MAPS Medical® Affairs Professional Society

Welcome!

Shifting the Paradigm (and Price) on Integrated Evidence Generation

Presenters

Sonja Wustrack

Managing Director, Integrated Evidence Generation, OM1

- Oversees design and execution of evidence programs and registries leveraging networks and automation platforms
- Prior experience at IQVIA, Verana Health and other research organizations
- Vassar College(BA) Tulane University(MPH)
- swustrack@om1.com

Joris Van Dam

VP, Clinical Trials Innovation
Exact Sciences

- Leads development and execution of the Real-World Data strategy in clinical research
- 18 years in Pharma R&D (Novartis, Janssen) leading variety of clinical trials innovation technologies and capabilities
- University of Amsterdam (PhD in AI)

Dr. Rich Gliklich

CEO, OM1

- 25 years in real-world evidence
- PI for HHS Outcome Measures Framework; and AHRQ Registries for Evaluating Patient Outcomes: A User's Guide,
- Founder, Outcome (now RWLP Div IQVIA)
- Yale (BA) Harvard (MD) Leffenfeld Professorship, Harvard
- richg@om1.com

Educational Objectives

This session will provide a learning opportunity for our audience by:

- Explaining the role of integrated evidence generation across the product lifecycle
- Identifying approaches to reducing study burden for providers and participants
- Describing ‘active’ and ‘passive’ data collection
- Delineating how automated collection of EMR data and extensive linkage to other data sources can enrich data breadth and completeness
- Exploring how evidence can better reach the bedside

Agenda

1. **Integrated Evidence Generation**
   - Simplifying a complex landscape
2. **Study Burden and Automation**
   - Opportunities in evidence generation
3. **Leveraging "passive" data collection through EMRs and linked data**
   - Using technologies for generating reusable, flexible and continuous evidence
   - Reducing burden, bias, and cost
   - Filling data gaps
   - Regulatory considerations
4. **Accelerating Evidence to the Bedside**
5. **Q & A**

Evidence Needs in the Product Life Cycle

Evidence for Investors, Internal Stakeholders, Regulators, Providers, Payers, Patients

Discovery	Preclinical	Clinical Development			Regulatory Submission	Phase IIIb/IV	Healthcare Delivery
		Phase I	Phase II	Phase III			
OBJECTIVES	**Is it viable?** *Efficacy, Toxicity, PK/PD*	**Is it safe?** *Establishing strategic direction and early proof of concept*	**Is it effective?** *Planning and scaling to prove safety and efficacy*		**Is it profitable?** *Reduce time to peak sales and speed formulary acceptance by demonstrating value*		**How does it work in the real world?**

Clinical Development Services

Real World Evidence Generation

Timeframe of a therapeutic agent through clinical testing to FDA approval is ~12 years, with costs estimated from $1 billion to $1.8 billion.

