

Piloting the Queen Mary

The Unique Challenges of Cardiovascular Outcome Studies



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WORLDWIDE CLINICAL TRIALS



SCIENTIFICALLY MINDED • MEDICALLY DRIVEN



Michael Murphy, M.D., Ph.D.

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Agenda

- A Unique Order of Complexity
Dr. Michael Murphy
- Supporting the Future of Cardiovascular Research
Karen Hill
- Trial Design Strategy
Dr. Toni Bransford
- eClinical Architecture: A Holistic Approach
Chris Standley
- Q & A

A Unique Order of Complexity

Multiple compartments; complex interrelated activities; difficult to launch; difficult to bring into port



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On The Pragmatic-Explanatory Continuum

On one hand...

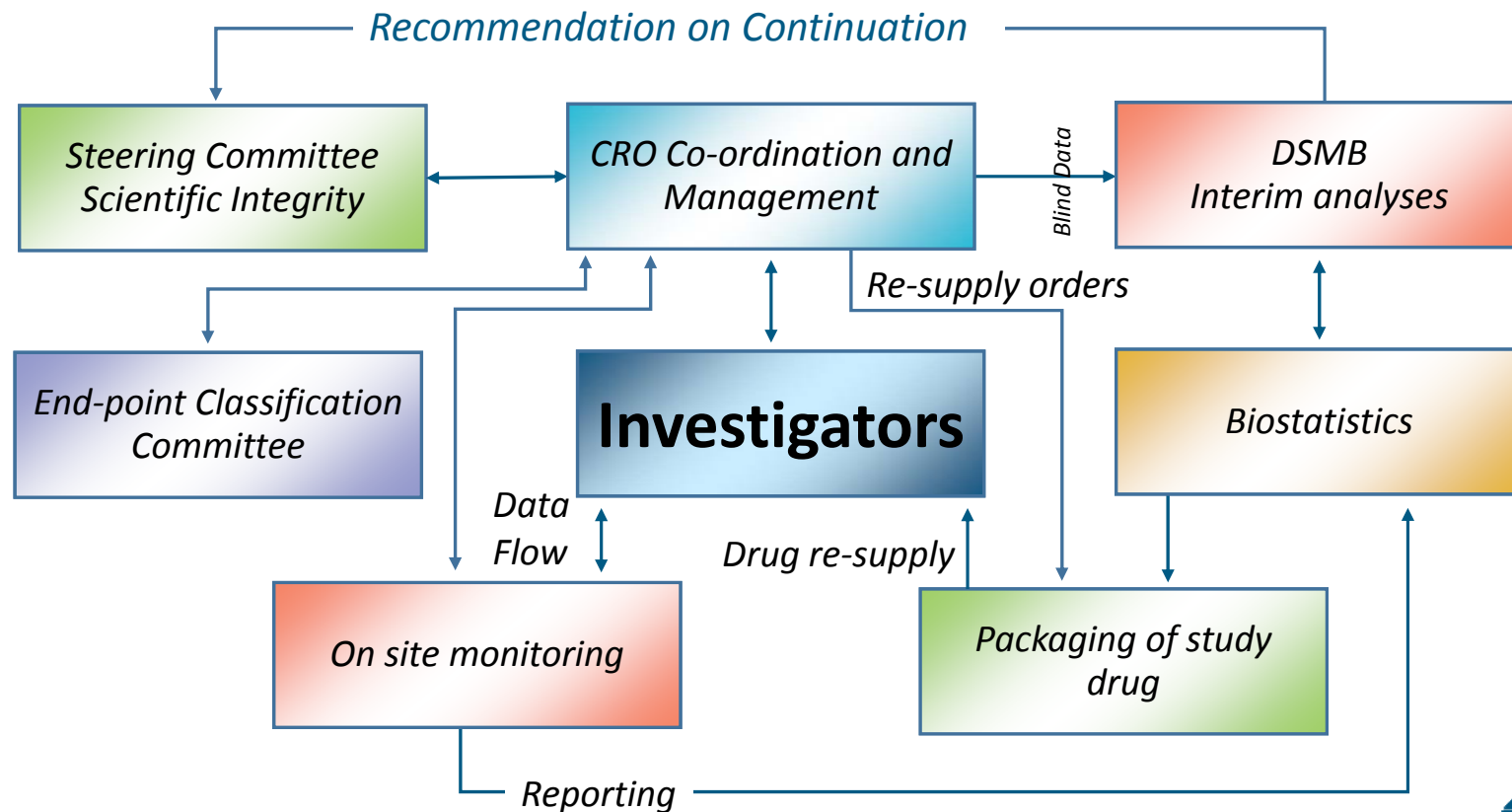
- Effect, efficacy, effectiveness
- Restrictive eligibility
- Leveraged samples
- Specialized centers
- Measures then outcomes
- Layered, “3 dimensional”, hierarchical assessments
- Study metrics imprecise
- “.....a dissertation on every patient”

On the other hand...

