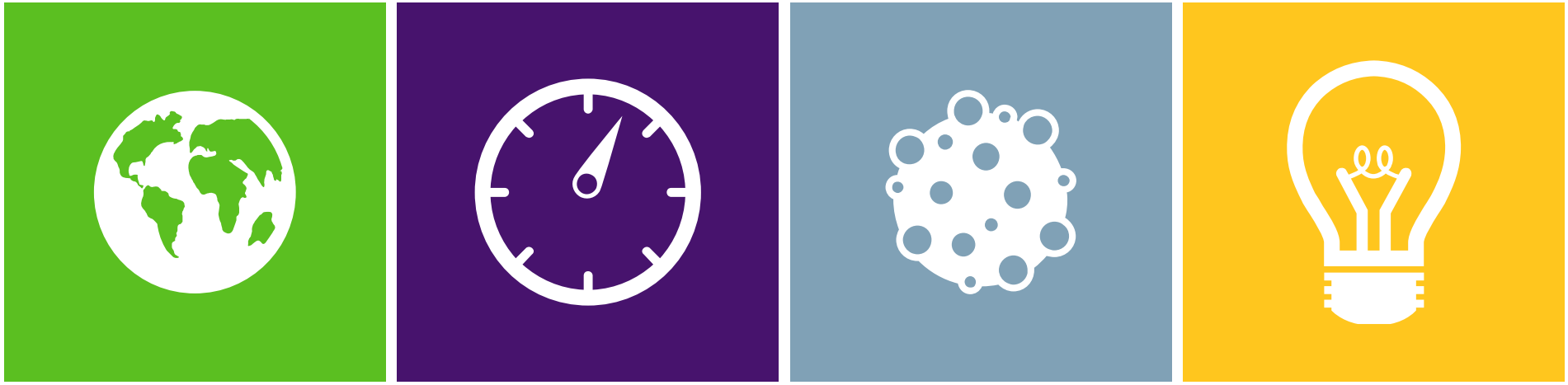

Evolution of Statistical Methodologies in Clinical Trials

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PPD®

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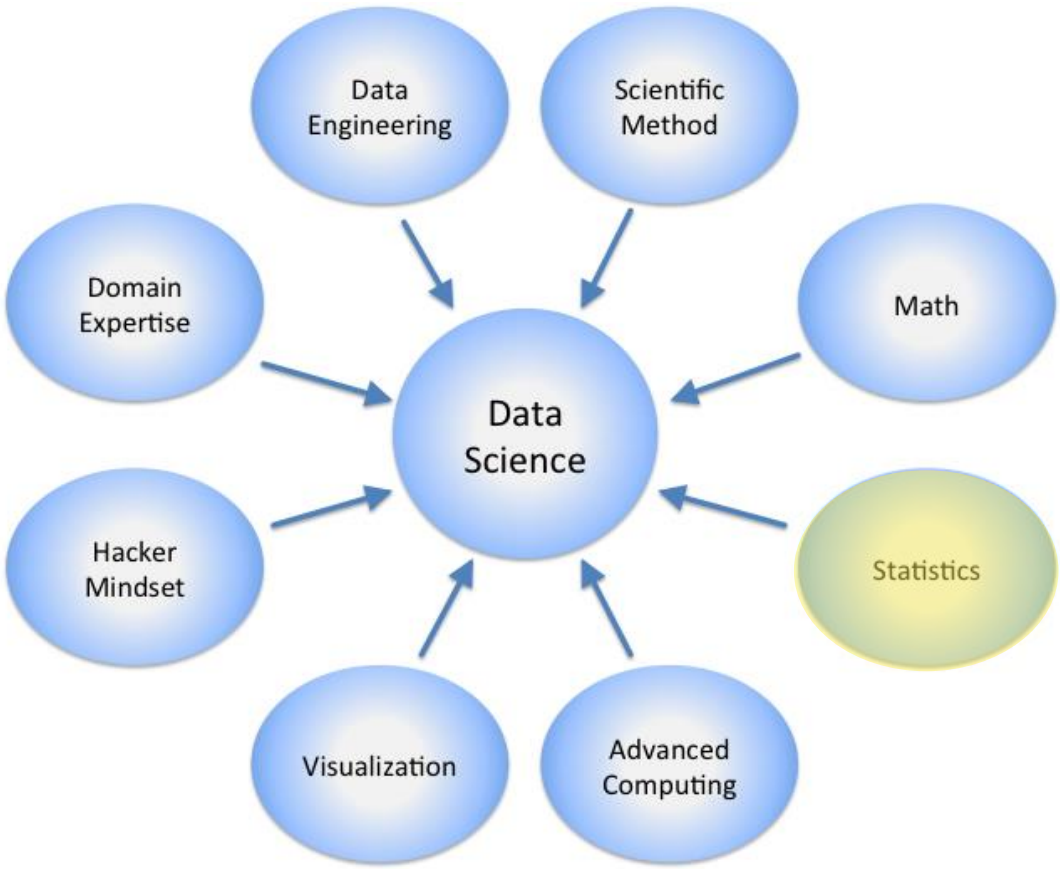
Agenda Slide

