SACRA
SOUTH AFRICAN CLINICAL RESEARCH ASSOCIATION

8th Clinical Research Conference

2018 26-28 SEPT

Innovative Technologies For Protocol Design, Site Selection and Patient Recruitment in Clinical Trials

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CLINERION
Real World Data Solutions

Clinical trial challenges ...

48%

of sites miss their targets[1]

57%

of trials have a protocol amendment[2]

80%

of trials are delayed, often recruitment related[3]

61%

increase in inclusion/exclusion criteria[4]

In an era of targeted therapies and tightly defined patient populations, we need a new data-driven approach.

1 Impact Report (2013) Tufts CSDD 15(1)

2 Impact Report (2016) Tufts CSDD 18(1).

3 Clinical Trial Delays: America's Patient Recruitment Dilemma (2012). Drugdevelopment-technology.com

4 Getz KA & Campo RA (2017) Nature Reviews Drug Discovery 16, 307

Global Technology Providers

Global companies provide the following services;

- Data Driven Protocol Design
- Data Driven Electronic Site Selection
- Data Driven Patient Recruitment
- Patient Engagement in RCT
- Patient Adherence in RCT
- Patient Reported Outcome with Surveys
- Social Listening
- Predictive Analysis
- Electronic Data Capture

REAL WORLD DATA

Definitions

RCT	• Only a small fraction of carefully selected patients are allowed to enroll in randomized controlled trials involving new compounds – the gold standard of drug assessment(?).
RWD	• Data collected in any setting which is not controlled, non-experimental; and usually follow the standard of care.
RWE	• Evidence derived from the aggregation and analysis of RWD elements.

- **Efficacy**
- **Safety**
- **Value/ Effectiveness**

RCT – RWD Difference

RCT: They excel at answering scientific questions about how well a treatment works and its potential side effects in controlled conditions with specific inclusion/exclusion criteria.

RWD: Real-world patients may be older, have different ethnicity, have more medical conditions, and have more advanced diseases.

Real World Evidence

Treatment Pattern	■ Which drug should be given first? ■ What's the best combination? ■ Analysis of index or event driven scenarios
Disease Burden	■ What is the cost of treatment? ■ What is the morbidity and death rate of the disease?
Patient Adherence to Therapies	■ What happens in real-life outside of RCTs? ■ What happens if the patient drops treatment?
Quality of Life	■ Patient Reported Outcomes

RWE Support Across The Product Lifecycle

Target Selection

- Understand unmet medical needs
  - How large is the patient population
  - How are they treated
  - Outcome / risk?
  - Which are the high risk groups?
  - What is the cost of treating/not treating them?

