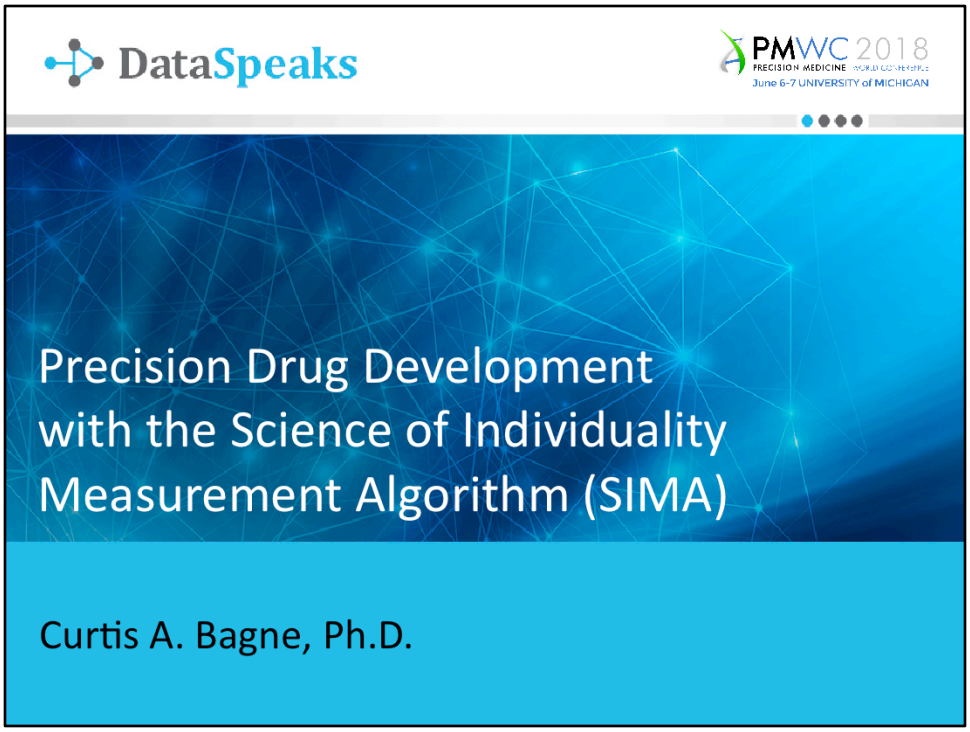



These slides were presented at https://www.pmwcintl.com/curtis-bagne-2018mich/.

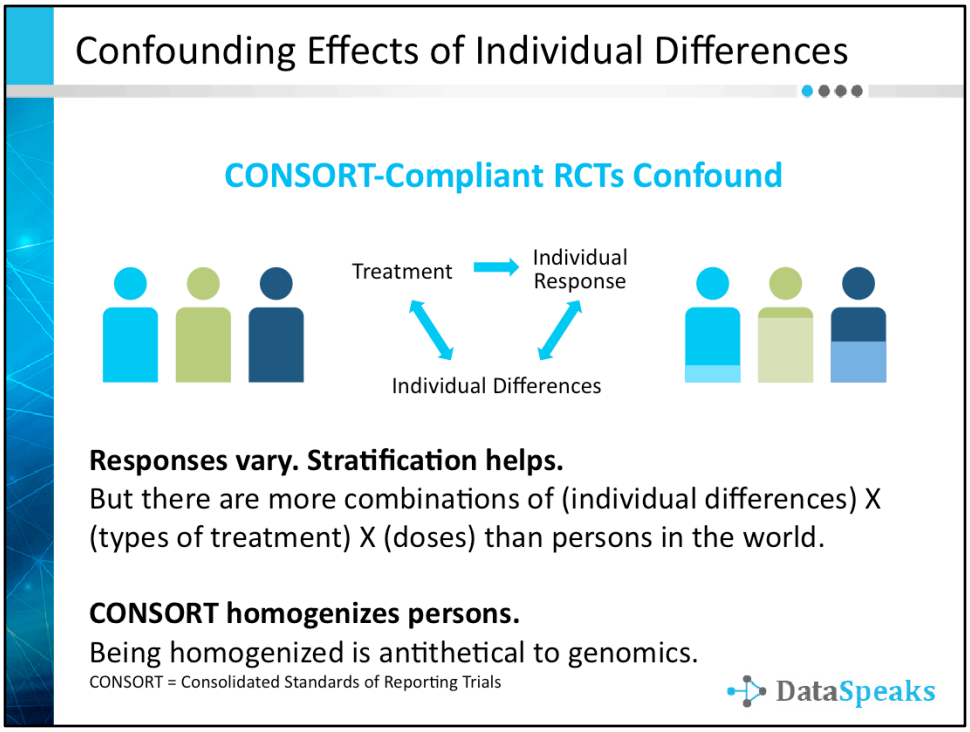
You will learn how to make drug development more scientific, precise, ethical, productive, and less costly.

Other presenters at this meeting are drivers of precision drug development. These include Lee Hood representing systems biology and P4 Medicine, Francis Collins representing modern genomics, and Eric Topol representing the science of individuality in his book, *The Creative Destruction of Medicine*.

# Motivation: Why SIMA?

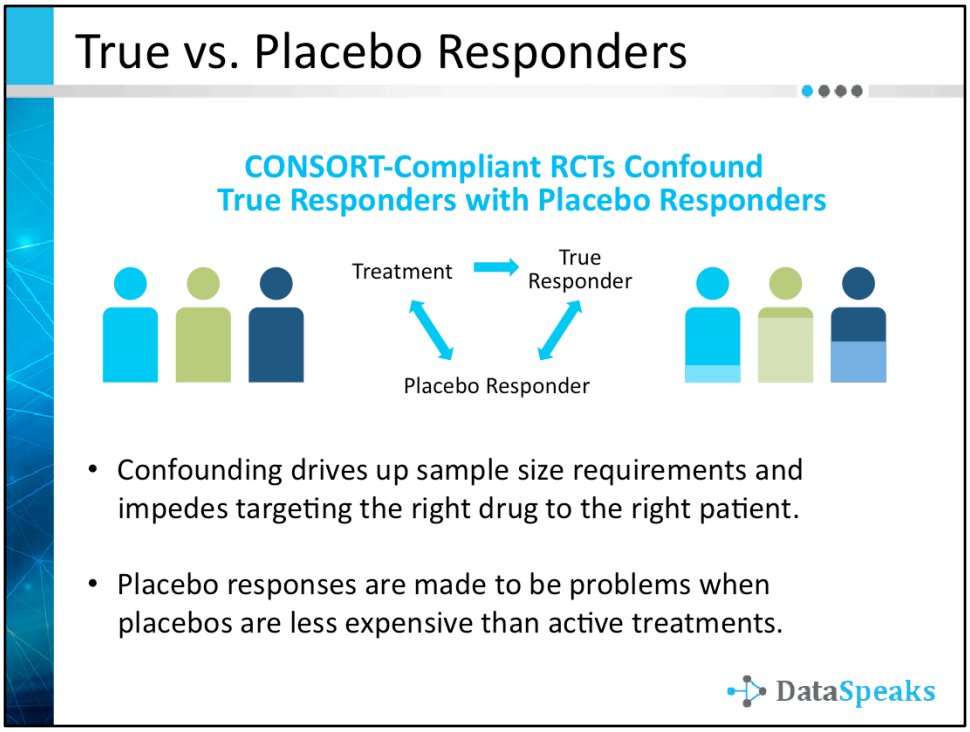
- Confounding of effects clouds distinctions crucial to precision drug development and medicine.
- Individuals respond to drugs differently.
  **SIMA measures individual responses accurately.**
- Accurate individual response measurement facilitates accurate identification of genetic predictors of differential response.