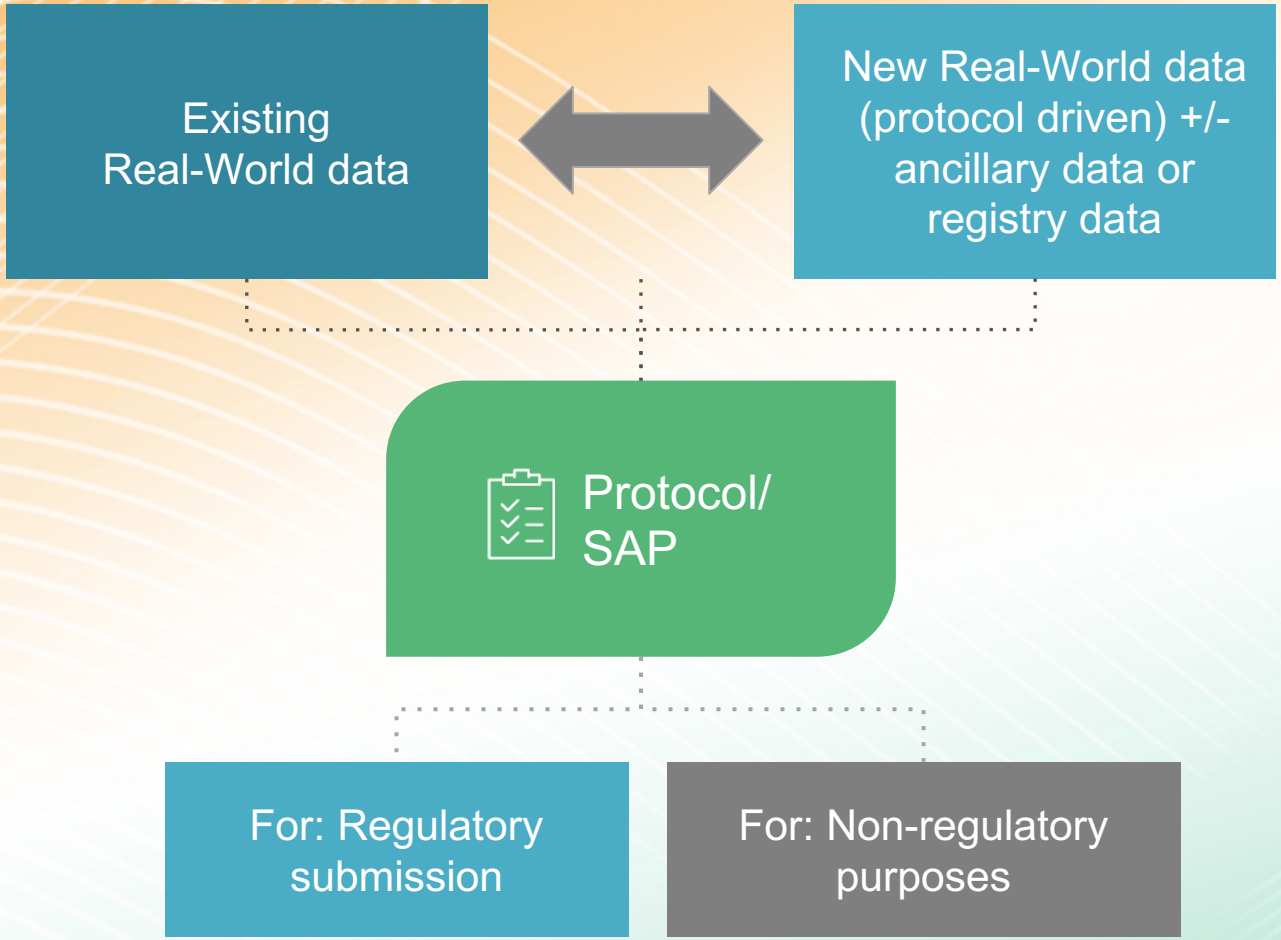
Use Cases for Real World Evidence

Disease Burden	Disease Mechanism	Trial Feasibility, Protocol Planning and Recruitment	Regulatory	Safety
Adherence	Effectiveness	Sub-types	Utilization	Value-based Contracting and Personalized Medicine

Integrated Real-World Evidence Generation

Integrated evidence generation (IEG) is a framework for generating evidence to support decision-making in healthcare.

- Involves the integration of multiple sources of real-world data (RWD), to provide a more comprehensive and accurate view of the effectiveness, safety, and value of healthcare interventions.
- Fit for purpose means that the data used and analyses generated meet the evidentiary standard for the particular use case.



What does integrated evidence generation mean to you?

Sonja Wustrack

Managing Director, Integrated Evidence Generation, OM1

Joris Van Dam

VP, Clinical Trials Innovation
Exact Sciences

Burden in Clinical Research

Patients

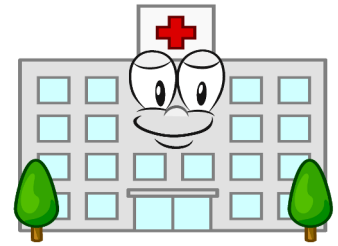
- Time commitment; in office and home
- Extra assessments; if doesn't match SOC
- Extra visit; waiting, parking
- May also burden caregivers

Clinicians

- Time required to identify, recruit, enter and review data
- Reduced number of patients that can be seen during clinic (and income)
- Frustrating duplication of efforts if not integrated with EMR

Sites

- Administrative hurdles including contracts, IRBs, audits, etc.
- Often multiple systems used
- Need to maintain and pay research staff to manage burden
- Challenges in identifying eligible patients without significant effort



Why is burden relevant to trial or study success?