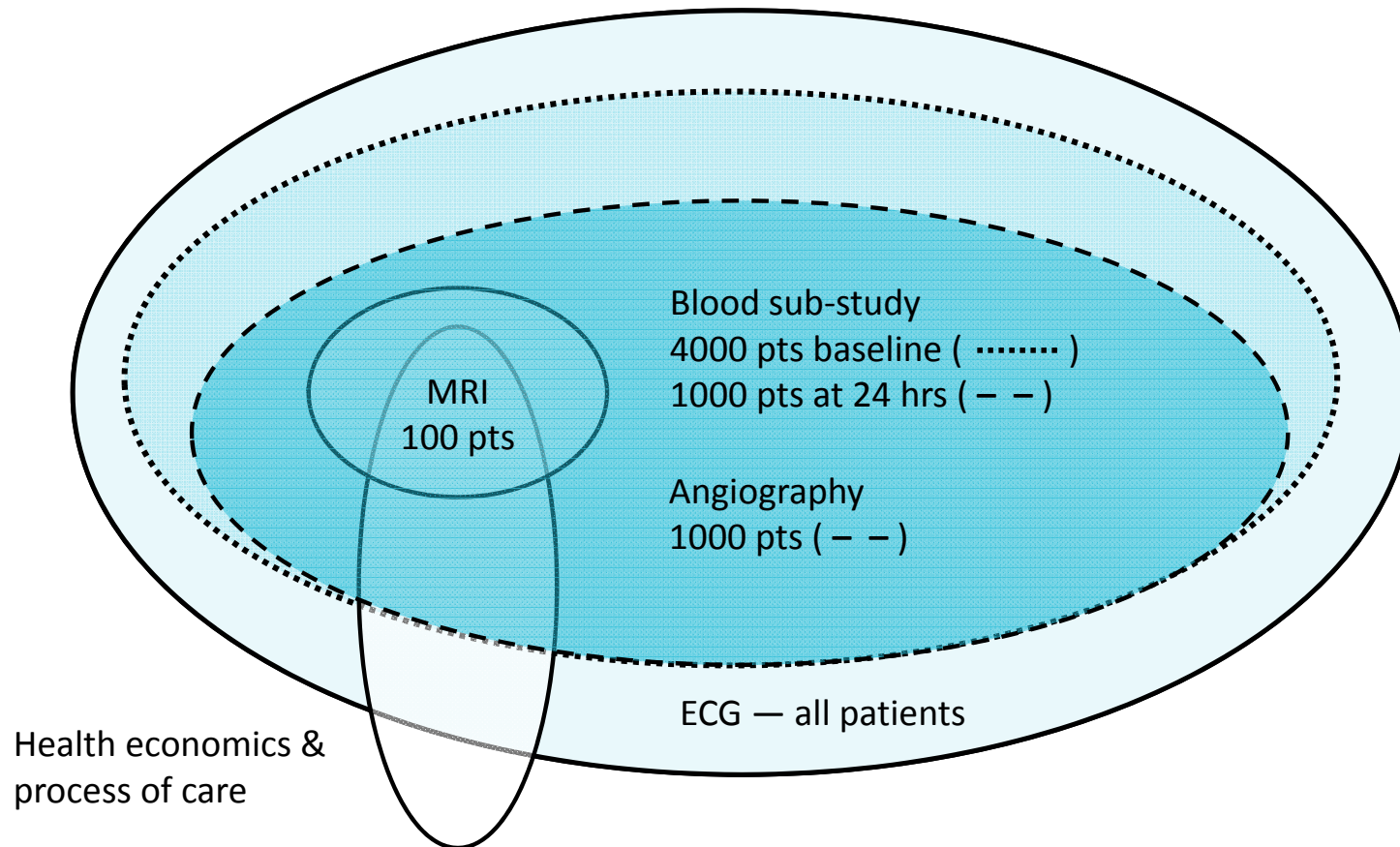
- Effectiveness, efficiency
- Inclusive eligibility
- The target population
- Representative sites
- Outcomes then measures
- Composites e.g., all mortality, cardiac death, major CV disability... (MACE)
- Study metrics predictable
- “data flow, processes, infrastructure”



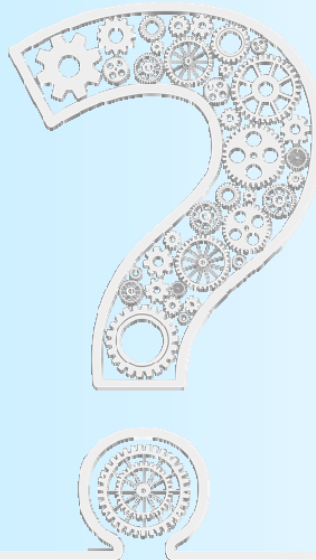
Assuring Quality – Managing Relationships



Studies, Within Studies, Within a Study



...and Asking a Few Questions



- What is implied by “scalable” operational infrastructure?
- What features of CVOT impact data acquisition and integrity?
- How are interests of diverse stakeholders adjudicated?
- Do regional differences in standards of care facilitate or encumber study execution?
- What do emerging trends in clinical trial methodology imply for study execution and interpretation?
- Why is technology “enabling” and where is it heading?



Karen Hill

Senior Vice President Global Therapeutic Lead, Cardiovascular



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Supporting the Future of Cardiovascular Research



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By Design

- Thousands of patients
- Hundreds of sites
- Tens of countries
- Multiple continents
- Millions of dollars



Importance of Setting the Right Path



- Once launched CV outcome studies are notoriously difficult and almost impossible to steer into a different direction
- Goals of the study remain focused
- Huge databases are extremely valuable
- See effects on an intervention but also the disease
- Answer more general medical questions related to the study population

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Common Challenges



- High financial cost
- Lengthy timelines
- Increased competition for qualified investigators and sites
- Large patient populations and long follow-up periods
- Regulatory and administrative barriers
- Sponsors imposed barriers
- Disconnect between clinical research and medical care
- Barriers at academic institutions
- Globalization of clinical research



Answer

When was the first treatment for a heart attack introduced into routine hospital practice?

- a. late 60's
- b. late 70's
- c. late 80's**
- d. late 90's

“Until then, somebody would come in with a heart attack and all we could do was give them a painkiller, put them in a bed and watch them either recover or die.”

In the late 90's, more than 200,000 were randomized in large-scale trials over the previous decade, making thrombolysis the most intensively studied medical intervention at the time.



Barrier Mitigation Measures and Associated Modelling Approach

Barrier mitigation measures	Approach to modelling	Sources
Widespread use of Electronic health records – EHR	<ul style="list-style-type: none"> • Patient recruitment costs (per patient): reduced by 35.9% • Number of patients per site: reduced by 12.3% 	US dept Health and Human services; Deloitte
Sponsors to reconsider enrolment restrictions	<ul style="list-style-type: none"> • Patient recruitment costs (per patient): reduced by 21.3% 	Getz 2008
Simplify clinical trial protocols and reduce amendments	<ul style="list-style-type: none"> • Data collection, management and analysis costs (per study): reduced by 22.5% • Number of IRB amendments (per study): reduced by 33% • Clinical procedures Total (per patient): reduced by 22.3% 	Tufts & Getz
Engage sponsors in discussion re: Data monitoring and SDV	<ul style="list-style-type: none"> • SDV cost (per data field): reduced in cardiovascular trials by 11.6% in phase II and 14.3% in phase III 	Tantsyura 2010
Use of mobile technologies – EDC – Central evaluation of sites performance	<ul style="list-style-type: none"> • Phase time (years): reduced by 17.6% in Phase I, II, III and IV • Reduction in site management, project management and site monitoring 	Neuer 2010
Utilise Lower cost facilities – local lab etc. - or home testing for data collection	<ul style="list-style-type: none"> • Phase time (years): reduced by 67% in Phase I, II, III and IV • Reduction in site management, project management and site monitoring 	Shapiro 2008

PATIENT RETENTION SUCCESS

Atherosclerotic Disease Patients

32 countries (6 regions)

- > 1,000 sites
- 26 month recruitment period
- > 26,000 patients randomized
- 212,689 eCRF visits recorded

Subject retention – *with an active retention plan:*

- Average follow-up: 2.5 years
 - 66,000 patient-years of follow-up overall
- 532 (2.0%) withdrew consent for follow-up
- 23% patients discontinued study drug prematurely

Only 0.1% out of > 26,000 subjects lost to follow-up

Key Success Factors

- Successful ARO/CRO Partnerships
 - Site identification
 - Key Opinion Leaders
- Integrated technologies
 - Streamlined data collection
 - Electronic document collection
 - Transparent metrics
- Competitive Investigator Fees
- Robust recruitment and retention plans
 - Up front pre-screening activities
 - Standard of care
- Smart and adaptive monitoring
 - Remote monitoring
 - Flexible on-site visit plan
 - Tiered SDV