1. Data Science & Statistics
2. Evolution of Statistical Methods in Clinical Trials
3. Change in Approach
4. Prospective Future of Statistics in Clinical Research
5. Q&A

Data Science & Statistics

- Data science is a "concept to unify statistics, data analysis, machine learning and their related methods" in order to "understand and analyse actual phenomena" with data.
- It employs techniques and theories drawn from many fields within the context of statistics, mathematics, information science and computer science.
- Data science started with statistics and has evolved to include concepts and practices such as artificial intelligence, machine learning and Internet of things, to name a few.



The Only Thing That Is Constant Is Change

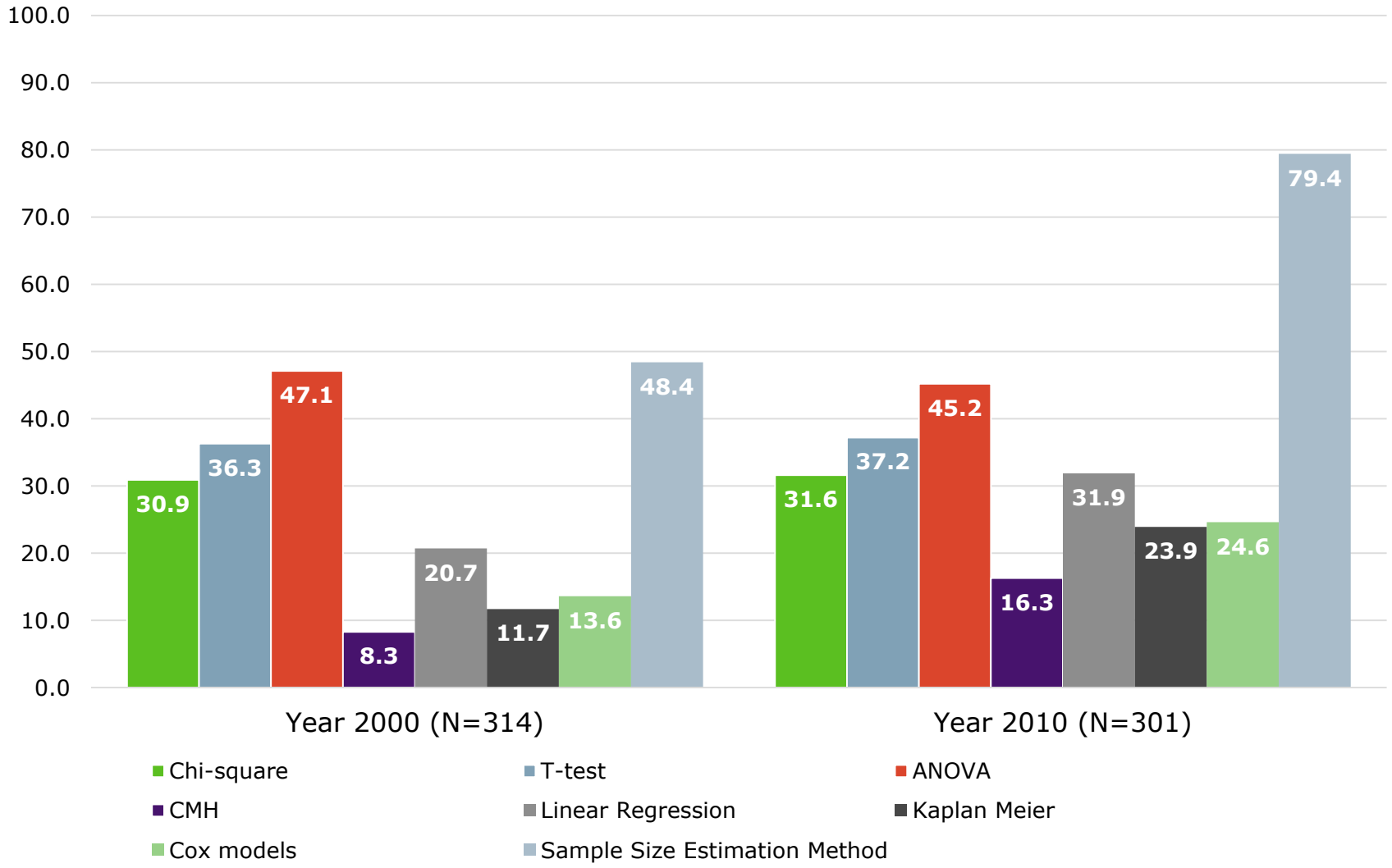
HERACLITUS

Evolution of Statistical Methods in Clinical Trials

The development of statistical methodology in the context of clinical research, in general, has been tremendous over the past couple of decades. Statistical analysis has become more complex, and role of statisticians in overall study design is well recognized.

We will trace how statistical methodologies and techniques evolved and its impact in clinical research.

Statistical Methods Published in 2000 and 2010



Root of Evolution

Application of statistics was never incorrect…..

- Emergence of oncology as one of the most important therapeutic areas to target and the complexities of its clinical trial designs as well as endpoints
- Availability of longitudinal data and repeated measurements
- Increased relevance of pharmacometrics (PK-PD modeling) in drug development
- Importance of adaptive designs to make the drug development programs more efficient and effective
- The reliance on meta-analysis for cumulative evidence
- Advances in diagnostic systems and the data they generate
- Shift of focus to benefit: Risk evaluation, emphasis on comparative effectiveness and real world evidence.