DataSpeaks




Prevailing randomized controlled trial designs, dating back to 1948, were an important scientific advance. However, RCT designs compliant to CONSORT, FDA guidelines, and PCORI Methodology Standards do have fundamental problems and limitations. Among these are confounding treatment effects with effects of individual differences, including genetic differences. Each patient could be a different **confounded mix** of active treatment and individual differences response. Genomics accentuates individual differences. Current RCT designs average them out. Homogenizing persons is antithetical to genomics.

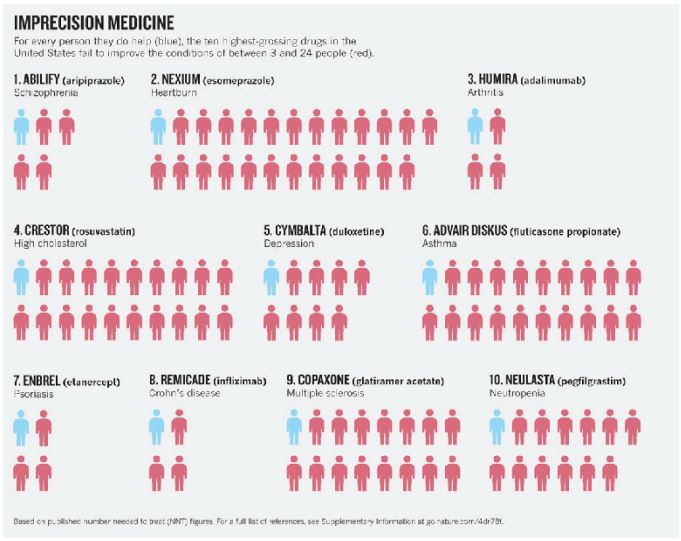
Stratification helps. However, there are more combinations of individual differences, types of treatment, and doses of treatment than there are person in the world. You will learn how to solve this problem with more randomization and SIMA.




Prevailing RCT designs also **confound true responders to active treatment with responders on active treatment that would have responded to placebo**. Each patient could be a different **confounded mix** of active treatment and placebo response.

In addition, classical-design RCTs that focus on efficacy neglect safety, preclude dose optimization for individual patients, are not well suited to account for delay and persistence of response, and do not capitalize on modern data collection and processing capabilities. You will learn how to address such problems as a set.

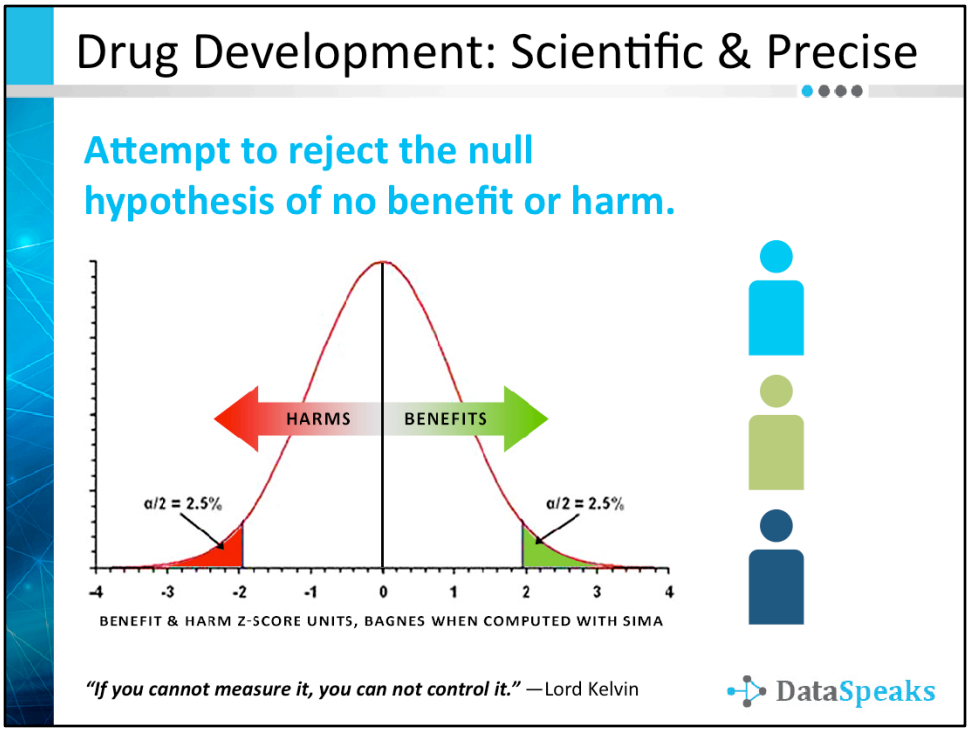
# “Imprecision Medicine” (Schork)




© https://www.nature.com/news/personalized-medicine-time-for-one-person-trials-1.17411

DataSpeaks

Confounding contributes to “imprecision medicine” as quantified by Nik Schork in *Nature*. Here are results for 10 top-grossing drugs. The blue persons are helped. The red persons are not. Imprecision drives up costs and clouds identification of genetic and other predictors of differential drug response.