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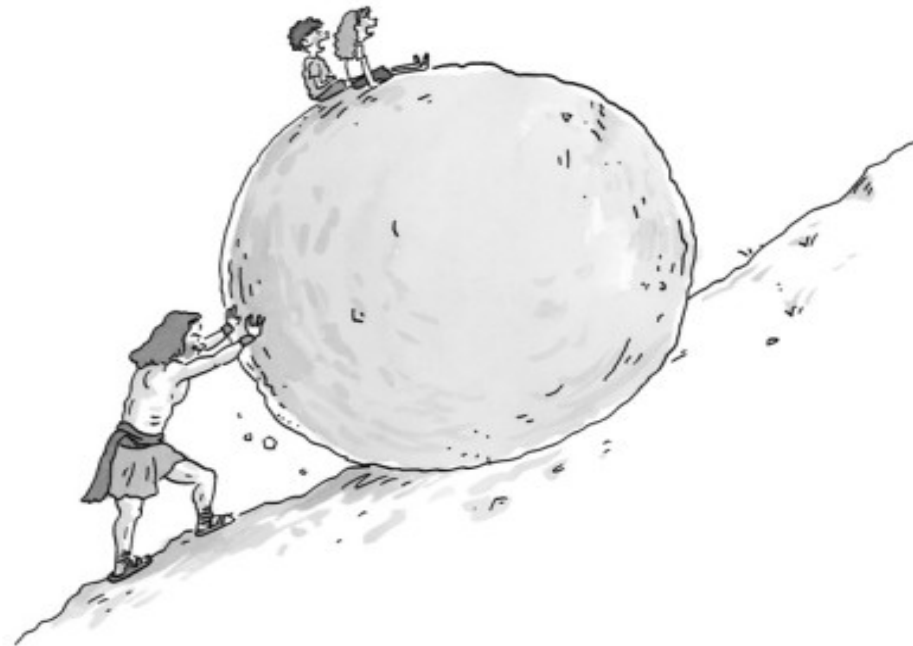
Trial Design Strategy

Promises to Keep...Miles to Go Before We Sleep



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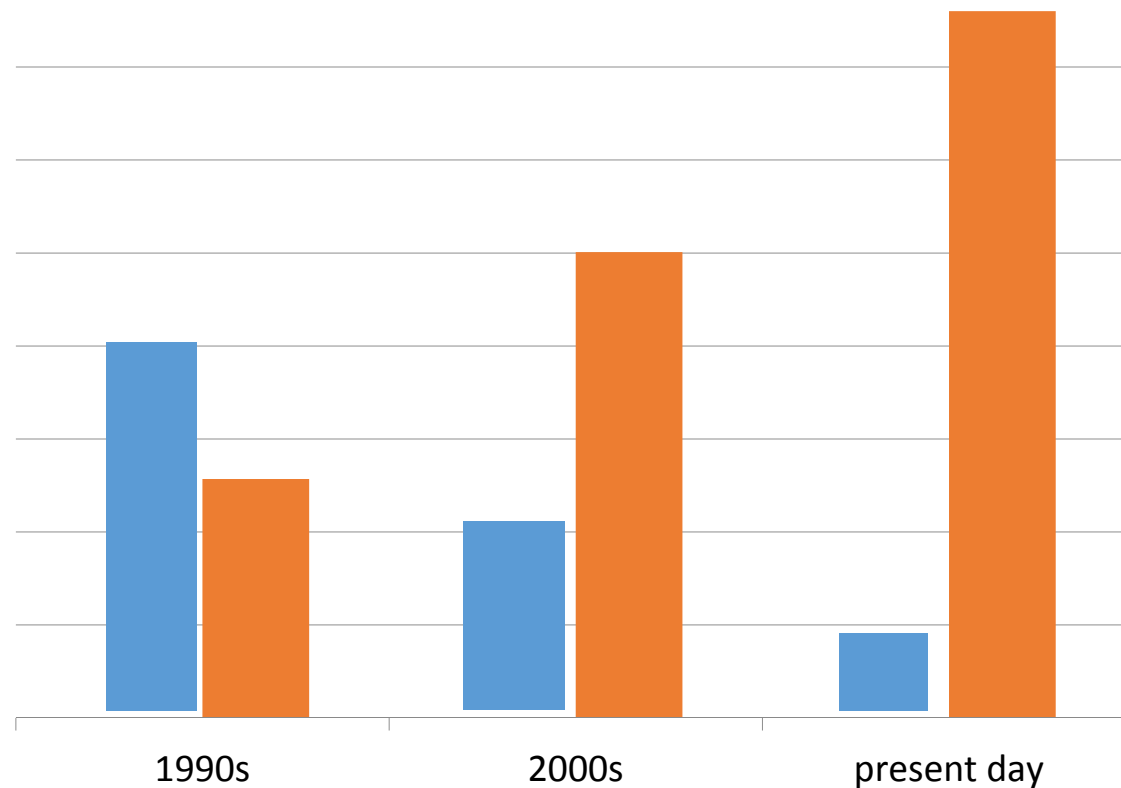
What can Sisyphus teach us about trial design strategy?



"Are we there yet?"



Cardiovascular Trial Sample Sizes Increase Relative to Improved Treatment and Unmet Need



"Are we there yet?"