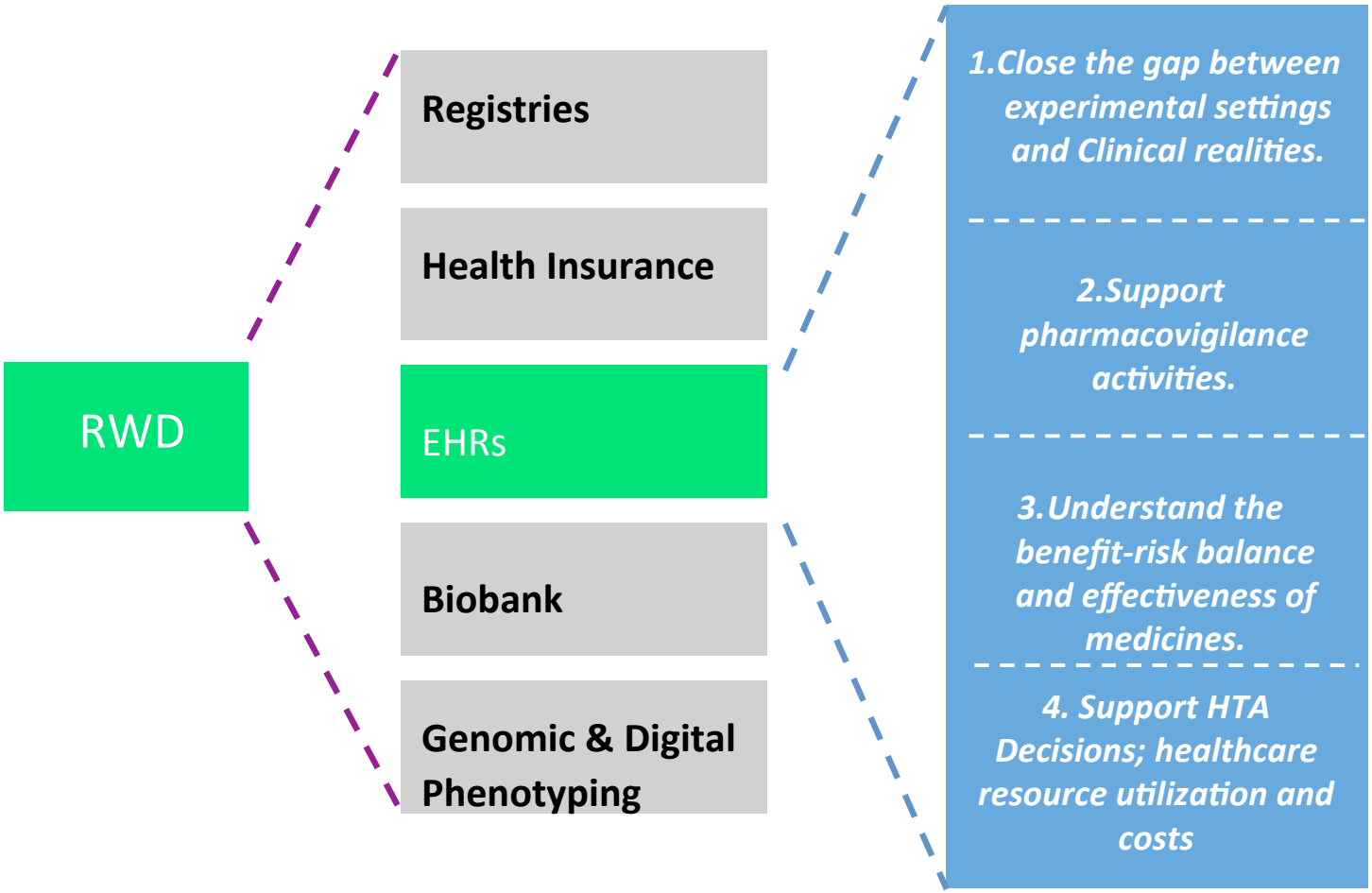
Launch

- Interpretation of trial results.
  - Who would benefit most from the treatment?
- Preparation of reimbursement and regulatory dossiers
- RWE insight into product go/no go decisions