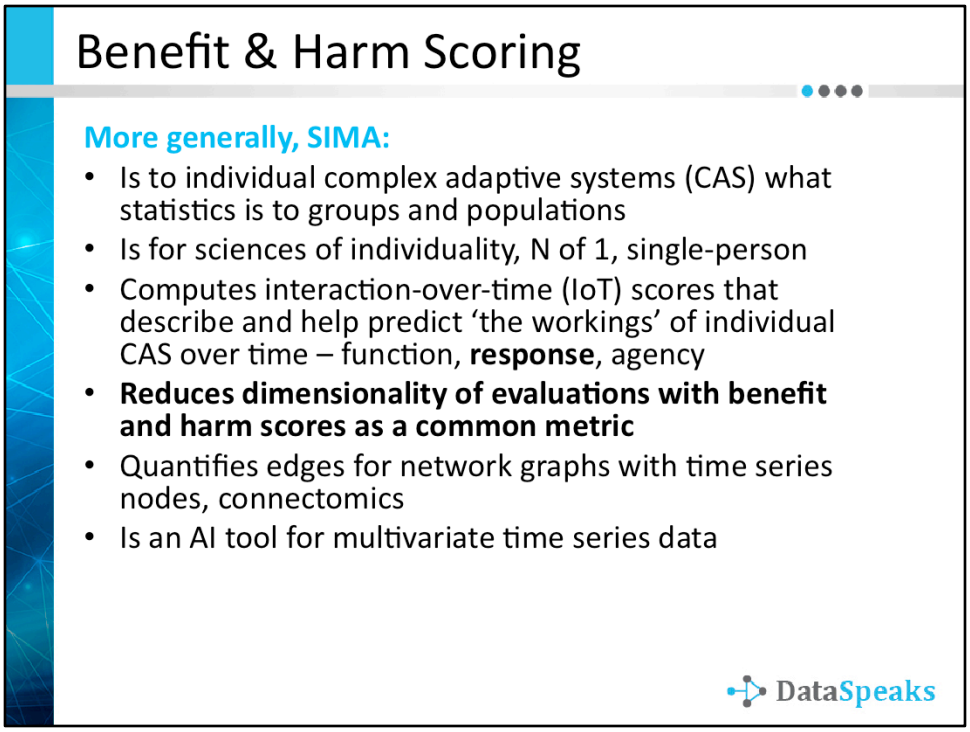

Drug development with SIMA can be simpler, more scientific, and more precise by measuring the benefits and harms of treatment. Measurement of benefit and harm **reduces the dimensionality** of treatment evaluation problems.

Randomized controlled trials can provide can provide accurate and integrated evaluations of safety and effectiveness for each person.

Rejection of the null hypothesis to the right indicates that benefits exceed harms. Rejection of the null hypothesis to the left indicates that harms exceed benefits.

In addition, SIMA provides scores that can be aggregated and analyzed statistically for population medicine.

This approach would help obviate the clinical research to clinical practice translation bottleneck.




SIMA is a tool to accelerate basic and applied sciences of complex adaptive systems.

SIMA measures interactions over time that describe and help predict how CAS work over time.

SIMA quantifies edges in network graphs when each node is a time series.

SIMA can be an AI tool.

Today I focus on measurement of benefit and harm for response.

# Demonstration

## A Single-Group, Multiple Single-Person Precision RCT

| PATIENT VARIBLE | WEEK 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | IoT Score | Toward or Untoward Direction | Bagne Z-score units | Weight | Overall Benefit Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pair 1 | | | | Pair 2 | | | | Pair 3 | | | | Pair 4 | | | | | | | | |
| | Period | | | | Period | | | | Period | | | | Period | | | | | | | | |
| | 1 | | 2 | | 1 | | 2 | | 1 | | 2 | | 1 | | 2 | | | | | | |
| **PERSON 1** | | | | | | | | | | | | | | | | | | | | | |
| Dose | 20 | 20 | 40 | 40 | 0 | 0 | 40 | 40 | 40 | 40 | 20 | 20 | 80 | 80 | 40 | 40 | | | | | |
| DBP | 96 | 98 | 85 | 81 | 91 | 96 | 84 | 87 | 80 | 78 | 93 | 98 | 82 | 77 | 81 | 78 | -8.92 | - | 8.92 | 4 | 4.64 |
| ED | 3 | 2 | 2 | 3 | 2 | 1 | 2 | 1 | 3 | 2 | 1 | 2 | 3 | 2 | 2 | 2 | 0.74 | - | -0.74 | 2 | |
| Energy | 4 | 3 | 4 | 5 | 4 | 3 | 4 | 3 | 2 | 4 | 3 | 3 | 4 | 4 | 2 | 3 | 1.46 | + | 1.46 | 2 | |
| **PERSON 2** | | | | | | | | | | | | | | | | | | | | | |
| Dose | 0 | 0 | 20 | 20 | 40 | 40 | 0 | 0 | 20 | 20 | 80 | 80 | 80 | 80 | 40 | 40 | | | | | |
| DBP | 98 | 91 | 89 | 88 | 89 | 84 | 96 | 98 | 89 | 93 | 86 | 86 | 76 | 75 | 86 | 92 | -9.16 | - | 9.16 | 4 | 6.67 |
| ED | 2 | 1 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 3 | 2 | 4 | 4 | 3 | 4 | 2 | 5.93 | + | 5.93 | 1 | |
| Energy | 2 | 3 | 2 | 2 | 3 | 1 | 2 | 3 | 2 | 2 | 3 | 3 | 4 | 3 | 2 | 3 | 3.05 | + | 3.05 | 2 | |
| **PERSON 3** | | | | | | | | | | | | | | | | | | | | | |
| Dose | 40 | 40 | 20 | 20 | 0 | 0 | 80 | 80 | 20 | 20 | 40 | 40 | 20 | 20 | 80 | 80 | | | | | |
| DBP | 76 | 79 | 74 | 80 | 88 | 90 | 78 | 68 | 75 | 77 | 81 | 78 | 73 | 79 | 76 | 82 | -7.81 | - | 7.81 | 4 | 4.11 |
| ED | 1 | 3 | 2 | 2 | 1 | 1 | 2 | 4 | 2 | 2 | 2 | 1 | 3 | 2 | 3 | 5 | 3.93 | - | -3.93 | 1 | |
| Energy | 4 | 3 | 2 | 2 | 3 | 4 | 3 | 2 | 5 | 3 | 4 | 3 | 4 | 4 | 1 | 2 | -2.67 | + | -2.67 | 1 | |
| GROUP AVERAGE | | | | | | | | | | | | | | | | | | | | | 5.14 t=6.59 p=0.0223 |

**DBP** = Diastolic Blood Pressure **ED** = Erectile Dysfunction

DataSpeaks

This is a set of three single-person RCTs that use the same type of drug, the same set of four doses including placebo, and the same three response variables. These are mock data for a 16 week trial with 4 pairs of 2-week periods.

Four doses, including placebo as zero-dose, were randomized over time for each of three patients. **Within-person randomization of doses eliminates both types of confounding shown before**. CONSORT-compliant RCTs do not randomize enough. See that **dose is investigated as a time-dependent dimensional variable**, NOT a categorical variable.