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Joris Van Dam

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Exact Sciences

We need to change the research paradigm

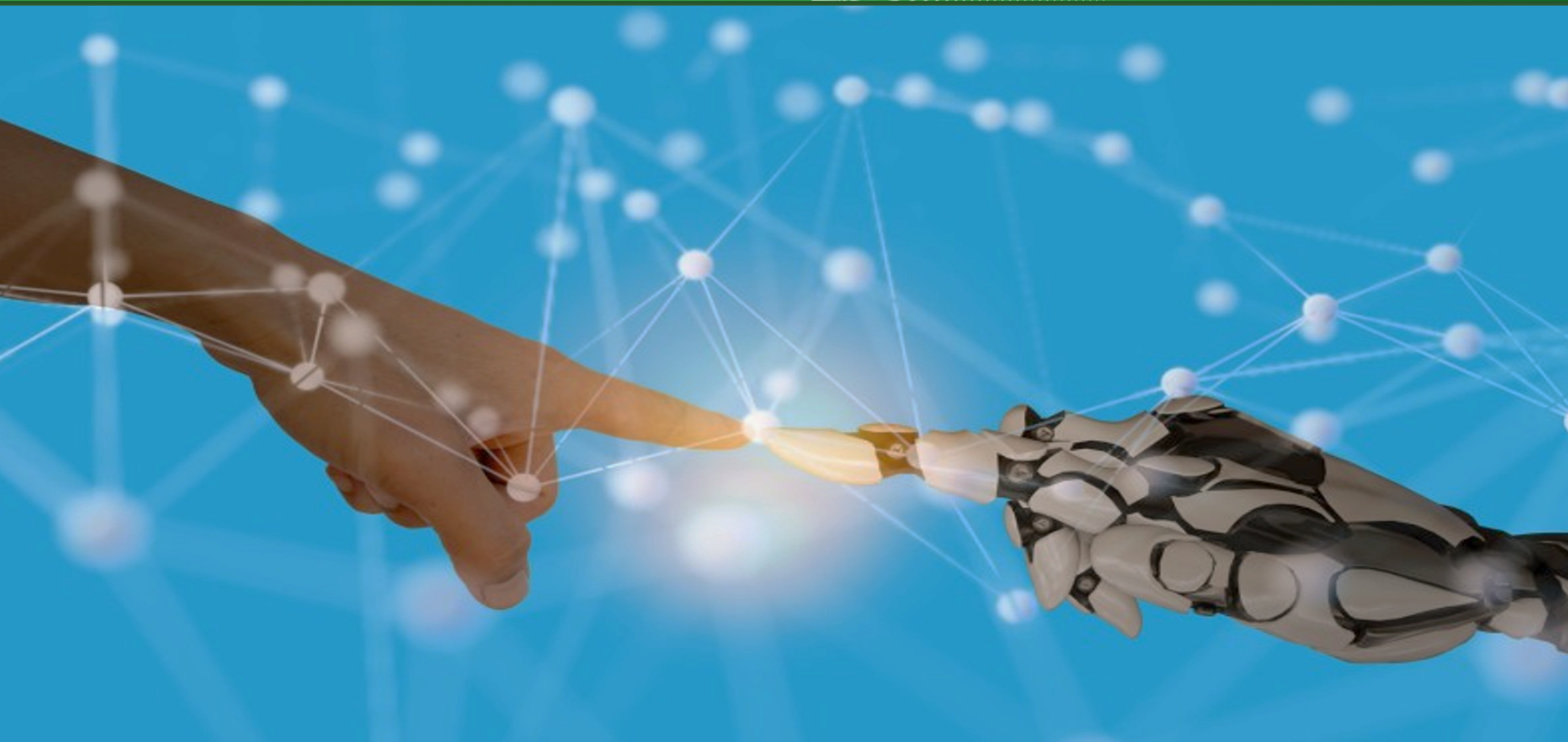
Traditional methods deliver the same results *and* limitations

- Linear, rigid design
- Costly and long delays to insights
- Selection bias and lack of diversity
- Extensive use of manual processes that are burdensome for HCPs and patients
- Gaps in data

Automation changes everything

- Flexible, reusable design
- Continuous stream of RWD
- Accelerate study timelines and drastically reduce costs
- Easily recruit high volumes of patients and minimize burden to sites and patients
- Increase patient diversity and reduce bias
- Linked data with the ability to adapt and expand

Automation = less burden on practices & study participants



Leveraging the EMR

EMR Connections

- Connected centers, patient-consented access
- Normalization, harmonization and enrichment

EMR & Systems of Record

Data Processing Platform

Processing EMR data from raw form to a common data model for a study

Study Databases

Data Sources & Data Standards

- Where to find data and how to use it
  - EHRs
  - Claims / administrative databases
  - Other registries
  - Patient-generated health data
  - Genomic data / biorepositories
  - Imaging data
  - Clinical data warehouses
  - Health information exchanges

- Understanding the role of data standards for supporting interoperability

From Gliklich RE, Dreyer NA, Leavy M: Registries for Evaluating Patient Outcomes: A User's Guide. 4th Edition. Agency for Healthcare Research and Quality. September 2020.