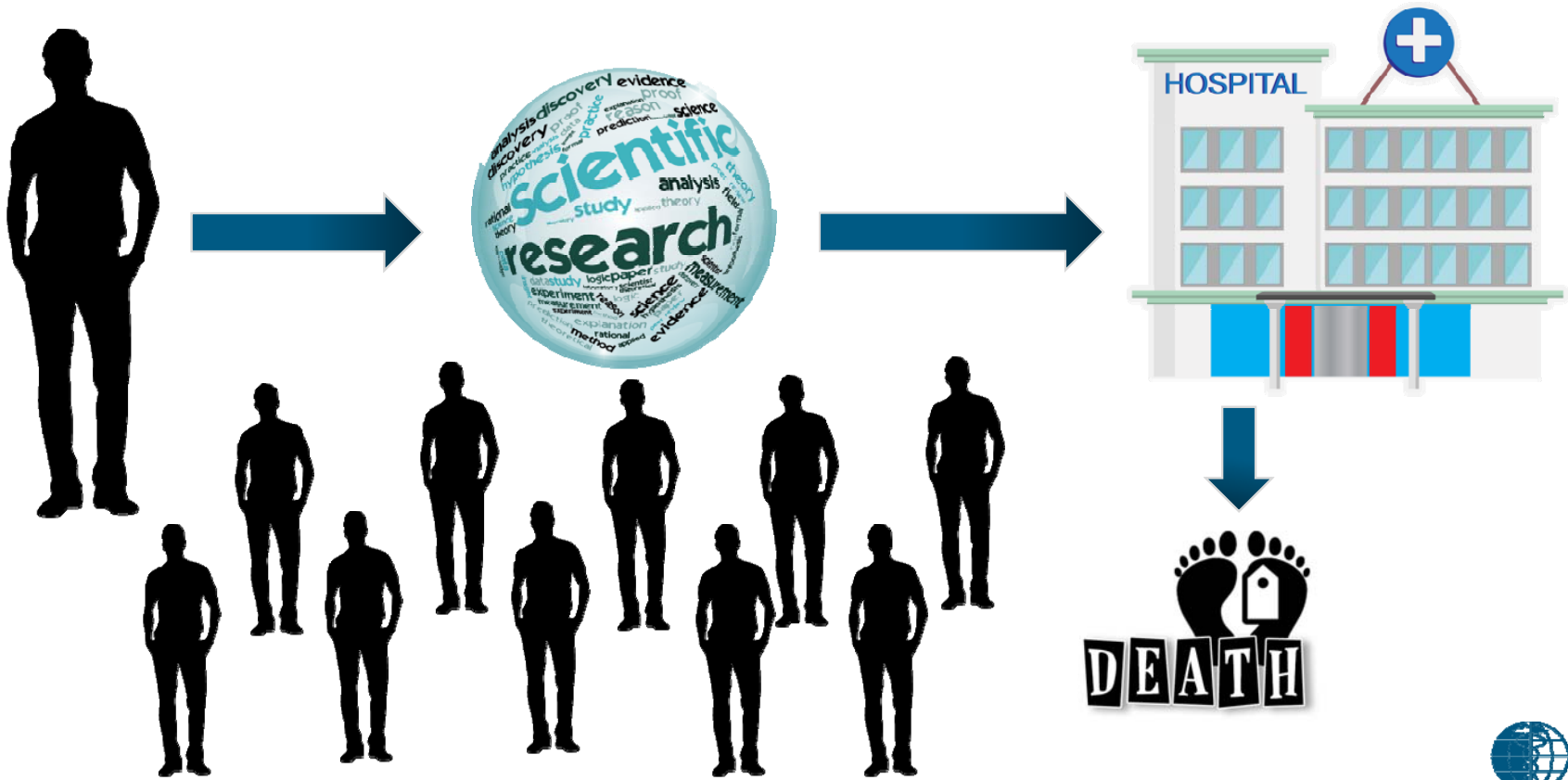
- Unmet Need
- Sample size



The Promises of a Conventional Trial... *Leaves a Lot to Be Desired*

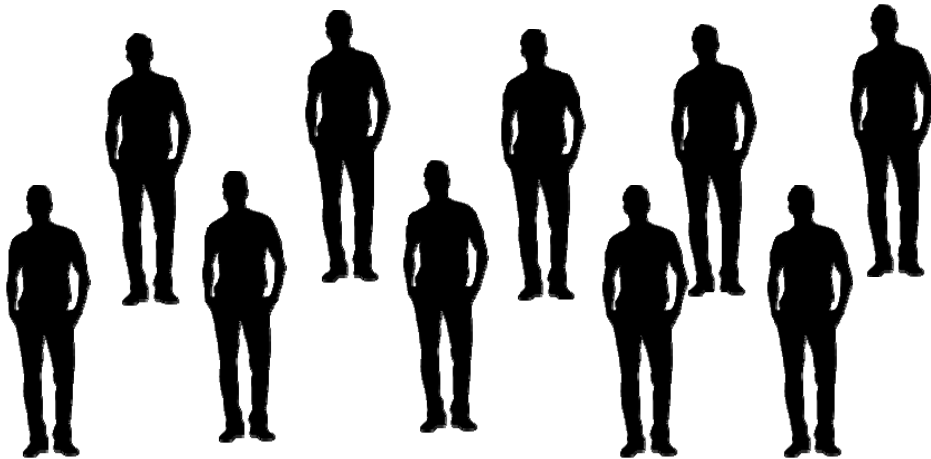


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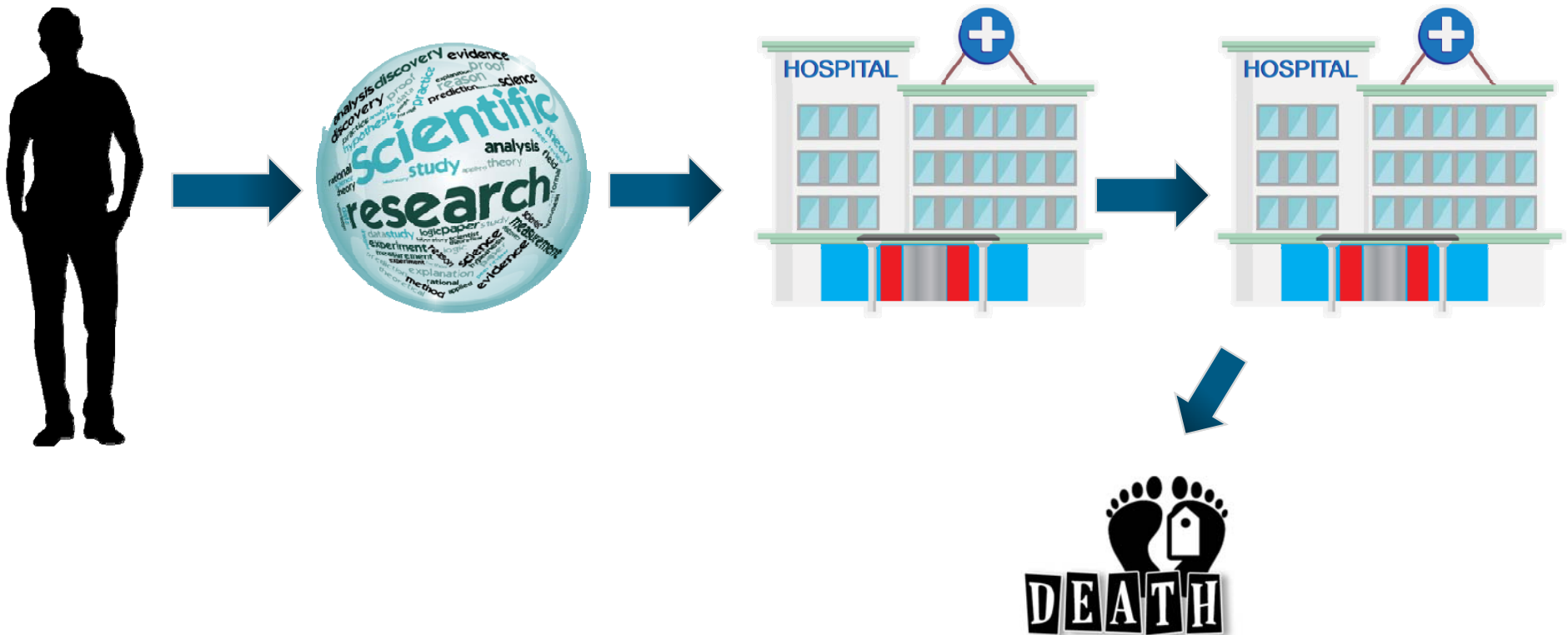


The Promises of a Conventional Trial...