This small-scale example has only three response variables. Ideally, use enough safety and effectiveness response variables to obtain comprehensive evaluations of safety and effectiveness.

These Interaction-over-Time scores, computed by SIMA, quantify the **amount of evidence for interactions over time**. Positive IoT scores quantify higher doses with higher response variable levels. Negative IoT scores quantify higher doses with lower response variable levels.

Users set toward and untoward direction in accord with clinical significance and patient preferences. Here higher blood pressure is untoward.

Here are the nine benefit and harm scores in bagne z-score units, three for each patient.

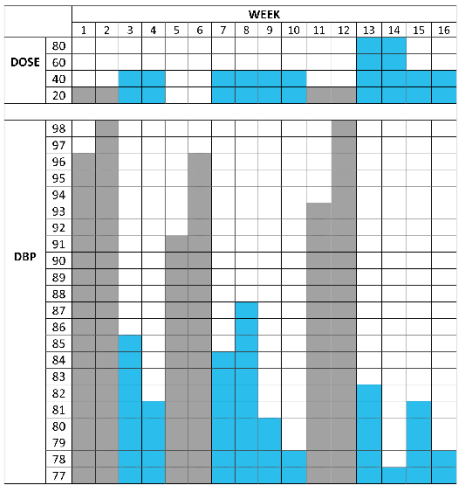
Weights also are set in terms of clinical significance and patient preferences.

Overall Benefit and Harm Scores are weighted averages for individual persons.



Now comes statistics after SIMA. The null hypothesis of no overall benefit and harm was rejected in the positive or beneficial direction with a two-tailed t-test on mean overall benefit and harm score.

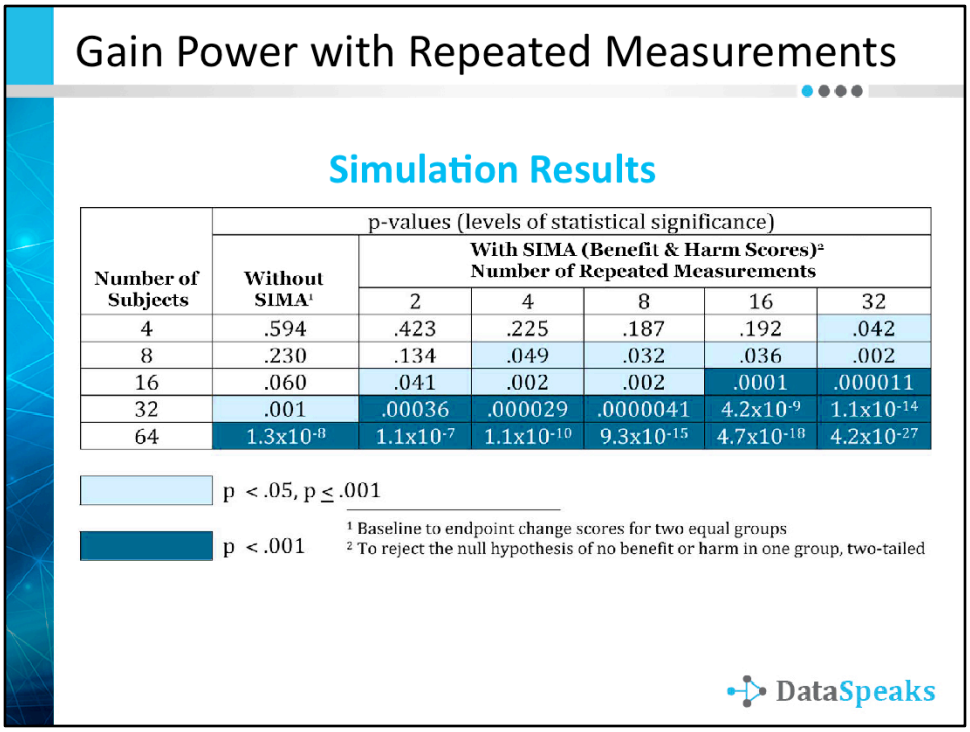
# Behind a Bagne of 8.92




- DBP never was higher than 87 when dose was 40+
- DBP never was lower than 91 when dose was < 40
- The probability of this happening by chance alone is small and yields a benefit score of 8.92 bagnes

DataSpeaks

This illustrates the amount of evidence quantified for a benefit score with a value of 8.92 bagne z-score units.

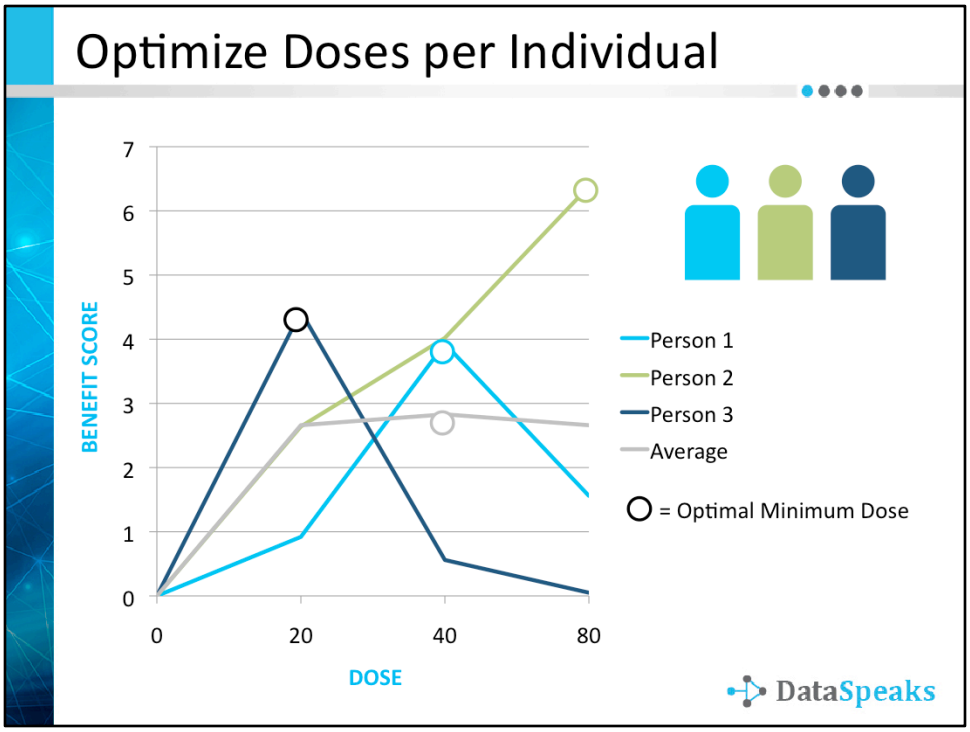



This is from a computer simulation that processed different portions of a dataset created by adding white noise – random normal deviates – to a given signal. Half of the repeated measurements were on treatment and half off.