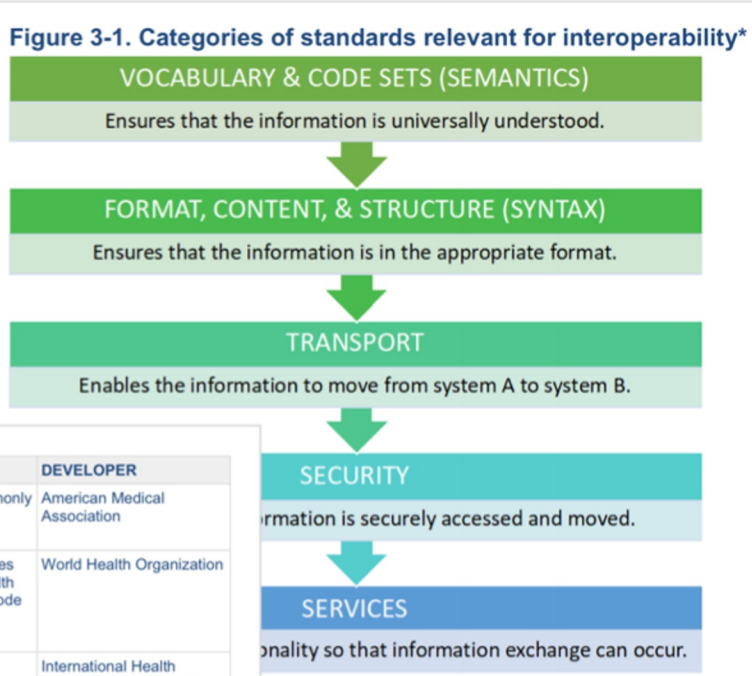


Table 3-1. Examples of vocabulary and terminology standards*

STANDARD	ACRONYM	DESCRIPTION	DEVELOPER
Current Procedural Terminology	CPT®	Medical service and procedure codes commonly used in public and private health insurance plans and claims processing.	American Medical Association
International Classification of Diseases	ICD-10	International standard for classifying diseases and other health problems recorded on health and vital records. The ICD is also used to code and classify mortality data from death certificates in the United States.	World Health Organization
Systemized Nomenclature of Medicine	SNOMED CT	Clinical healthcare terminology that maps clinical concepts with standard descriptive terms.	International Health Terminology Standards Development Organization
National Drug Code	NDC	Unique 3-segment number used as the universal identifier for human drugs.	U.S. Food and Drug Administration
RxNorm	RxNorm	Standardized nomenclature for clinical drugs. The name of a drug combines its ingredients, strengths, and/or form. Links to many of the drug vocabularies commonly used in pharmacy management and drug interaction software.	National Library of Medicine
World Health Organization Drug Dictionary	WHODRUG	International drug dictionary	World Health Organization
Logical Observation Identifiers Names and Codes	LOINC®	Concept-based terminology for lab orders and results.	Regenstrief Institute for Health Care

Adapted from "Data Elements for Registries," in Registries for Evaluating Patient Outcomes: A User's Guide.[2]

How do you view the role of automation (and ready access to EMR data) in trials, studies and registries?

Sonja Wustrack

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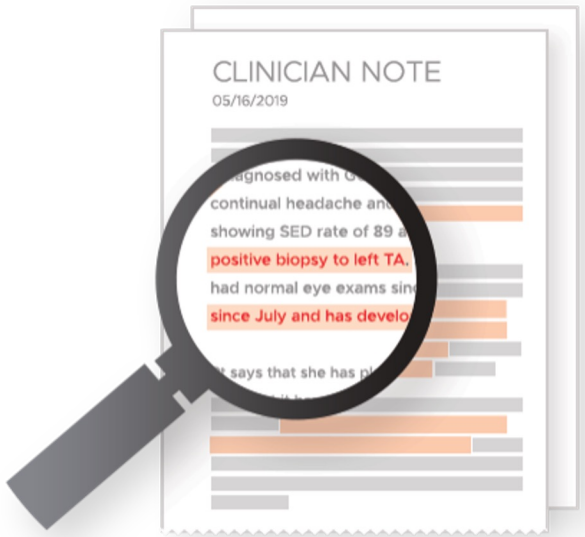
Joris Van Dam

VP, Clinical Trials Innovation
Exact Sciences

Unstructured Data

Derive structured information from unstructured data in a *validated and reliable* manner.

Unstructured Data → Structured Data



Apply machine learning and MLP

Valid and reliable data points

Disease severity, flaring and variable symptom presentation

Associated symptoms include **arthralgias, pleuritic pain, Raynauds phenomenon, rash and serositis**. Pertinent negatives include dizziness, fatigue, GI symptoms, muscle weakness, pericarditis, retinitis, unexplained fever and unexplained weight loss. Additional information: f/u SLE -- good days and bad - **leg weakness/vertigo**

