

# Precision Science for Precision Medicine

Curtis A. Bagne, PhD

Measure to know.

Measure to manage.

Measure for precision science as for precision medicine.

Now you will learn about a measurement-by-computation toolkit that quantifies time-dependent phenomena that bring molecules to life.

Time dependent phenomena such as function, response, and mechanisms are quantified with interaction-over-time scores computed from longitudinal data about two or more time-dependent variables.

Archimedes has been said to have jumped from his bath shouting “Eureka!” upon realizing that density could be ‘computed’ as weight per unit volume of displaced water. A new category of computed measurements will make science and medicine more precise. Eureka for precision medicine.



# “Imprecision Medicine” (Schork)

## IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

### 1. ABILIFY (aripiprazole) Schizophrenia



### 2. NEXIUM (esomeprazole) Heartburn



### 3. HUMIRA (adalimumab) Arthritis



### 4. CRESTOR (rosuvastatin) High cholesterol



### 5. CYMBALTA (duloxetine) Depression



### 6. ADVAIR DISKUS (fluticasone propionate) Asthma



### 7. ENBREL (etanercept) Psoriasis



### 8. REMICADE (infliximab) Crohn's disease



### 9. COPAXONE (glatiramer acetate) Multiple sclerosis



### 10. NEULASTA (pegfilgrastim) Neutropenia



Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at [go.nature.com/4dr78f](http://go.nature.com/4dr78f).

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

DataSpeaks—From Genomes to Health™

2

Schork quantified “imprecision medicine” for 10 top-selling drugs. Blue patients are helped. Red patients are not.

We must do better.



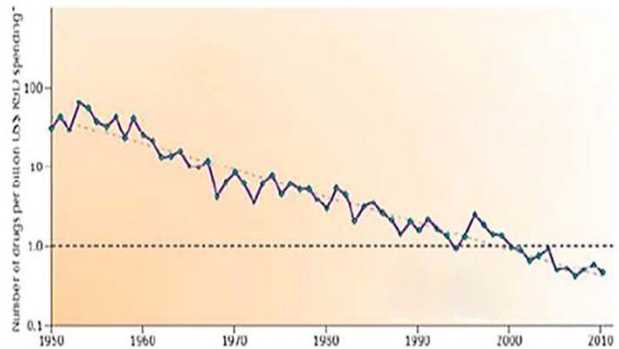
# Imprecision Stifles Productivity

## Eroom's Law:

Number of New  
Drug Approvals Per  
Billion US Dollars  
Halved Every Nine Years

DataSpeaks—From Genomes to Health™

a Overall trend in R&D efficiency (inflation-adjusted)



Adapted from: Nature Reviews – Drug Discovery; Diagnosing the decline in pharmaceutical R&D efficiency Vol 11, March 2012, page 191 - 200

3

Six decades of scientific and technical advancements. Six decades of declining productivity.

The authors quantified Eroom's law. Have we had an actionable diagnosis?

Imprecision resulting from not adequately measuring time-dependent phenomena appears to be a major cause of Eroom's law.



# Costs of Imprecision



Morbidity  
Mortality  
Monetary  
Legal liability  
Lost opportunity



Truthfulness to nature  
Pharma reputation  
Respect for  
biomedical science

With imprecision, bad things are high and good things are much lower than they need to be.

Time-dependent phenomena are facts of nature that do need to be measured for science to be true.

Poor reputation and low respect impair clinical trial recruitment. There is a human guinea pig problem.





Imprecision Biomedical Science



“Imprecision Medicine”

Medicine is imprecise because biomedical science is imprecise.



# Two Ways for Data to be Big

## 1. Cross-Sectional Data about Groups – Data Snapshots

### Examples – Big N Science:

- 1,000,000 sequenced persons
- Census

N = number of subjects

## 2. Time-Series Data about Individuals – Data Movies

### Examples – Big N of 1 Science:

- Streaming data (e.g., intensive care monitoring)
- Functional brain imaging
  - 500,000 voxel-specific time series
  - Every 2 seconds for hours

DataSpeaks—From Genomes to Health™

6

To gain precision, start by distinguishing two different types of data.