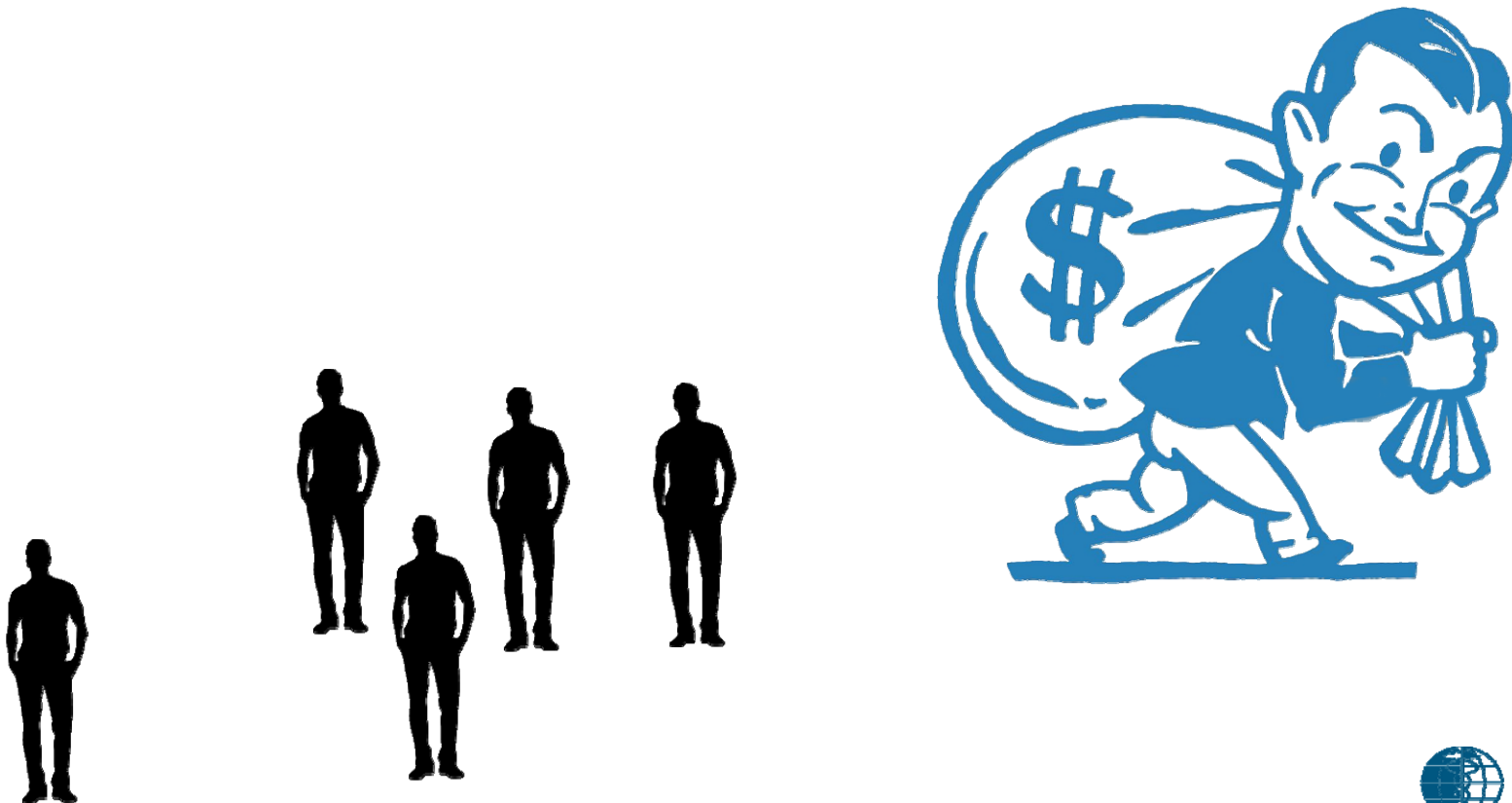
Leaves a Lot to Be Desired



However... recurrent events allows the trial to capture all events in the patient's clinical course and reduce sample size

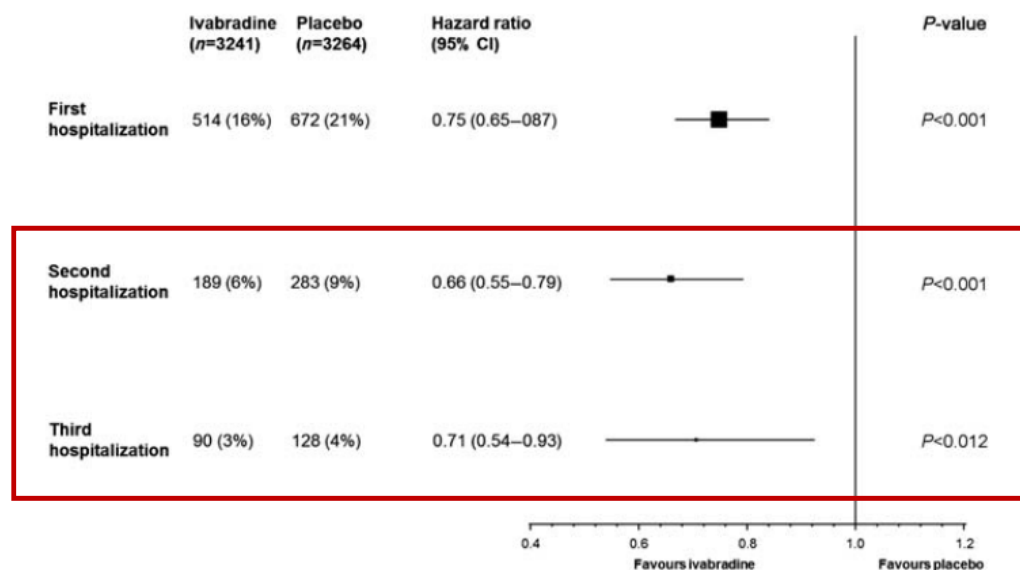
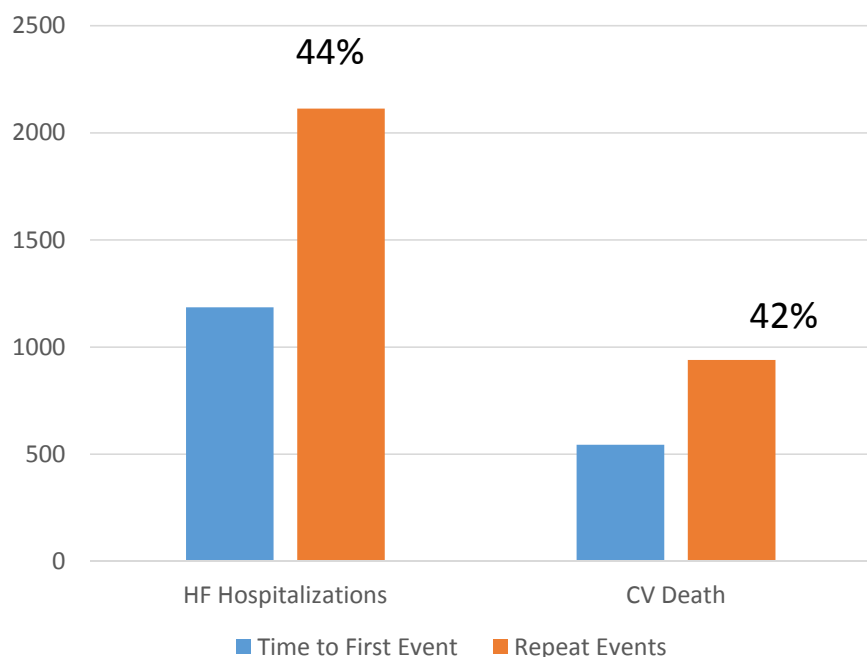