Advantages and Disadvantages of Complex Methods

Advantages:

+ There are three broad reasons for using statistical models: causation, prediction, and description
+ Handling of important confounding factors
+ Handling of missing values
+ Useful for future studies

Disadvantages:

+ Difficult to interpret
+ All complex statistical solutions require extra information in the form of either additional data or additional assumptions.
+ Researchers sometimes use statistical models simply for prediction even though they do not understand the causal mechanisms in the observed data
+ Complex methods are expensive
+ Complex method can be under or over-powered if its not planned

Change in Approach..

Sample Size Calculation | Role of Statistician in Study Designs | Use of Software

SS Based on clinical Judgment and Feasibility

SS Based on Statistical Formula

Simulation Based SS

Literature Based

Using various software like nQuery, EAST, SAS etc.

1. Simulate a large data set based on the design parameters
2. Analyze the simulated data set to obtain the test statistics
3. Calculate the expected test statistics depending on the distribution of the test statistics

Accurate Sample Size Calculation → Accurate Power of Test

Change in Approach..

Sample Size Calculation | **Role of Statistician in Study Designs** | Use of Software

Calculation of Sample Size, Statistical Section

Calculation of Sample Size, Statistical Section, Inputs to Study Design

Calculation of Sample Size, Statistical Section, Inputs to Study Design

- Randomization Method
- Statistical Analysis Method
- Missing Data Handling
- Other statistical considerations

- Dose-finding models
- Adaptive Design – sample size recalculation, groups sequential
- Defining endpoints
- Interact with clinicians

Advance methods:

- Simulation
- Bayesian
- Real word data and PROs
- AI Driven Data Analysis???