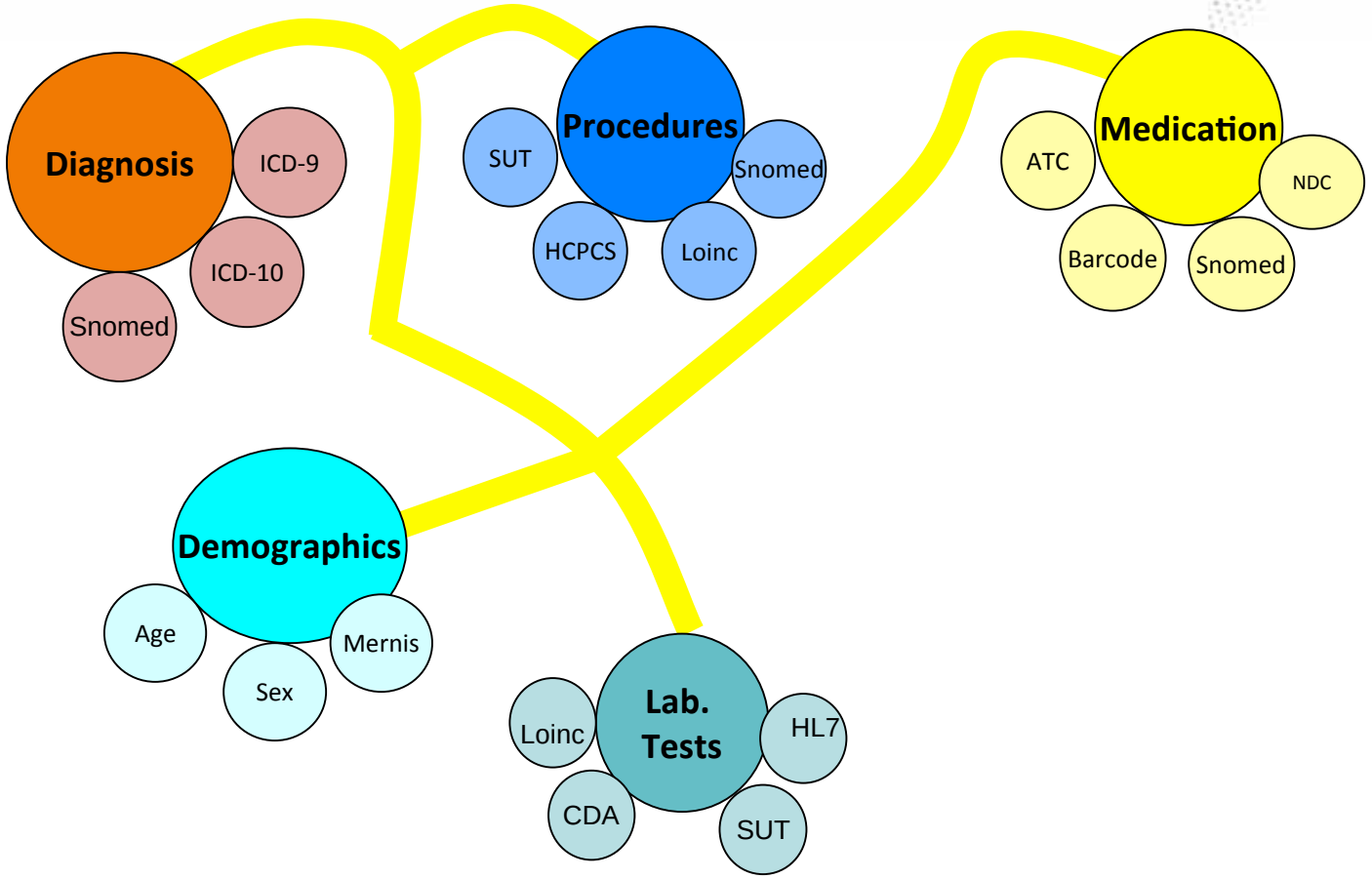
Commercialization

- RWE insights to support reimbursement and market access.
- RWE comparative effectiveness evidence relative to competitors.
- Long-term safety and effectiveness evidence
  - Who are treated? For how long?
  - Switch pattern?

Real World Data



Electronic Health Record (EHR)



FDA - Use of EHRs

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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News & Events

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FDA In Brief

FDA issues policy to facilitate the use of electronic health record data in clinical investigations

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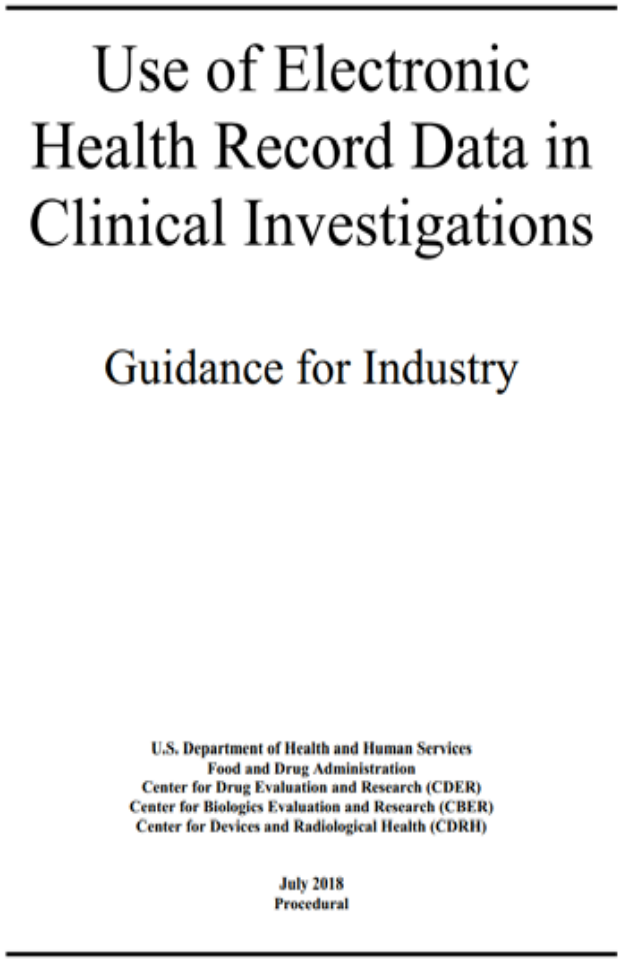
July 18, 2018