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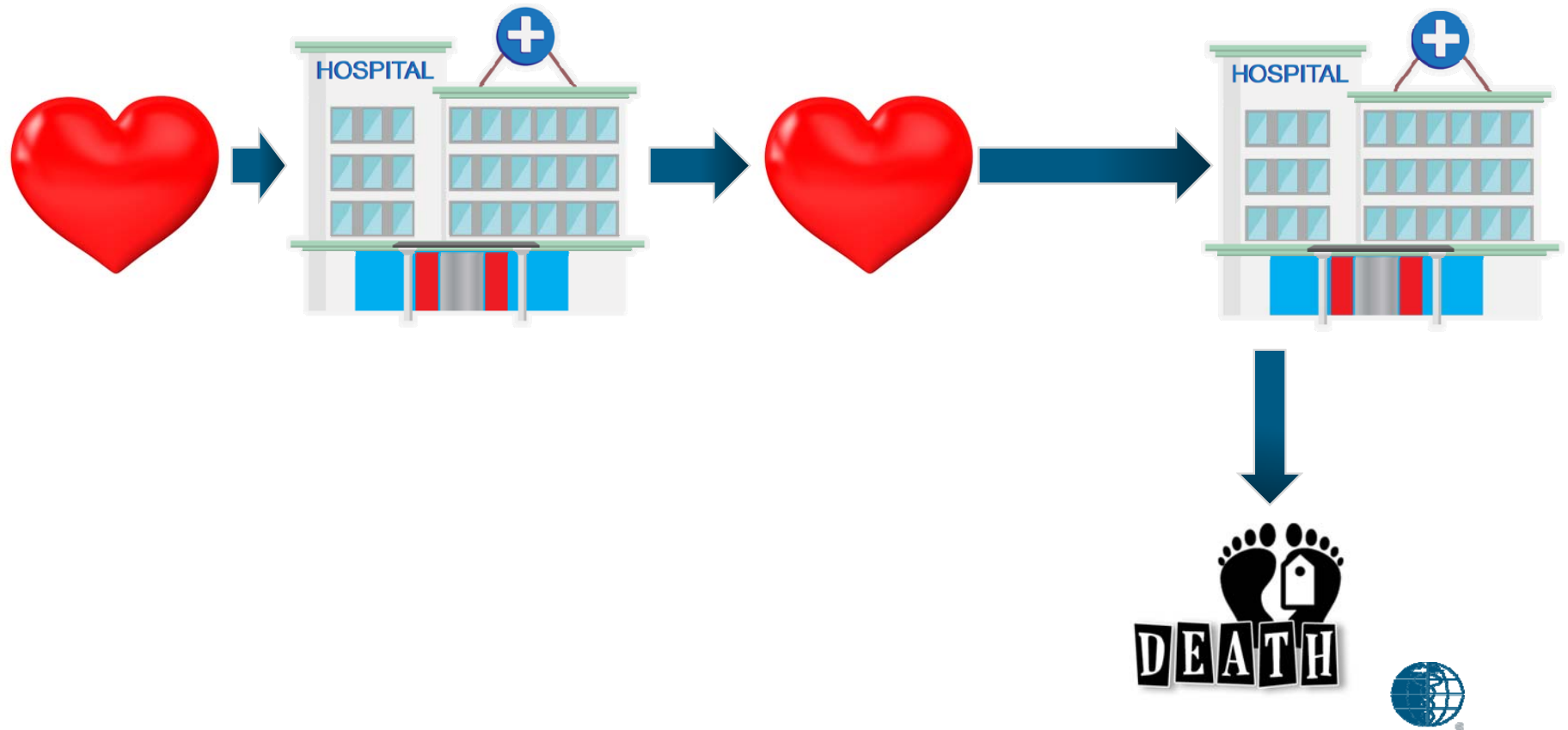
How Do Different Analyses Compare in Treating Events

More Events ignored in TTFE



Swedberg K. Lancet 2010;376:875–885
 Borer, JS. European Heart Journal 2012; 33:2813–2820

Recurrent events analysis takes into account time as well as number



Key Points Crucial for Prompt and Expeditious Acceptance by Health Authorities

- 1** Use an evidence-based, novel endpoint that mitigated risks for a low mortality trial based on current design challenges
- 2** Focus on the impact on patients and the health care system
- 3** Collaborate with leading global experts in multiple fields to generate novel alternatives with the highest probability of acceptance





Chris Standley

Vice President, Trial Technologies



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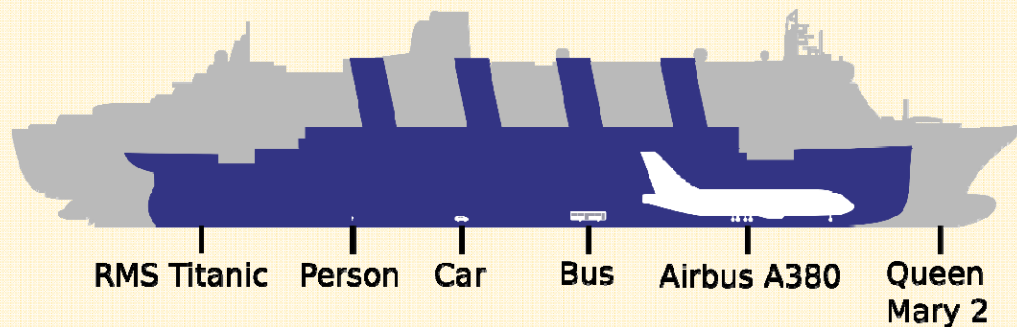
eClinical Architecture: A Holistic Approach

“A life on the ocean wave! A home on the rolling deep!”