See how significance levels increase with the number of subjects as expected using change scores and without SIMA.

Also see how significance levels increase with number of repeated measurements and SIMA.

Using more repeats is better when one wants to avoid confounding the effects of individual differences with treatment effects, when more repeats are less expensive than more subjects, and for rare disorders. More disorders are becoming rare as diagnostic specificity increases. The current version of SIMA software can process up to 500 repeated measurements.

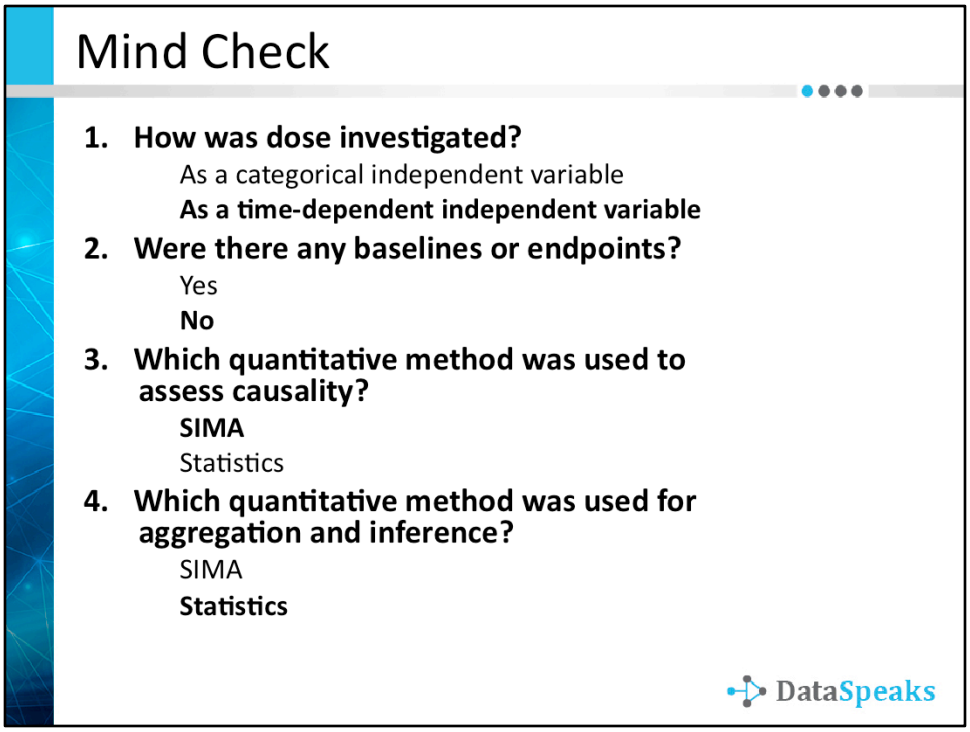



This shows how you could drill down from the statistically significant demonstration result to identify the optimal minimum dose across response variables for each person.

SIMA enables randomized titration to optimal dose for each person.

See how these optimal minimum doses are 40, 80, and 20 for persons 1, 2, and 3 respectively.

See how the group-average result clouds the person-specific results.

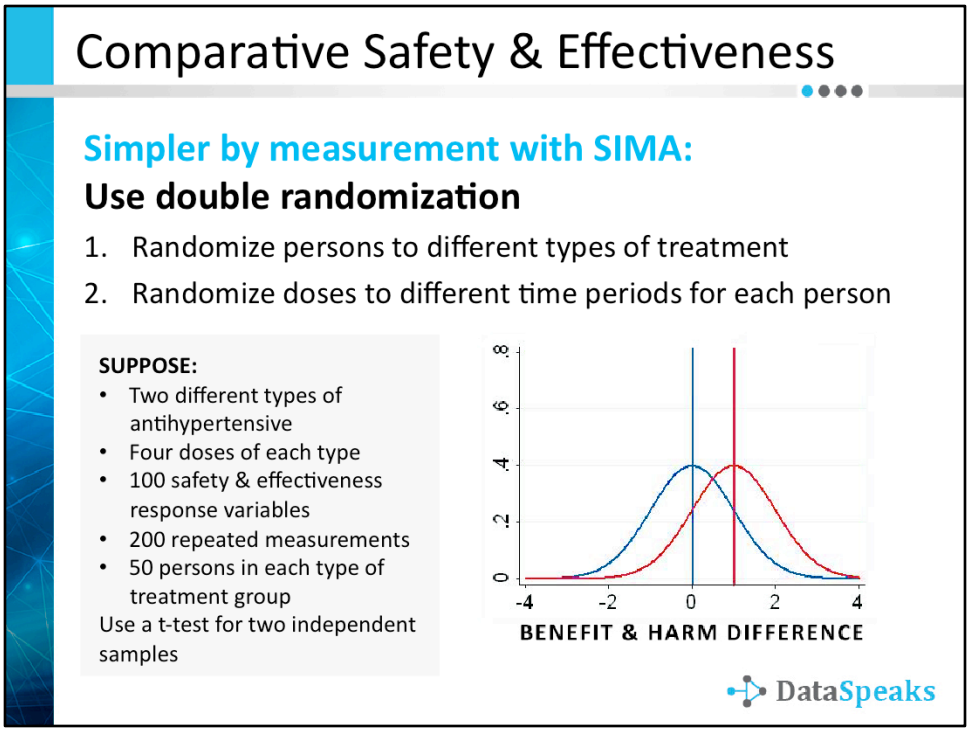



The correct answers are in bold.

This helps show how SIMA and statistics are two distinct and often complementary methods that do apply to different types of data and do different things.

Precision drug development and medicine need both quantitative methods.

Death is a real endpoint. Blood pressure is not. CONSORT-compliant RCTs often also confound real endpoints with artificial endpoints.