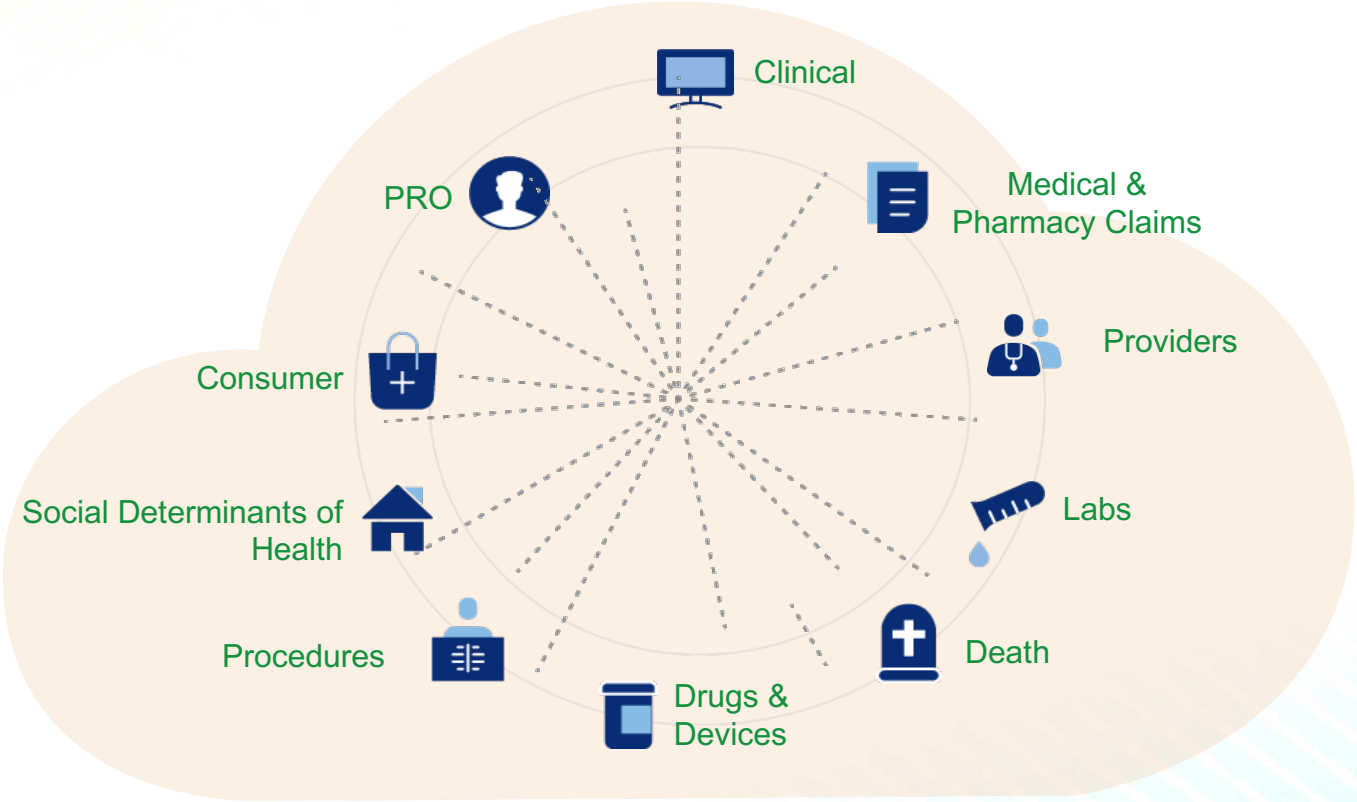
She was only able to take **1/2 a tab of plaquenil** due to **diarrhea**. She has had a few episodes of **blurry vision**, but it is far. We agreed f/u in 6 months but she will call if it worsens.

Feeling great on **Benlysta SQ weekly x 4m**. Remains on **PLQ 400mg/d and prednisone 5mg/d**. Only lupus complaint is **mild fatigue at end of day**.

Her **plaquenil dose was cut to 200 mg** daily after an **abnormal eye exam** but the f/u exam showed slight improvement.

Key information is in the Clinical Note

Linkage to other data sources



How important is unstructured data or linkage to other data sources to increase evidence value?

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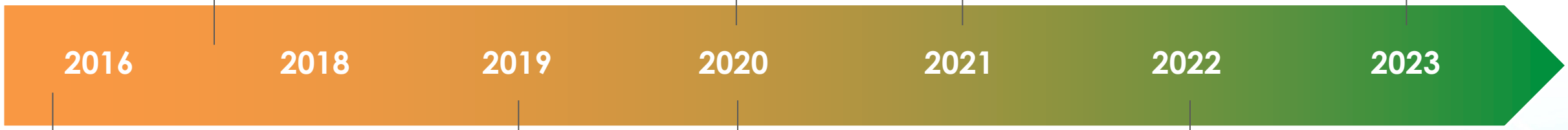
Managing Director, Integrated Evidence Generation, OM1

Joris Van Dam

VP, Clinical Trials Innovation
Exact Sciences

RWE guidance and achievements

The Cures Act enhances our ability to modernize clinical trial designs, including the use of RWE, and clinical outcome assessments, which will speed the development and review of novel medical products



21st Century cures act FDA*

Framework for Real World Evidence FDA

1 in 2 NDAs included an RWE study to support safety and/or effectiveness

25 FDA approvals with an RWE study

FDA discusses how PRO data can be used throughout the total product life cycle of medical devices

4th Edition of 'Registries for Evaluating Patient Outcomes' published (by Nancy Dreyer and ***Richard E. Gliklich***)

FDA publishes examples of RWE used in medical device regulatory decisions here

FDA publishes 4 draft guidances on how it will consider real-world data (RWD) in regulatory decision-making, from the **use of EHRs and registries** to RWD in non-interventional studies

The FDA have issued draft guidance on leveraging ECAs, such as **use data from registries and EHR,** in lieu of data from RCTs to demonstrate the safety and effectiveness of new drugs and biologics

Coming Soon: FDA draft guidance on diversity in clinical trials

*Note: Timeline is not all-inclusive

Has the FDA been clear enough on what it will accept for new indications or post-marketing commitments?