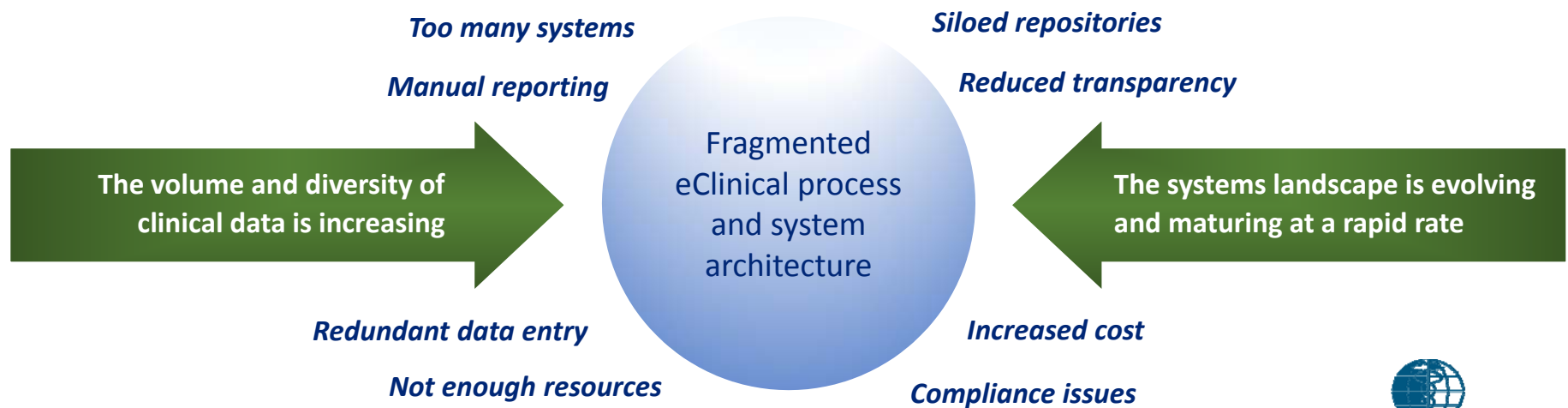


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Smooth Sailing?



- Tonnage: 151,400 tons (Gross)
- Length: 1132 feet
- Height: 236ft 2in
- Cost \$550 million
- Capacity: 3090 guests, 1238 crew

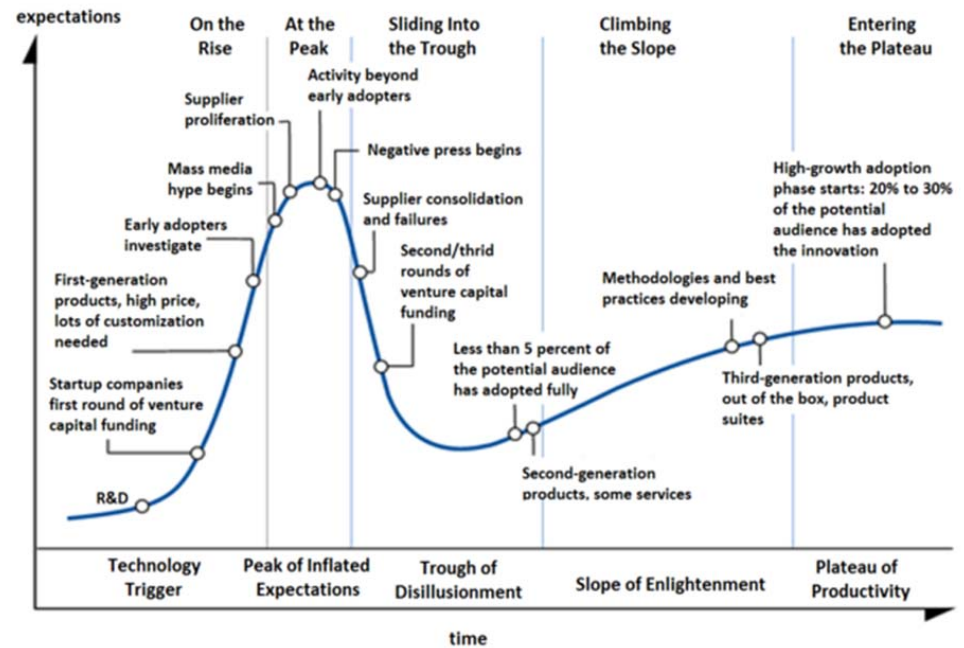


The Future is Now

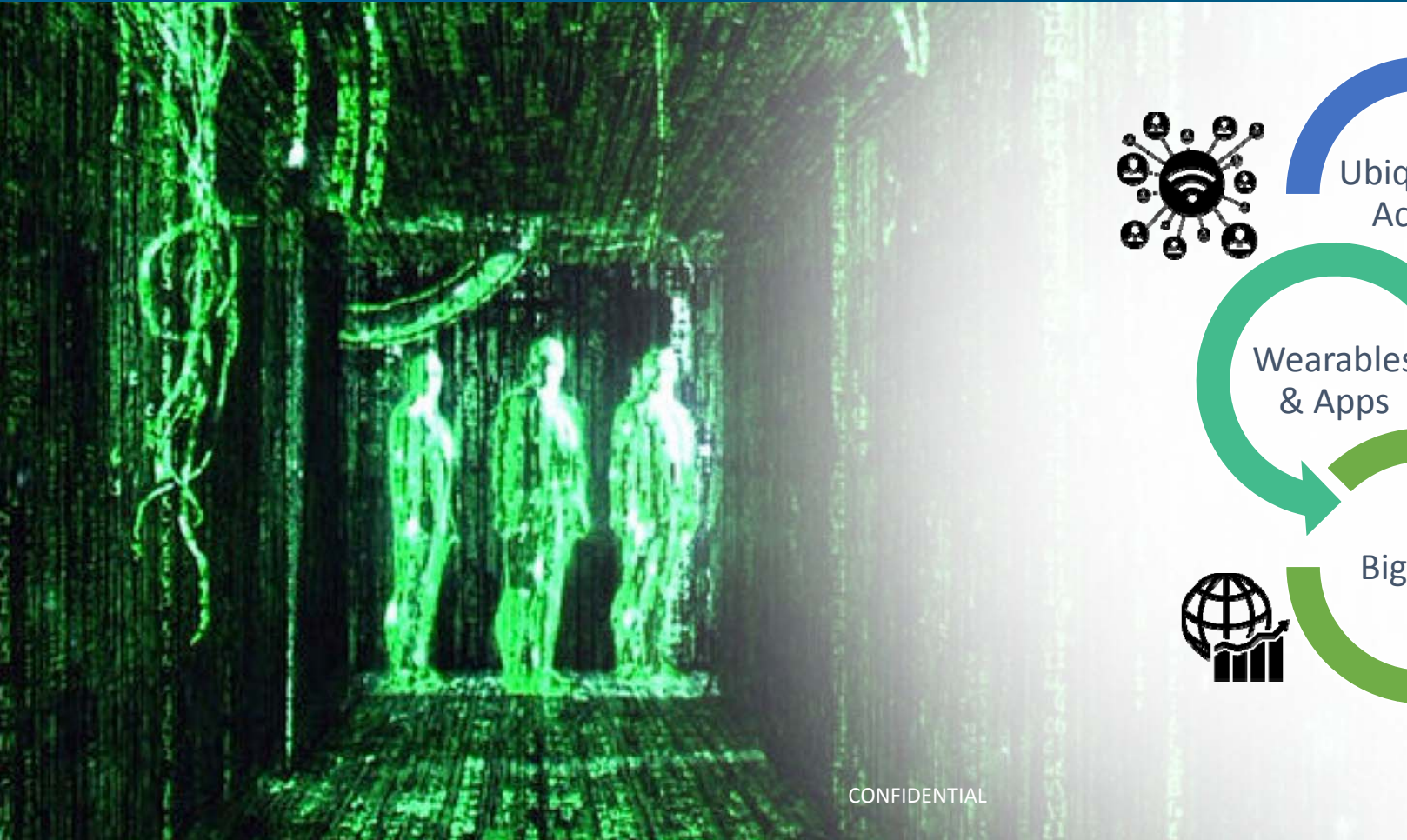
A typical monitoring visit?