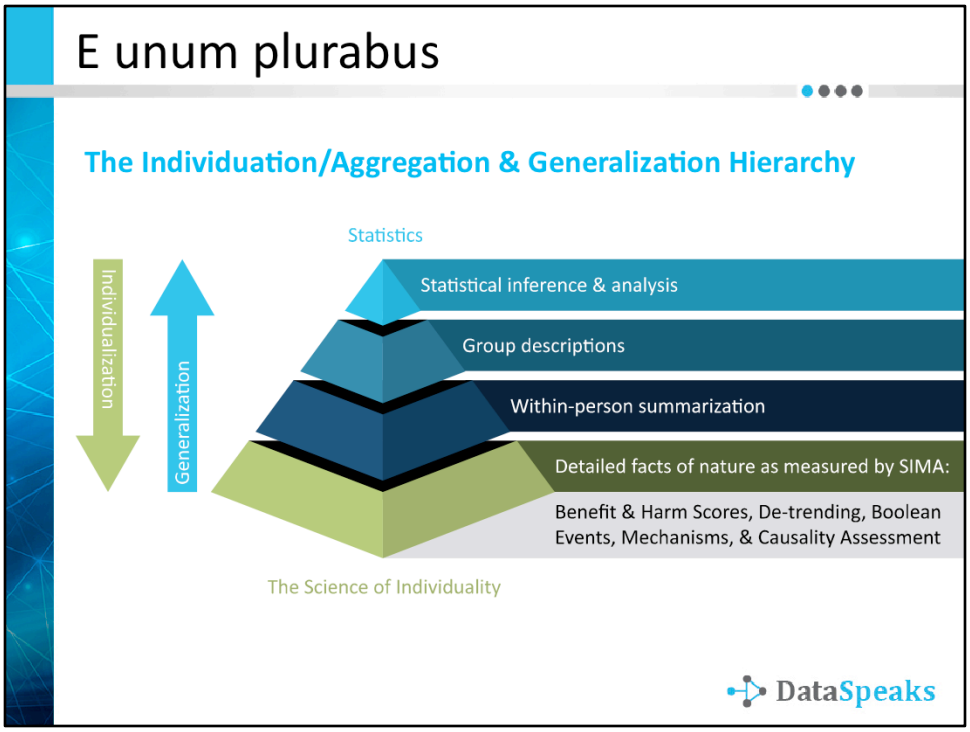



SIMA helps enable truly patient-centered **comparative safety AND effectiveness research**.

Increasing numbers of drugs mean that more treatments need to be compared.

Follow this with a single-sample t-test for each type of treatment to see if either treatment is beneficial or harmful.

SIMA can greatly simplify statistical analyses.




Our national motto is *E pluribus unum* – Out of many, one. This slide is about establishing the science of individuality, *E unum pluribus* and a two-way street between individuals (SIMA) and populations (statistics).

You've already seen how the 3-person demonstration yielded a statistically significant result. That represents generalization at the top of the pyramid.

You saw the group average overall benefit and harm score, the second level down.

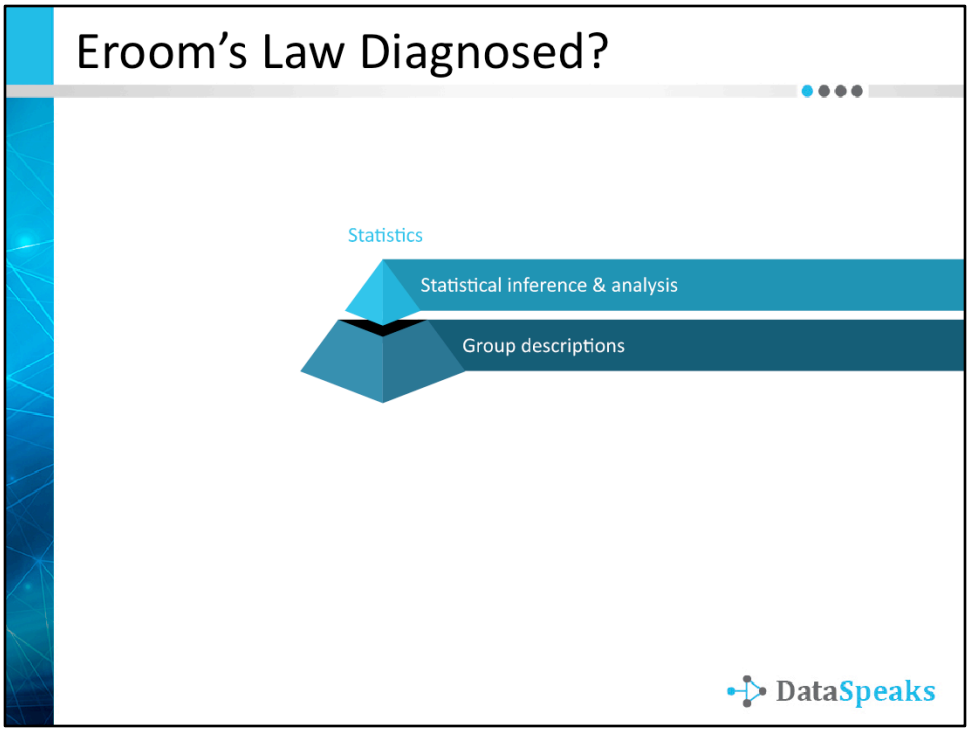
You also saw how SIMA quantified overall benefit and harm as nonlinear functions of dose for each person from the response variable specific dose-response relationships. This represents within-person summarization. These were differentially weighted and averaged for the group of three persons – the second level down.

You saw the response-variable-specific benefit and harm scores for each person. Such detailed results illustrate the science of individuality.

In addition, SIMA can quantify benefit and harm as nonlinear functions of response variable level, delay and persistence of response, etc. SIMA can use de-trending to distinguish treatment effects for disease progression and spontaneous recovery. SIMA can use Boolean independent events for drug-drug interactions and drug cocktails. SIMA can use Boolean dependent events for syndromes such as metabolic syndrome and depression. SIMA can quantify mechanisms of disease and treatment effect. SIMA can help quantify evidence for causality within persons or other individuals.

This approach has potential to accelerate both highly patient-centric precision medicine and population medicine.

This approach can help obviate the clinical research to clinical practice translation problem with both drugs and services.