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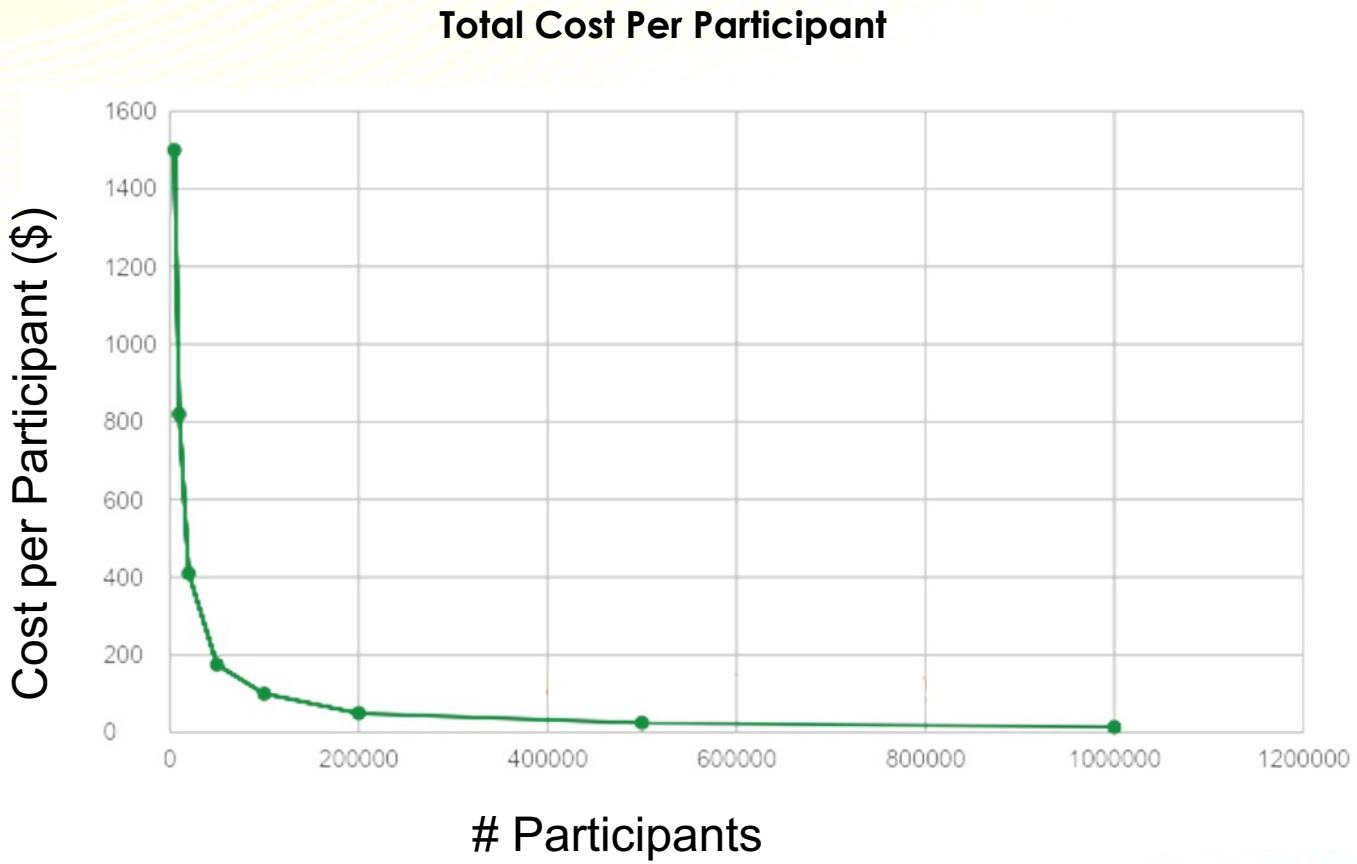
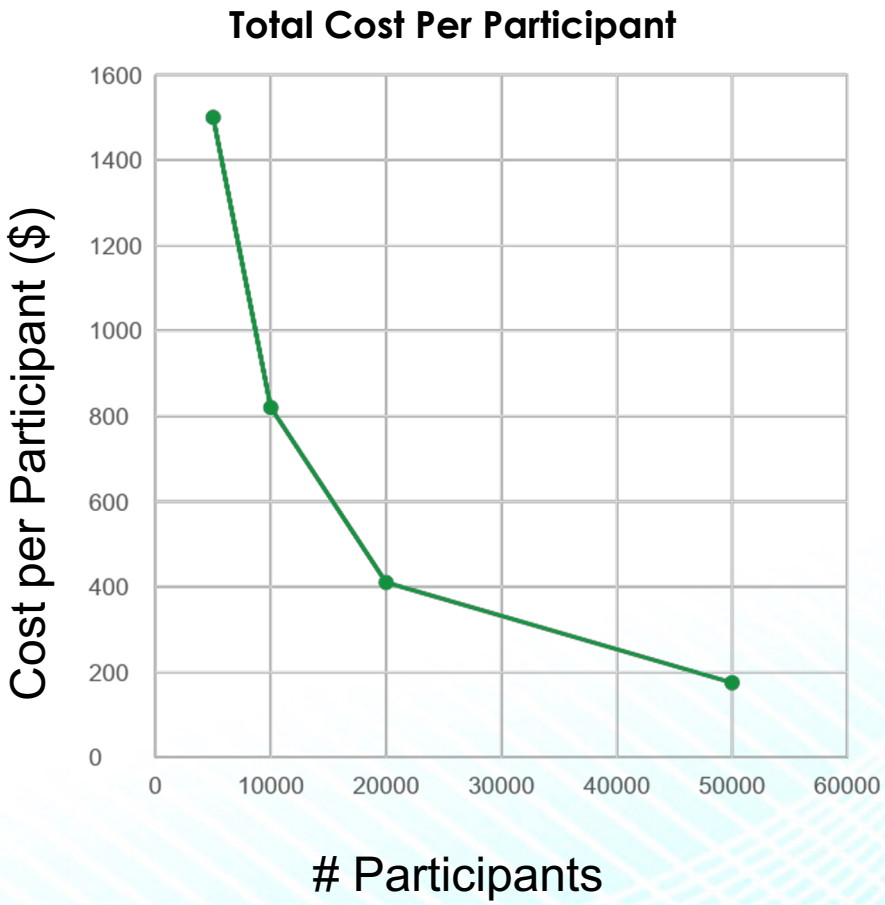
Exact Sciences