Data snapshots include baseline to endpoint change scores.

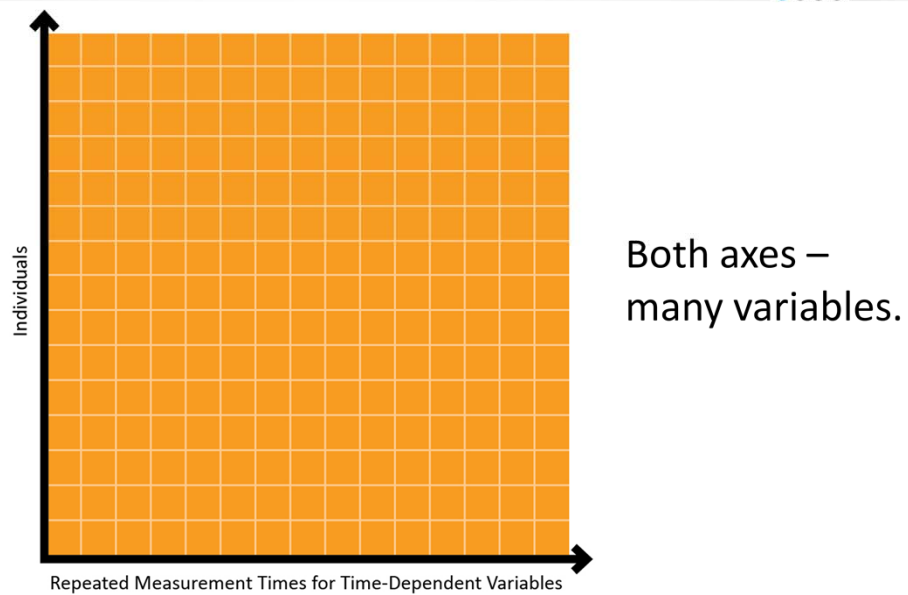
Data movies help capture time-dependent phenomena.

Knowing and managing Earth's biosphere as a whole is an important big N of 1 science opportunity. There is no group to average.

Many people value their individual differences.



# Amount of Data Is Only Multiplicative



7

Big N science is based primarily on just one column – many individuals.

Big N of 1 science is based primarily on just one row – many repeated measurements.

Being able to use both types of data and science effectively starts by offering a multiplicative advantage.

However, the advantage of being able to use both types of data and science together is far more than multiplicative.





Precision, veracity, insight, and value  
gained can be >> than multiplicative...  
**with the right data processing methods.**



# The Big Gap in Data Processing Methods

**Cross-sectional Data**  
**Statistics is the**  
**method of choice**



DataSpeaks—From Genomes to Health™

## **Multivariate Time Series**

(two or more repeated  
measurements of two or more  
time-dependent variables)

## **What is the method of choice?**

The Science of Individuality  
Algorithm (SIMA) from DataSpeaks

Statistics based on groups, samples, and populations is a dominate data processing method for biomedical science. However, statistics is of limited value for multivariate time series and N of 1 science.

Limitations of established methods to process multivariate time series are represented by the fact that statistical measures of correlation often are used as to quantify brain functional connectivity even though brains exhibit nonlinear relationships and repeated measurements are not independent. This violates assumptions upon which correlation coefficients are based.

SIMA enables the science of individuality as presented in Chapter 11 of Eric Topol's book, *The Creative Destruction of Medicine*.





SIMA quantifies time-dependent phenomena with Interaction-over-Time (IoT) scores computed from data about time-dependent variables.

IoT scores are in standard deviation units –  
bagnes when computed with SIMA.

I use the name bagne to emphasize that IoT scores are offered as a unit of measurement.

Bagnes have meaningful values of 0 that indicate no evidence for an interaction over time.

Positive bagnes indicate higher with higher.

Negative bagnes indicate higher with lower.



