the mean of the Overall Benefit & Harm Scores. Conclude that benefits across five doses and six response variables outweighed harms if the null hypothesis is rejected in the positive direction. Conclude that harms outweighed benefits if the null hypothesis is rejected in the negative direction.

Identify subgroups of responders by examining distributions of Benefit & Harm Scores for multimodality to identify subgroups of responders. Drill down for more detailed targeting information.

Conducting a group RCT as series of Single-Patient RCTs can:

- Vastly increase statistical power because the use of many repeated measurements provides Benefit & Harm Scores that are more reliable than baseline-to-endpoint change scores.
- Vastly increase validity because evidence for causality is assessed for each person BEFORE statistical aggregation and analysis.
- Provide Precision Quantitative Treatment Response Phenotypes needed to help identify genetic and other predictors of differential response and optimal doses.

COMPARISON:

Conventional RCTs use ONE patient to obtain ONE baseline to endpoint change score toward testing ONE primary hypothesis defined on ONE primary response variable. Contrast the scope and detail of conventional RCT results about individuals with all the results you could achieve by applying SIMA to streaming data. The ONE that should matter most is the patient.

ADVANTAGES:

Quantifying and evaluating safety and effectiveness from streaming data with SIMA offers to help:

1. Capitalize on molecular drug discovery investments;
2. Improve productivity by improving scientific reliability, validity, veracity, and reproducibility through measurement with SIMA;
3. Improve ethics of clinical practice and clinical research;
4. Integrate safety and effectiveness evaluations regarding time-dependent response variables;
5. Integrate clinical research with clinical practice;
6. Cut time requirements and costs dramatically.

CONCLUSIONS:

Clinicians and clinical trialists should measure and test the safety (harms) and effectiveness (benefits) of time-dependent treatments regarding time-dependent response variables to the extent of significant uncertainty about safety and effectiveness.

Precision medicine must assess causality for individuals, not just group-average differences. No one is average.

SIMA = Science of Individuality Measurement Algorithm

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