Automation, Scale and Cost: Phase III and IV





How important is it to optimize ROI with study design so that we can generate more representative evidence?

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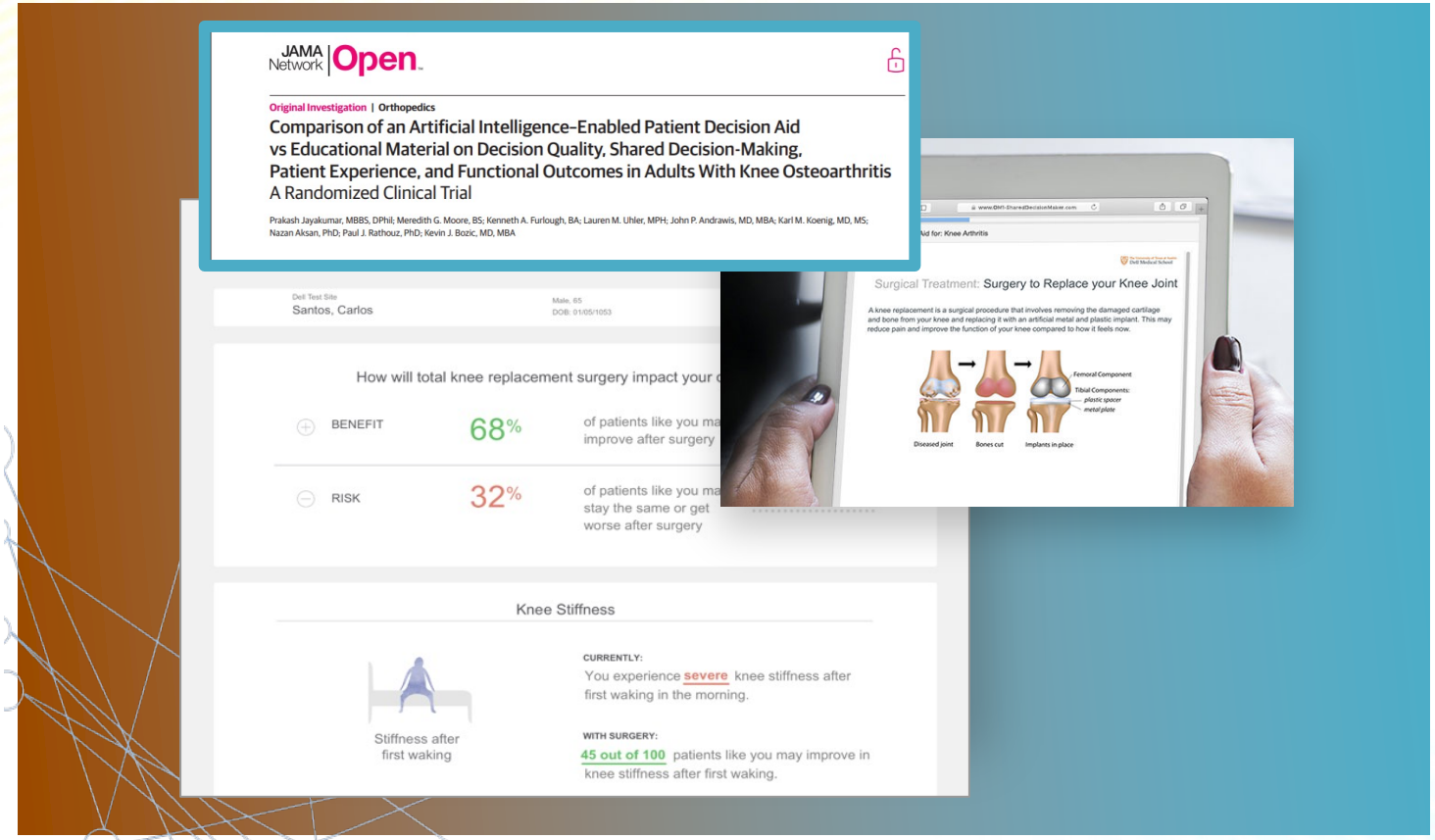
Exact Sciences