# Different Data, Different Methods

## Statistics

1. Groups, samples, populations
2. Categorical independent variables (IVs)
3. Subjects randomized to groups
4. Independent measurements
5. Analog, uses models
6. Gains power and significance from more subjects
7. Only group average results
8. Group average results are not precise for anyone

## SIMA

1. Individual complex adaptive systems (CAS)
2. Time-dependent IVs
3. Doses randomized to time periods
4. Repeats serially dependent
5. Digital, model free
6. Gains power and significance with more repeated measurements
7. Results only for individual CAS
8. Precise results for each individual

DataSpeaks—From Genomes to Health™

11

SIMA helps investigate individual persons as the complex adaptive systems that they really are.

SIMA is digital in a way that statistics is not. Statistics is like film. Key capabilities of SIMA derive from the fact that it is more like digital photography. SIMA enables truly digital medicine starting at the level of each person.



# SIMA and Statistics

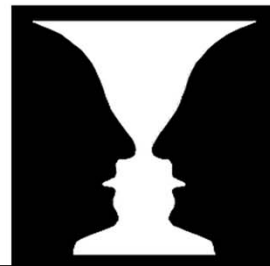
## Distinct and Complementary Disciplines

**Do the science of individuality with SIMA  
before using statistics to:**

- Aggregate
- Describe and compare groups
- Make inferences from samples to populations
- Identify genetic predictors of disease susceptibility and differential response and dose requirements

**Complementarity:**

- SIMA for individuals
- Statistics for groups and populations



DataSpeaks—From Genomes to Health™

12

You will understand my proposal well when you can distinguish SIMA and statistics as easily as well as you can distinguish one vase from two faces – and shift between the two at will.

The key to my proposal is to collect more multivariate time series processed with SIMA before using statistics.



# SIMA from Different Perspectives

## SIMA:

- Is to individual CAS what statistics is to groups and populations.
- Quantifies edges for time series nodes, internal & external.
- Is a common metric to quantify safety & effectiveness.
- Quantifies value – benefit & harm.
- Is a machine learning tool.
- Quantifies effects of time-dependent inputs on time-dependent outputs (e.g., soft sensors).
- Quantifies network signaling and distinguishes it from noise.
- Quantifies the chronnectome – time-dependent functional connectivity.

DataSpeaks—From Genomes to Health™

13

Here are some different perspectives on SIMA for audience members with different backgrounds.

For those into network graphs, SIMA quantifies edges when two or more nodes are time series.

For those who care about value, SIMA is a common metric of value much as money is a common metric of cost.

SIMA is a machine learning tool to the extent that the internet of things collects time-ordered data.

SIMA is probabilistic in a way that can help distinguish signaling from noise.

The chronnectome is a powerful way to understand brains. Brains epitomize complex adaptive systems.





Models and artificial intelligence do  
*not* substitute for measurement.

SIMA can inform model development  
and add power to AI.

Which would you prefer – to measure reality or model what might or might not be true?

SIMA offers new measures to model.



## Inadequately Measured Time-Dependent Phenomena

- Function, **response**, and agency (how systems work)
- Safety and effectiveness for time-dependent response variables – benefit and harm scores
- Delay and persistence of response, episodes of events
- Evidence for causality and predictive power
- Mechanisms
  - **Disease**
  - **Treatment effect**
  - **Up and down regulation**
- Adaptation (e.g., tolerance, sensitization, dependence)
- Time-dependent emergent properties
- Coordinated action (e.g., molecular, brain activity, motor)
- Time-dependent phenotypes

DataSpeaks—From Genomes to Health™

15

Function is when all variables are about the individual as to diagnose disorders. Response is about how an individual responds to its environment. Agency is how an individual acts on its environment.

Part of my presentation focuses on response as in evaluating safety and effectiveness in clinical trials.

SIMA can help quantify all these phenomena with explicitly demonstrable capabilities validated by ground truth detection.



# SIMA Accelerates Systems Science

“Systems biology is the comprehensive and quantitative analysis of the interactions between all of the components of biological systems over time.”

**SOURCE:** <https://www.ncbi.nlm.nih.gov/pubmed/19120490/>

**SIMA quantifies interactions over time.**

DataSpeaks—From Genomes to Health™

16

This definition, presented in the context of immunology, is from the Institute for Systems Biology. Lee Hood has inspired for my work.