Media Inquiries

Stephanie Caccomo
301-348-1966

"The FDA is committed to developing policies and tools to help researchers access and use data collected from all sources to support a finding of safety and efficacy. This includes ways to expand our methodological repertoire to build on our understanding of medical products throughout their lifecycle – for example, every day, health care professionals are updating patients' electronic health records with data on clinical outcomes resulting from medical interventions used in routine clinical practice," said Jacqueline Corrigan-Curay, M.D., J.D., director of the Office of Medical Policy in FDA's Center for Drug Evaluation and Research. "As our experience with new medical products expands, our knowledge about how to best maximize their benefits and minimize potential risks sharpens with each data point we gather. Every clinical use of a product produces data that can help better inform us about its safety and efficacy. This guidance issued today facilitates the use of electronic health record data in clinical investigations and helps integrate data collected in routine care settings into clinical trials. Harnessing the real-



Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

Common Challenges

Data Security,
Privacy & Ethics

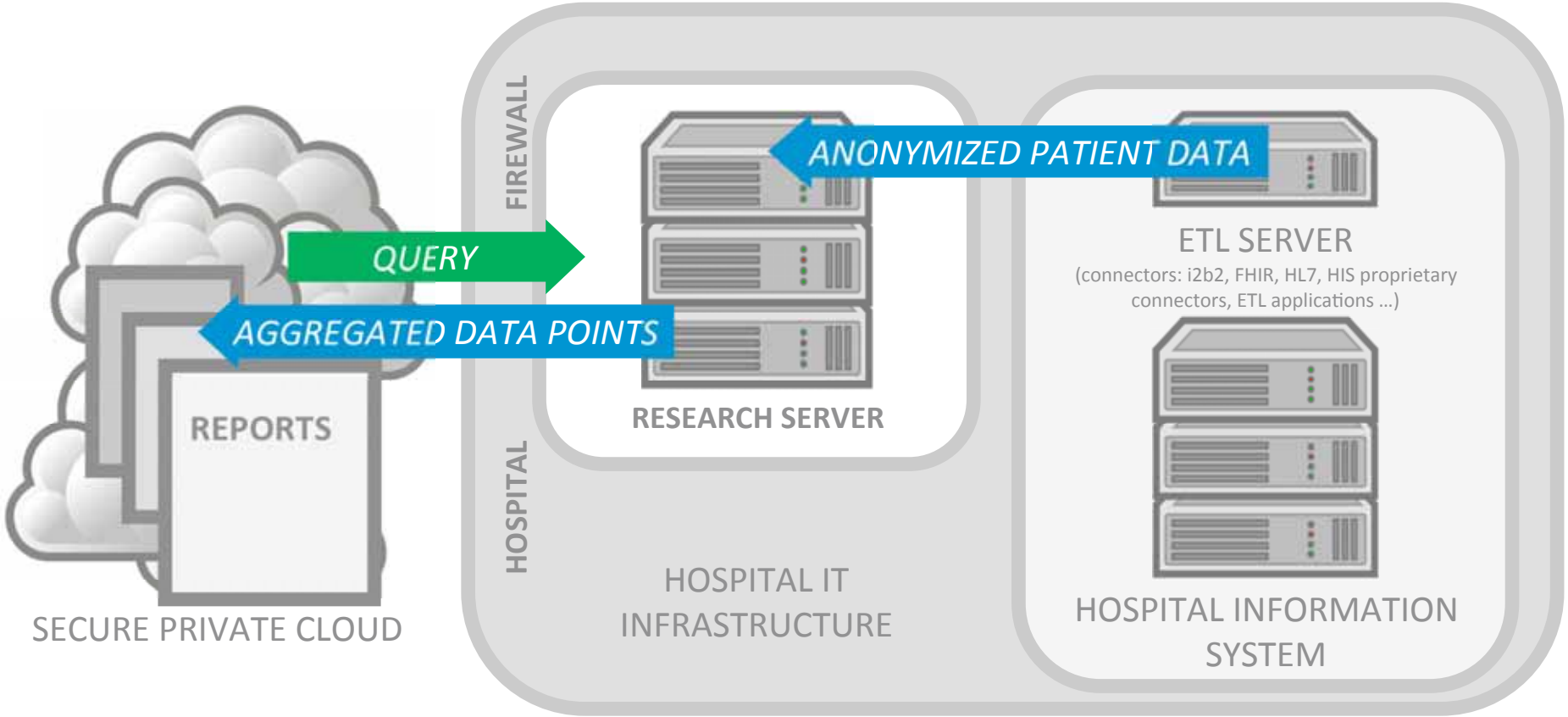
Interoperability

Scalability &
Sustainability

Data Quality

Data Flow within Hospital

Patient data does not leave the hospital



Data Governance + Patient Privacy Issues

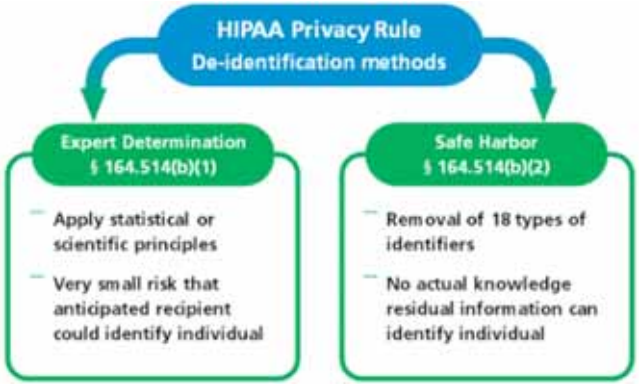
Principles

Of *paramount* importance as the value of what we offer is based on patient data.

We have to be committed to the responsible and trustworthy re-use of health data for research.

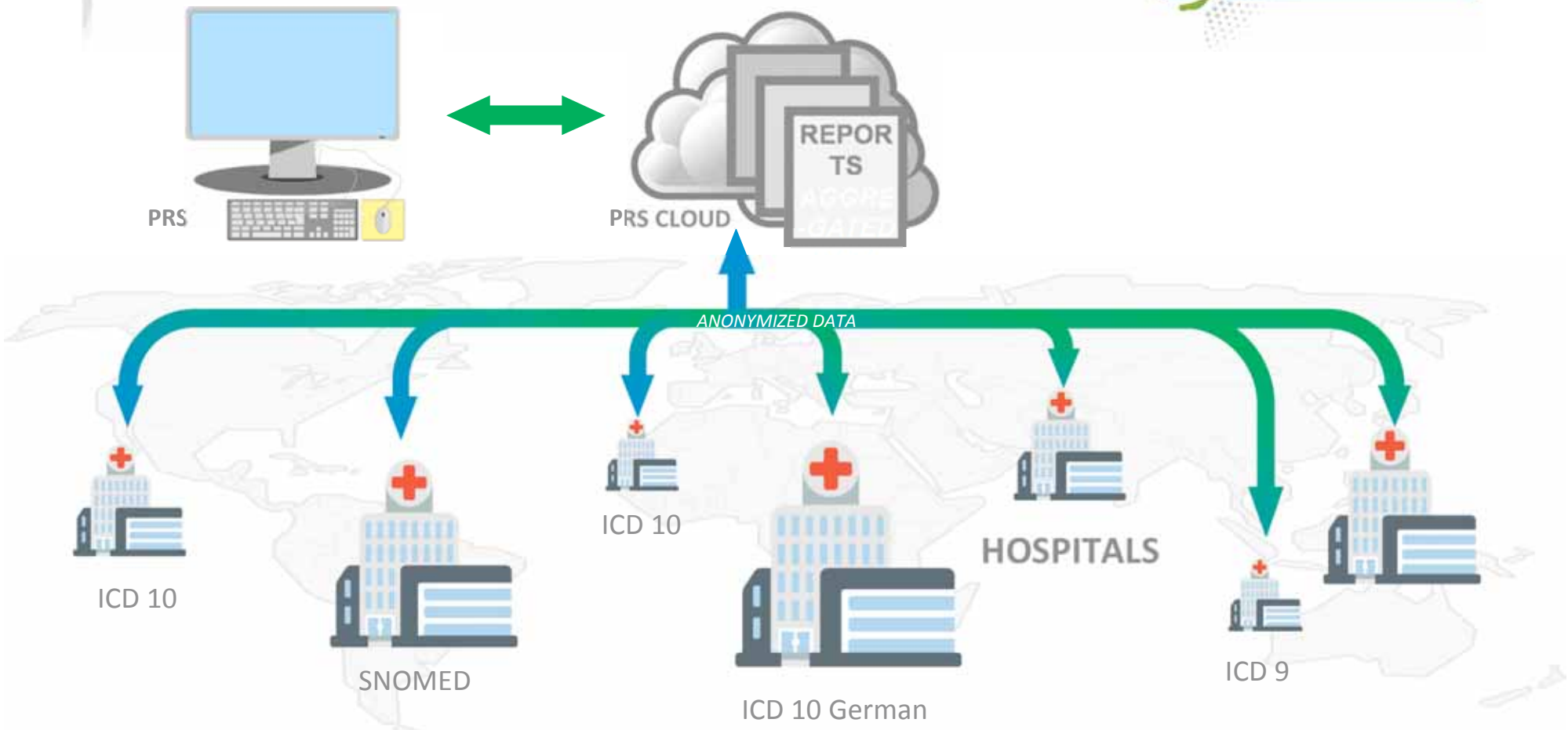
We have to develop systems following “Privacy by Design” principle.