Studies show there is an estimated 17-year lag in the incorporation of evidence into routine clinical care

- Simply generating evidence is **slow** to close the gap between evidence and current care
- ***Integrated evidence*** aims to shift this lag through both faster and more complete evidence that is applicable to a broader range of patients
- Faster paths from evidence to practice will **benefit more patients sooner**

Using evidence for personalized treatment planning



Finding rare disease patients for treatment

Predictive Model AUC: 0.82

Jefferies et al.
Orphanet Journal of Rare Diseases (2021) 16:518
https://doi.org/10.1186/s13023-021-02150-3

Orphanet Journal of Rare Diseases

RESEARCH Open Access

A new approach to identifying patients with elevated risk for Fabry disease using a machine learning algorithm

John L. Jefferies[1], Alison K. Spencer[2], Heather A. Lau[3], Matthew W. Nelson[4], Joseph D. Giuliano[4], Joseph W. Zabinski[2*], Costas Boussios[2], Gary Curhan[2], Richard E. Gliklich[2] and David G. Warnock[5]

Abstract

Background: Fabry disease (FD) is a rare genetic disorder characterized by glycosphingolipid accumulation and progressive damage across multiple organ systems. Due to its heterogeneous presentation, the condition is likely significantly underdiagnosed. Several approaches, including provider education efforts and newborn screening, have attempted to address underdiagnosis of FD across the age spectrum, with limited success. Artificial intelligence (AI) methods present another option for improving diagnosis. These methods isolate common health history patterns among patients using longitudinal real-world data, and can be particularly useful when patients experience non-specific, heterogeneous symptoms over time. In this study, the performance of an AI tool in identifying patients with FD was analyzed. The tool was calibrated using de-identified health record data from a large cohort of nearly 5000 FD patients, and extracted phenotypic patterns from these records. The tool then used this FD pattern information to make individual-level estimates of FD in a testing dataset. Patterns were reviewed and confirmed with medical experts.

Results: The AI tool demonstrated strong analytic performance in identifying FD patients. In out-of-sample testing, it achieved an area under the receiver operating characteristic curve (AUROC) of 0.82. Strong performance was maintained when testing on male-only and female-only cohorts, with AUROCs of 0.83 and 0.82 respectively. The tool identified small segments of the population with greatly increased prevalence of FD: in the 1% of the population identified by the tool as at highest risk, FD was 23.9 times more prevalent than in the population overall. The AI algorithm used hundreds of phenotypic signals to make predictions and included both familiar symptoms associated with FD (e.g. renal manifestations) as well as less well-studied characteristics.

Conclusions: The AI tool analyzed in this study performed very well in identifying Fabry disease patients using structured medical history data. Performance was maintained in all-male and all-female cohorts, and the phenotypic manifestations of FD highlighted by the tool were reviewed and confirmed by clinical experts in the condition. The platform's analytic performance, transparency, and ability to generate predictions based on existing real-world health data may allow it to contribute to reducing persistent underdiagnosis of Fabry disease.

Keywords: Fabry disease, AI, Patient identification, Phenotypic biomarker

Should we use RWD to bring evidence into the clinic faster?

Sonja Wustrack

Managing Director, Integrated Evidence Generation, OM1

Joris Van Dam

VP, Clinical Trials Innovation
Exact Sciences

Q&A

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