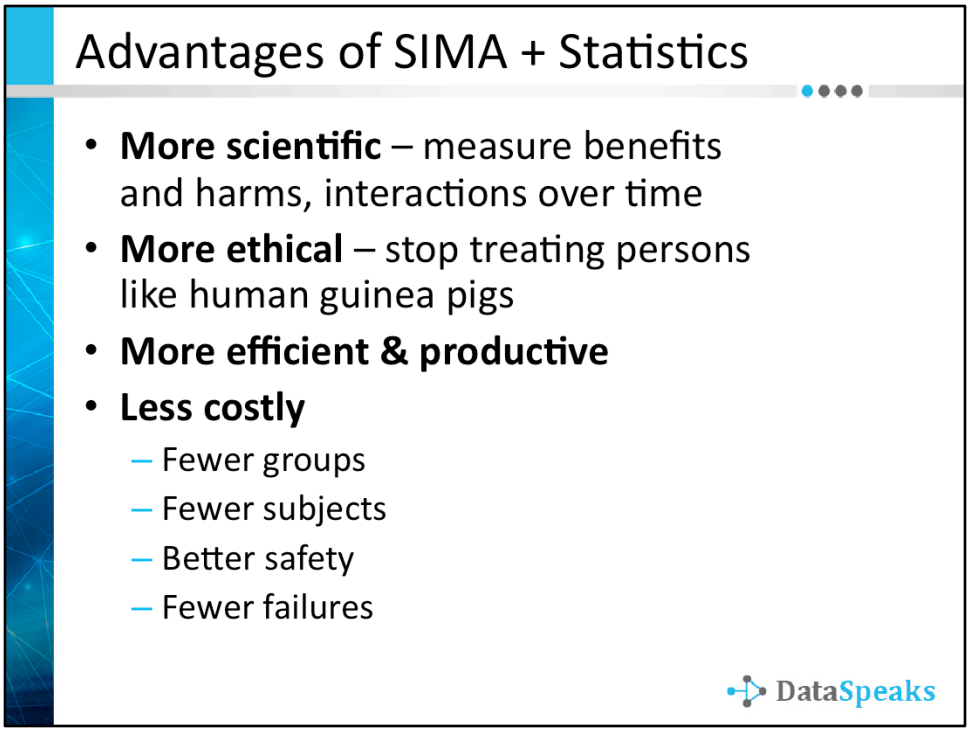

Eroom's law states that pharmaceutical industry productivity halved about every 9 ½ years in inflation-adjusted $ despite all the intervening scientific and technical advances.

Could it be that the regulatory science gateway is bottlenecked by clinical trials that use categorical independent variables and group averages at endpoints?

Might we need to know individuals well through the science of individuality before we can classify them well?

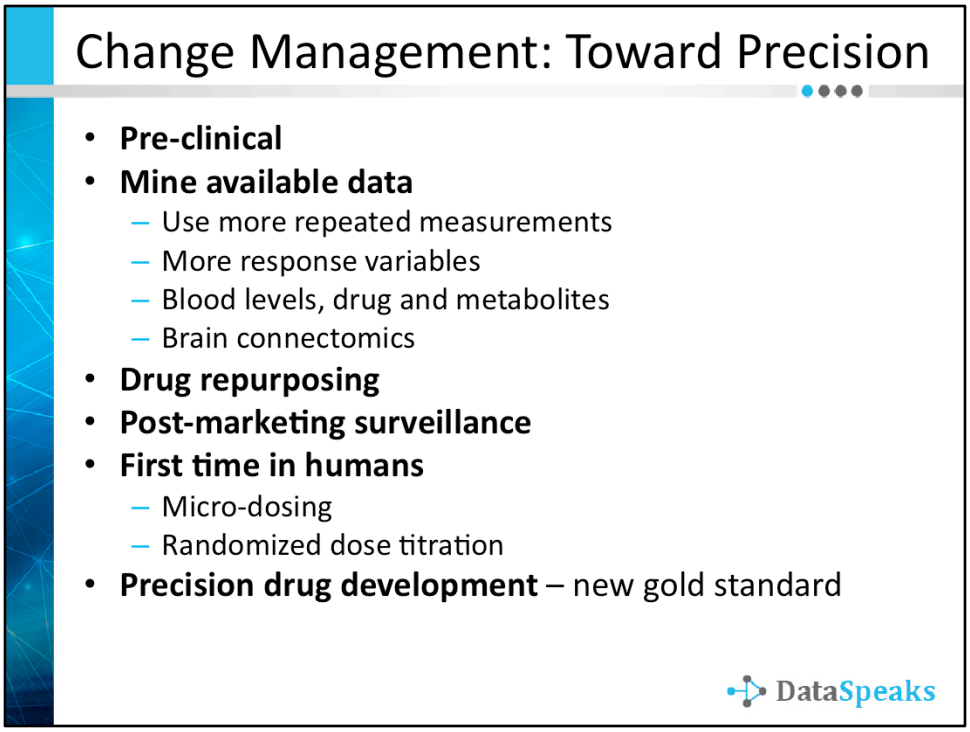
Clinicians treat individuals. Might the science of individuality, enabled by applying SIMA to multivariate time series data, be the heretofore **missing foundation** for much of evidence-based precision drug development and medicine?

Might this approach help reverse Eroom's law?

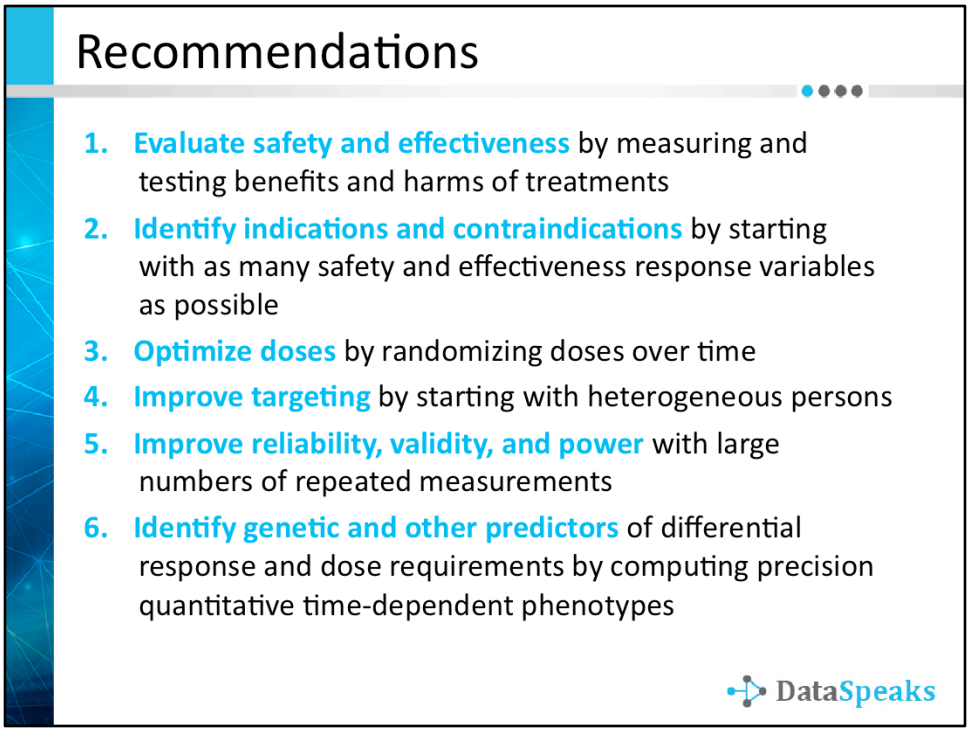



You saw, albeit with mock data, how it might be possible to achieve statistically significant results in randomized single-group RCTs with small numbers of persons.