# High-Veracity Biomedical Science

High veracity biomedical science would **measure** time-dependent phenomena.

Time-dependent phenomena distinguish living systems from dead bodies.

1,000,000 genomes will not distinguish being alive from being dead.

Disorders and diseases are more subtle.

Genotypes need phenotypes of comparable quality.

DataSpeaks—From Genomes to Health™

17

High-veracity science is considered to be true to facts of nature.

Genotypes need phenotypes of comparable quality to be of much value for research and practice.

The value of GWAS is being challenged. The problem appears to be due to low quality phenotypes that are not mechanism specific.

Now genotype-phenotype mapping is too much like trying to nail phenomic jelly to a wall with genetic nails.

Use SIMA to compute high quality time-dependent phenotypes. And so the trademark: "From Genomes to Health."



# High-Veracity Biomedical Science

- More generally, accounts for **facts of nature** with precise measurement
  - Individuality (individual differences)
  - Time-dependent phenomena
  - Inherent stochasticity
  - Cross-level integration (e.g., molecular plus physiological, psychological, social)
  - Personhood (e.g., personalized & P4 medicine)
- Distinguishes facts of nature from noise
- Improves ethics – persons, not human guinea pigs

DataSpeaks—From Genomes to Health™

18

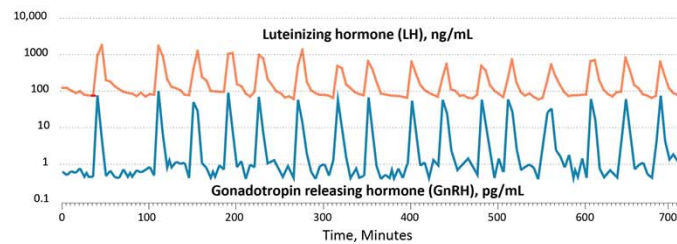
Inherent stochasticity becomes a factor as when there are only a few molecules to interact within a single cell.

Medicine is more than molecular. SIMA also helps integrate and account for physiological, psychological, and social levels of investigation – molecules AND patient-reported outcomes.

Weak methodology yields weak results that can be hard to reproduce. Weak methodology contributes to what some have called a reproducibility crisis in science – especially for sciences of complex adaptive systems.

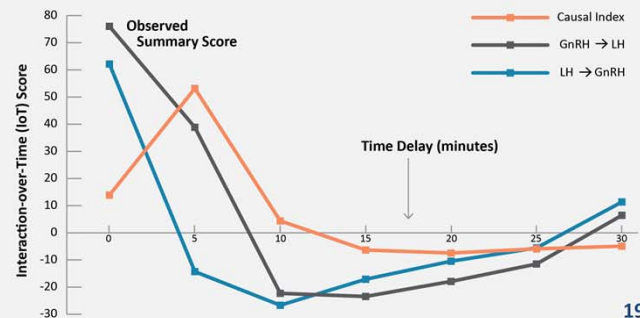


# Validation: SIMA Quantifies Known IoT



## SIMA Scoring Protocol & Summary Result

- IoTs were scored for both GnRH → LH and LH → GnRH with a 4-dimensional array of 4,032 (12x12x7x4) bagnes.
  - 12 levels of *both* GnRH & LH
  - 7 levels of delay of response, 0 to 6
  - 4 levels of persistence, 1 to 4
- Summary IoT score = 76.028 bagnes,
- SIMA significance << .001



19

These data – 143 repeated measurements of two hormones every five minutes in a female sheep – exemplify a time-dependent mechanism of function that can be up- or down-regulated by treatment. GnRH increases levels of LH.

Interactions over time were scored with a four-dimensional array of standardized IoT scores that includes delay and persistence of response.

The IoT score graph provides very strong evidence that higher levels of GnRH cause higher levels of LH and not vice versa. The IoT score at a 5-minute delay is much larger for GnRH to LH compared to LH to GnRH – causes before effects.