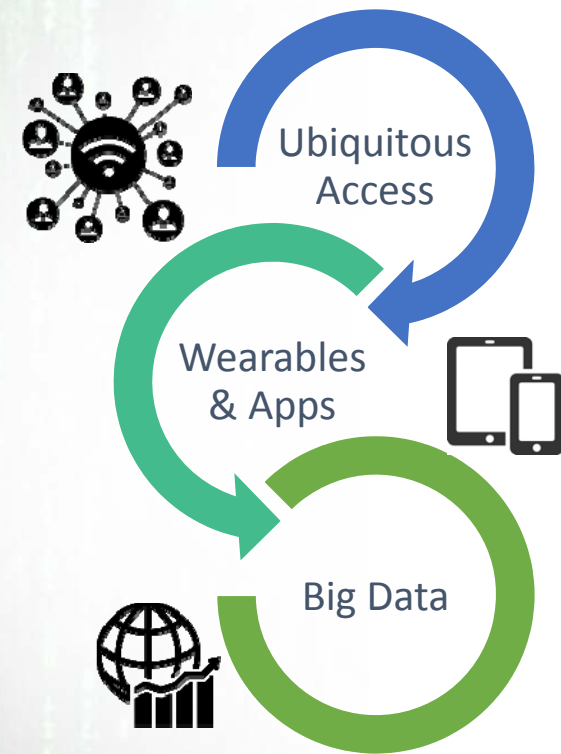
The Gartner Hype Cycle:



Life in the Matrix

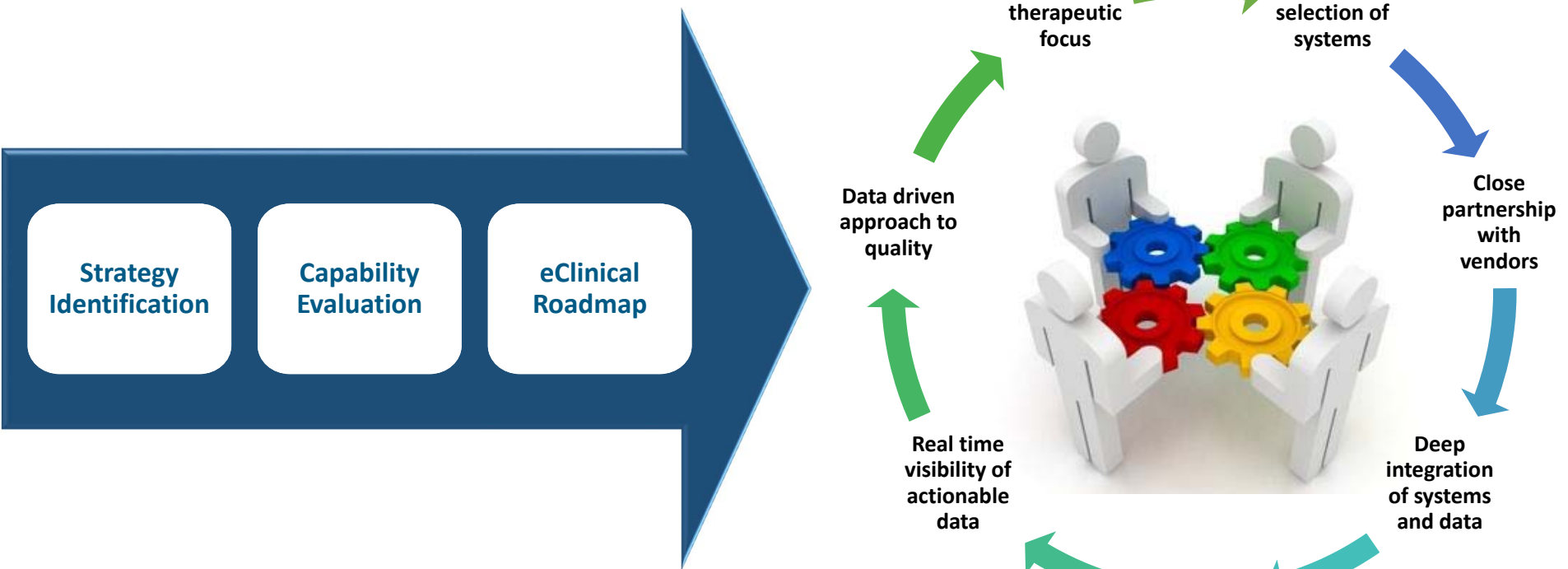


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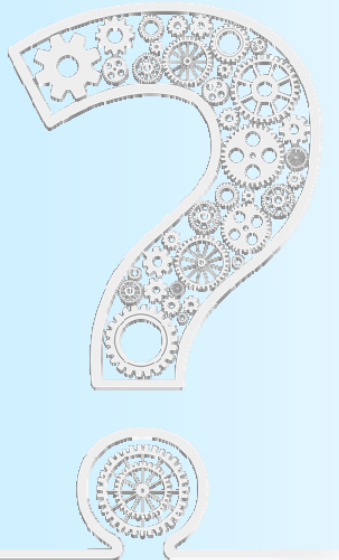


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A Holistic Approach



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Thank You!

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