Might it be possible to largely end clinical drug safety problems?




There are many ways to help validate SIMA on the way to precision drug development.




With SIMA, drug development becomes more like using a funnel large end up. SIMA helps provide information needed to target the right drug at the right dose to the right person.

## Phenomics Impedes Applied Genomics

- **Genetic nails**
  - Hundreds of millions of single-nucleotide polymorphisms alone
  - Many more combinations
- **Phenomic jelly**
  - ICD
  - DSM
  - Confounded responder, non-responder
- Applied genomics is too much like trying to nail phenomic jelly to a wall with genetic nails

DataSpeaks

Genomics is miles ahead of phenomics. Whole genome sequencing is becoming feasible for many. However, we are still using outmoded disease classifications and confounded categories of responder and non-responder.

This problem can be likened to trying to nail phenomic jelly to a wall with genetic nails.

# Accelerate Applied Genomics

**Apply SIMA to compute precision quantitative time dependent phenotypes for chronic disorders, e.g.**

- Hippocampal connectivity is time-dependent
- Hippocampal volume is static and timeless

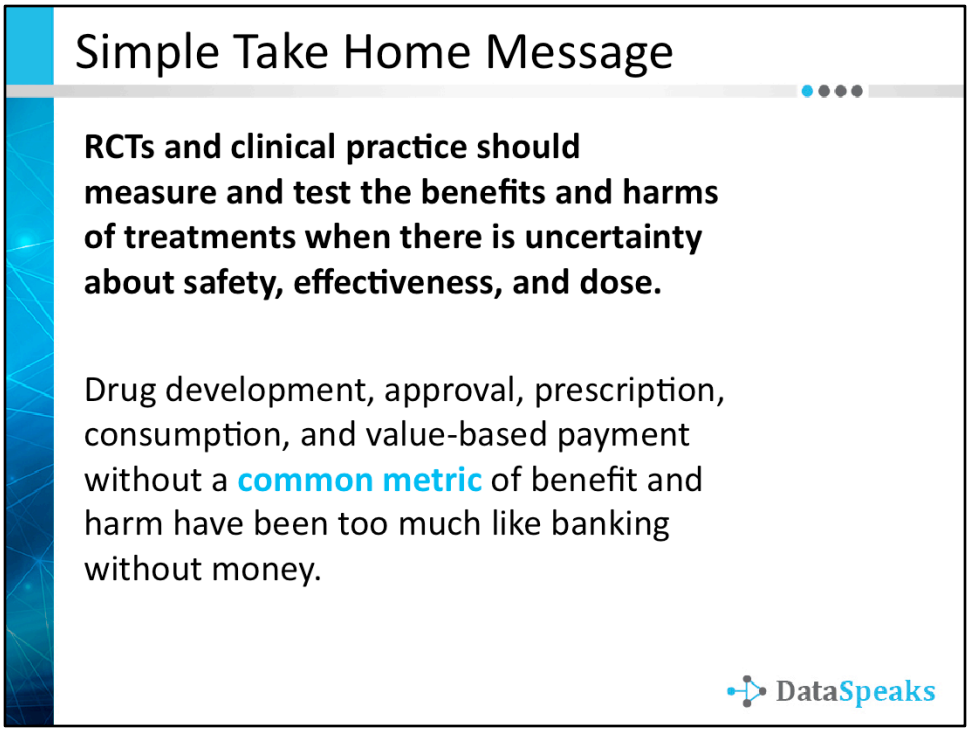
- **Diagnostic phenotypes:** Objective, reliable, specific, mechanistic, actionable
- **Treatment response phenotypes:** Reliable, valid, comprehensive of many treatment effects, detailed
- **Agency phenotypes:** everyone is an agent

Phenotype 1, Phenotype 2, Phenotype 3

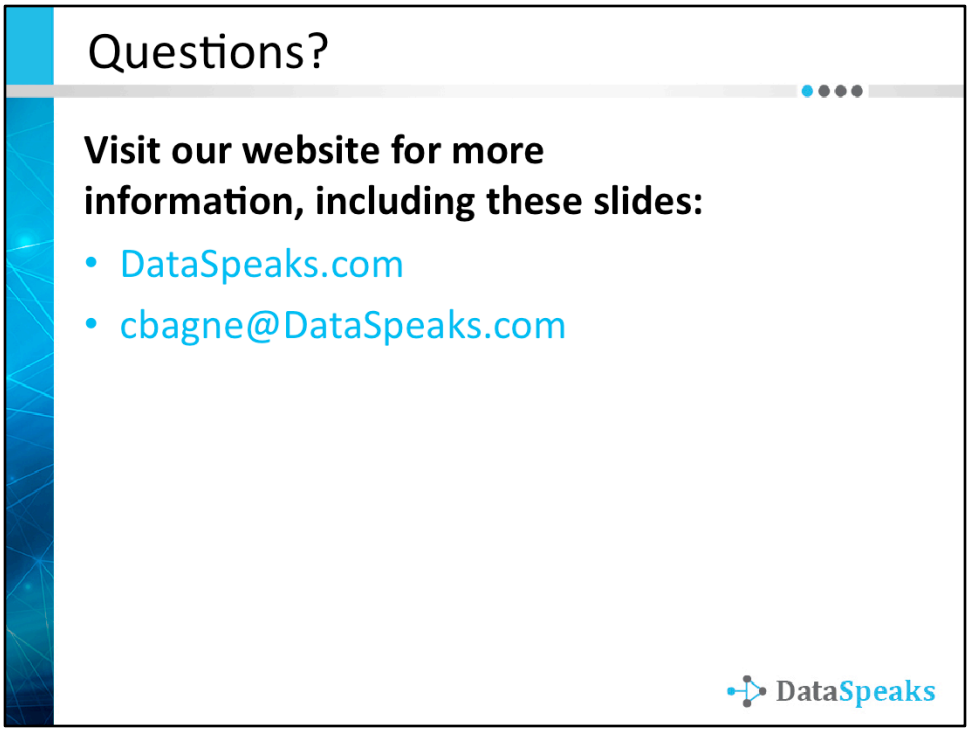
DataSpeaks

This slide emphasizes mechanisms. Mechanisms and response take time. SIMA computes time-dependent mechanism-specific phenotypes from multivariate time series data.

These three categories – diagnostic, treatment response, and agency – are distinguished by how time series internal or external to the individual are selected to operate as independent and dependent variables when applying SIMA.




Measurement of benefits and harms is needed whenever there is uncertainty about benefits, harms, and doses.




DataSpeaks is dedicated to accelerating precision drug development and medicine for everyone.