Once mechanisms are quantified with SIMA, it becomes easy to quantify how treatments such as GnRH agonists or antagonists might up- or down-regulate function to quantify mechanisms of treatment effect.



## SIMA Simplifies Statistical Analysis: **Clinical Trial Example**

- **Single-group RCT with:**
  - 50 persons
  - Four doses including placebo randomized to time periods for each person
  - Monitor 100 differentially weighted safety and effectiveness response variables (RV)
  - 56 repeated measurements
- **Single-group t-test** on mean overall benefit and harm score from SIMA
  - Rejection in + direction, drug preponderantly beneficial
  - Rejection in - direction, drug preponderantly harmful
- **Drill down – next slide**

DataSpeaks—From Genomes to Health™

20

Anyone who does not love doing complex statistics might appreciate this example.

This is a single-group randomized controlled trial. Causality is assessed for each person BEFORE any statistical analysis.

Measuring and testing overall benefit and harm scores eliminates the multiple-testing problem while evaluating safety and effectiveness regarding time-dependent treatment and response variables.

Many repeated measurements provide high power to achieve significance when there is a real treatment effect.



# Drill-Down Capabilities, RCTs

## Results for each person

- SIMA significance
  - Overall benefit and harm
  - RV specific
- RV specific and overall benefit and harm as nonlinear functions of:
  - Dose
  - RV level
  - Delay of response
  - Persistence of response

## Group average results

RV specific and overall benefit and harm as nonlinear functions of:

- Dose
- RV level
- Delay of response
- Persistence of response

**SIMA: An ethical imperative?**

21

Combined use of SIMA and statistics opens a two-way street between individuals and populations, between clinical research and clinical practice.

SIMA's drill-down capabilities help enable medicine to be truly person-centric.



## Decision Time for Drug Developers, Regulators, & Providers

- Statistics without SIMA – **Legacy RCT Designs** with:
    - “Imprecision Medicine”
    - Eroom’s law
    - Costs of imprecision
  - Try SIMA before Statistics – **Precision RCT Designs**
  - Integrate:
    - Comprehensive safety and effectiveness evaluations with a common benefit and harm metric
    - Clinical research and practice with higher standards for both
  - Obviate translation problem
  - Reverse Eroom’s law
  - Avoid costs of imprecision
- or

DataSpeaks—From Genomes to Health™

22

Legacy RCT designs date back to 1948 – streptomycin for tuberculosis. Eroom’s law was quantified from 1950 to 2010.



## SIMA Computes Precision Quantitative Time-Dependent Phenotypes

### Diagnostic

- Objective
- Reliable
- Mechanism-specific
- Actionable

Synergize genomics  
with better phenomics

### Treatment Response

- Reliable
- Valid
- Comprehensive of a multitude of beneficial and harmful effects
- Detailed
  - RV specific
  - Dose specific, etc.

SIMA can help synergize the Precision Medicine Initiative – All of Us.



# Measurement Begets Precision & Veracity

Computing precision quantitative time-dependent phenotypes with the Science of Individuality Measurement Algorithm (SIMA) from DataSpeaks **begets precision and veracity for science and medicine.**

DataSpeaks—From Genomes to Health™

24

Go boldly with confidence based on measurement.



## Contact, License, Partner



- [cbagne@DataSpeaks.com](mailto:cbagne@DataSpeaks.com)
- [www.DataSpeaks.com](http://www.DataSpeaks.com)





Thank you for your time.

I welcome your questions!



# Backup Slides





## Selected SIMA Capabilities: The Science of Individuality

- Time series preprocessing options
  - None
  - Successive differences
  - Linear and polynomial regression residuals
- IoT and benefit and harm scores as functions of:
  - IV and DV levels
  - IV and DV episode length and criterion
  - Delay and persistence of response
- Causal index
- Iterative processing – monitoring, adaptation
- Boolean independent and dependent events
- SIMA significance

DataSpeaks—From Genomes to Health™

28

For living systems, SIMA can process and help integrate data from two or more repeated measurements of two or more time-dependent variables. Such variables can be from transcripts as in cell-cycle control to patient-reported outcomes as for pain, symptoms of IBD, and neuropsychiatric disorders.