We must follow international standards, e.g. the US Health Insurance Portability and Accountability Act (HIPAA) and the European General Data Protection Regulation (GDPR) (EU 2016/679).



NOTE: We should only process anonymized patient data, and anonymized patient data in itself does not fall under GDPR, nor HIPAA.

Scalable Systems



Interoperable System Features

Interoperability with multiple systems

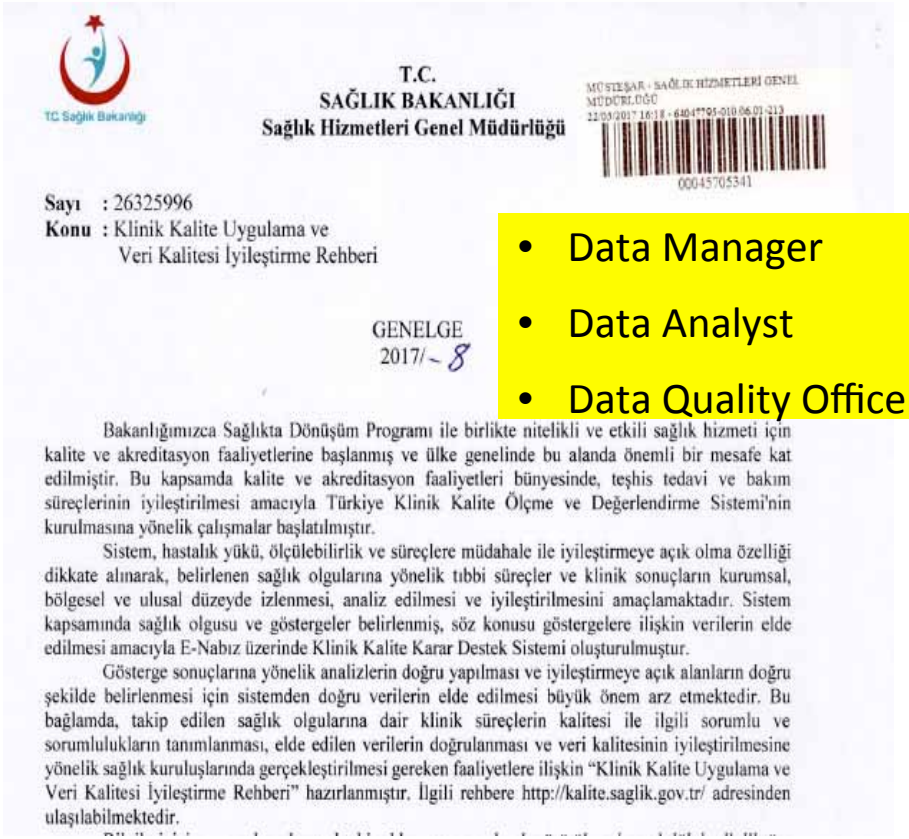
- Legacy and homegrown systems
- Stand-alone systems
- Cloud-based 3rd party data systems

Capability to deliver real-time and historical information

- Current medications, historical medications
- Current vitals, health status, notes
- Longitudinal disease progression for chronic diseases

Ontology management to map different coding sets of countries/hospitals

Data Quality



T.C.
SAĞLIK BAKANLIĞI
Sağlık Hizmetleri Genel Müdürlüğü

Sayı : 26325996
Konu : Klinik Kalite Uygulama ve Veri Kalitesi İyileştirme Rehberi