Efficient Study Design Required Good Statistical Collaboration

Change in Approach..

Sample Size Calculation | Role of Statistician in Study Designs | **Use of Software**

- SAS is used in clinical research traditionally for performing statistical analysis.
- There has been various updates in SAS since its development.
- Example of new analytic procedures in SAS 9.4 :
  - HPBNET: predictive modelling based on Bayesian network
  - PSMATCH: performs propensity analysis
  - TRAJ: Group based modeling of longitudinal data. It identifies clusters of individuals following similar progressions of an outcome over time by fitting a group based model

- R is a high-level, interpreted programming language-based software.
- It allows data analysis, manipulation, graphical presentation in easy and effective way.
- The use of R increased exponentially over last decade considering its easy access and popularity
- There is misconception that R is not validated and cannot be used for clinical trials.

Prospective Future of Statistics in Clinical Research

Statistical Methods that Rule!

Simulation

- Main Purpose of Simulation – running scenarios, interpret & understand results
- Extremely Important to Plan before simulating
  - Just trying different scenarios, models in a random fashion is an inefficient way to learn
  - Careful planning of simulations -> Improves efficiency
- Simulation is an EXPERIMENT.

Where it can be used?

- Use simulations to determine the study design with the highest power under a variety of scenarios
- Use simulations to estimate type I error and bias under a variety of scenarios
- Use simulation to determine sample size calculation

BETTER PLANNING!

Bayesian

posterior information = prior information + data information

+ Bayesian statistics provide a formal mathematical method for combining prior information with current information for calculating the likelihood of a future event
+ The posterior distribution may be used to calculate the probability that a particular hypothesis is true, given the observed data
+ The prior distribution is usually based on data from previous trials and should be carefully selected and incorporated into the analysis
+ Today's posterior probabilities become tomorrow's prior probabilities

Where it can be used?

+ Adaptive Trial Design
+ Continual Reassessment Method (CRM) for determining the maximum tolerated dose (MTD) of a drug molecule
+ Postmarketing surveillance
+ Meta-analysis

OPTIMIZE CLINICAL TRIAL USING PRIOR INFORMATION!

Real-World Data

Real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

+ Electronic health records (EHRs)
+ Claims and billing activities
+ Product and disease registries
+ Data gathered from other sources that can inform on health status, such as mobile devices

Where it can be used?

+ FDA: to monitor post-market safety and adverse events and to make regulatory decisions
+ Health care community: to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice
+ Medical product developers: to support clinical trial designs and observational studies to generate innovative, new treatment approaches

BRING INNOVATIVE THERAPIES TO THE MARKET FASTER!

Patient Reported Outcome (PRO)

A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

+ Various Symptoms e.g. fatigue, headache, depression
+ Nature and severity of disability
+ Health-related quality of life (HRQL)
+ Perception of patient towards treatment given

Where it can be used?

+ PROs are also used to measure risks and benefits of treatments
+ PRO data are collected as endpoints of a clinical trial to support marketing approval and/or assessment to support reimbursement or coverage decision of a health plan
+ Exploratory work from the field of oncology suggests that PROs can be used for adverse event reporting with a high degree of patient engagement and compliance

PATIENTS FIRST!

Future…

- Statistics will continue to be a critical aspect of clinical research
- Statisticians will have to play a more prominent role as an integral part of product lifecycle
- As the variety of data to be analyzed increases, and more exploratory analysis and data mining are required, use of other tools and software (e.g., R) will increase

- Statisticians will need to have a better understanding of therapeutic areas and mechanisms of action etc.
- Statisticians will have to be effective communicators in cross-functional team discussions
- Statisticians, and programmers will have to gear up for the changes in terms of the kind of methods, analyses, and the tools to be used

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Thank You!


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