“Successive differences” are used when changes per unit time are more important to interactions over time than absolute levels of time-dependent variables. Regression residuals are used as when there is need to separate relatively short-term treatment effects and signaling from longer-term trends such as spontaneous recovery, disease progression, development and aging.

“Iterative processing” occurs when SIMA is applied repeatedly after the addition of each additional repeated measurement as to monitor drug safety and effectiveness. Inflections in the slopes of iterative processing graphs indicate adaptation as in the development of drug tolerance.

Boolean independent events can be used as when two or more proteins or drugs act jointly to produce an effect. Boolean dependent events can be used as for syndromes such as major depression.



# Demonstration

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

PATIENT VARIABLE	WEEK																IoT Score	Toward or Untoward Direction	Benefit or Harm (Bagne Z- score units)	Weight	Overall Benefit Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16					
	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					4.64
DBP	96	98	85	81	91	96	84	87	80	78	93	98	82	77	81	78	-8.92	-	8.92	4	
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																					6.67
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	
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																					4.11
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	
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

29

This is a mock precision or person-centric, single-group randomized controlled trial for a hypertension drug with three persons, four doses including placebo, three response variables, and 16 repeated measurements. This RCT tested the null hypothesis of no overall benefit and harm across persons, doses, response variables, and repeated measurements. Users could drill-down from here as introduced by Slide 20.

Four doses were randomized using pairs of two-week periods. To protect person safety, the highest dose (80) was not administered until benefit and harm could be monitored with lower nonzero doses. For simplicity, this simulation assumed no delay and persistence of response. SIMA could be used to quantify delay and persistence explicitly. This simulation uses dose as a time-dependent independent variable. Similarly, users could use SIMA to explore benefit and harm as functions of dispensed dose and consumed dose as well as blood levels of drug, drug metabolite, or drug marker.

See that response variable directionality and weights can be person-specific in accord with differences in person-specific preferences and assessments of clinical significance.


The null hypothesis of no overall benefit and harm was rejected in the positive direction (lower-right corner) indicating that the drug was preponderantly beneficial in accord with the way statistical testing was presented in Slide 19.



# Gain Power with Repeated Measurements

## Simulation Results

Number of Subjects	p-values (levels of statistical significance)					
	Without SIMA <sup>1</sup>	With SIMA (Benefit & Harm Scores) <sup>2</sup>				
		Number of Repeated Measurements				
		2	4	8	16	32
4	.594	.423	.225	.187	.192	.042
8	.230	.134	.049	.032	.036	.002
16	.060	.041	.002	.002	.0001	.000011
32	.001	.00036	.000029	.0000041	4.2x10 <sup>-9</sup>	1.1x10 <sup>-14</sup>
64	1.3x10 <sup>-8</sup>	1.1x10 <sup>-7</sup>	1.1x10 <sup>-10</sup>	9.3x10 <sup>-15</sup>	4.7x10 <sup>-18</sup>	4.2x10 <sup>-27</sup>

 p < .05, p ≤ .001

 p < .001

<sup>1</sup> Baseline to endpoint change scores for two equal groups

<sup>2</sup> To reject the null hypothesis of no benefit or harm in one group, two-tailed

This simulation of a single-group randomized controlled trial is based on one dataset with 64 subjects, 32 repeated measurements, a fixed treatment signal, half of the repeated measurements on treatment and half off, one response variable, with the treatment effect signal obscured by Gaussian noise. This simulation did not assess delay and persistence of response, which also could be assessed with SIMA. Expanding portions of this one dataset were used for the different results in the slide table.

See how significance and power increase both by more subjects and more repeated measurements. Legacy RCTs often use only two repeated measurements – baseline and endpoint – to test a primary hypothesis. Gain power and significance by using or adding more repeated measurements to test one primary hypothesis. Slide 29 used 16 repeated measurements to achieve statistical significance with only three persons.

Use of more repeated measurements can yield more reliable quantitative treatment response phenotypes (see Slide 23). Use of more repeated measurements can be less expensive and more ethical than more subjects.