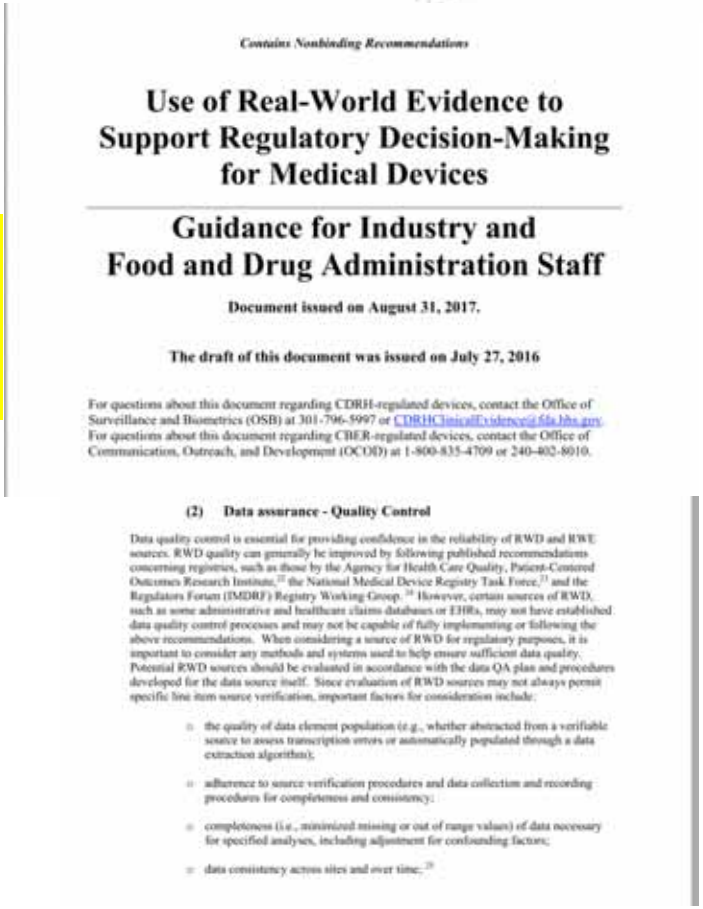
GENELGE
2017/ 8

Bakanlığımızca Sağlıkta Dönüşüm Programı ile birlikte nitelikli ve etkili sağlık hizmeti için kalite ve akreditasyon faaliyetlerine başlanmış ve ülke genelinde bu alanda önemli bir mesafe kat edilmiştir. Bu kapsamda kalite ve akreditasyon faaliyetleri bünyesinde, teşhis tedavi ve bakım süreçlerinin iyileştirilmesi amacıyla Türkiye Klinik Kalite Ölçme ve Değerlendirme Sistemi'nin kurulmasına yönelik çalışmalar başlatılmıştır.

Sistem, hastalık yükü, ölçülebilirlik ve süreçlere müdahale ile iyileştirmeye açık olma özelliği dikkate alınarak, belirlenen sağlık olgularına yönelik tıbbi süreçler ve klinik sonuçların kurumsal, bölgesel ve ulusal düzeyde izlenmesi, analiz edilmesi ve iyileştirilmesini amaçlamaktadır. Sistem kapsamında sağlık olgusu ve göstergeler belirlenmiş, söz konusu göstergelere ilişkin verilerin elde edilmesi amacıyla E-Nabız üzerinde Klinik Kalite Karar Destek Sistemi oluşturulmuştur.

Gösterge sonuçlarına yönelik analizlerin doğru yapılması ve iyileştirmeye açık alanların doğru şekilde belirlenmesi için sistemden doğru verilerin elde edilmesi büyük önem arz etmektedir. Bu bağlamda, takip edilen sağlık olgularına dair klinik süreçlerin kalitesi ile ilgili sorumlu ve sorumlulukların tanımlanması, elde edilen verilerin doğrulanması ve veri kalitesinin iyileştirilmesine yönelik sağlık kuruluşlarında gerçekleştirilmesi gereken faaliyetlere ilişkin "Klinik Kalite Uygulama ve Veri Kalitesi İyileştirme Rehberi" hazırlanmıştır. İlgi rehbere http://kalite.saglik.gov.tr/ adresinden ulaşılabilmektedir.

- Data Manager
- Data Analyst
- Data Quality Officer



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

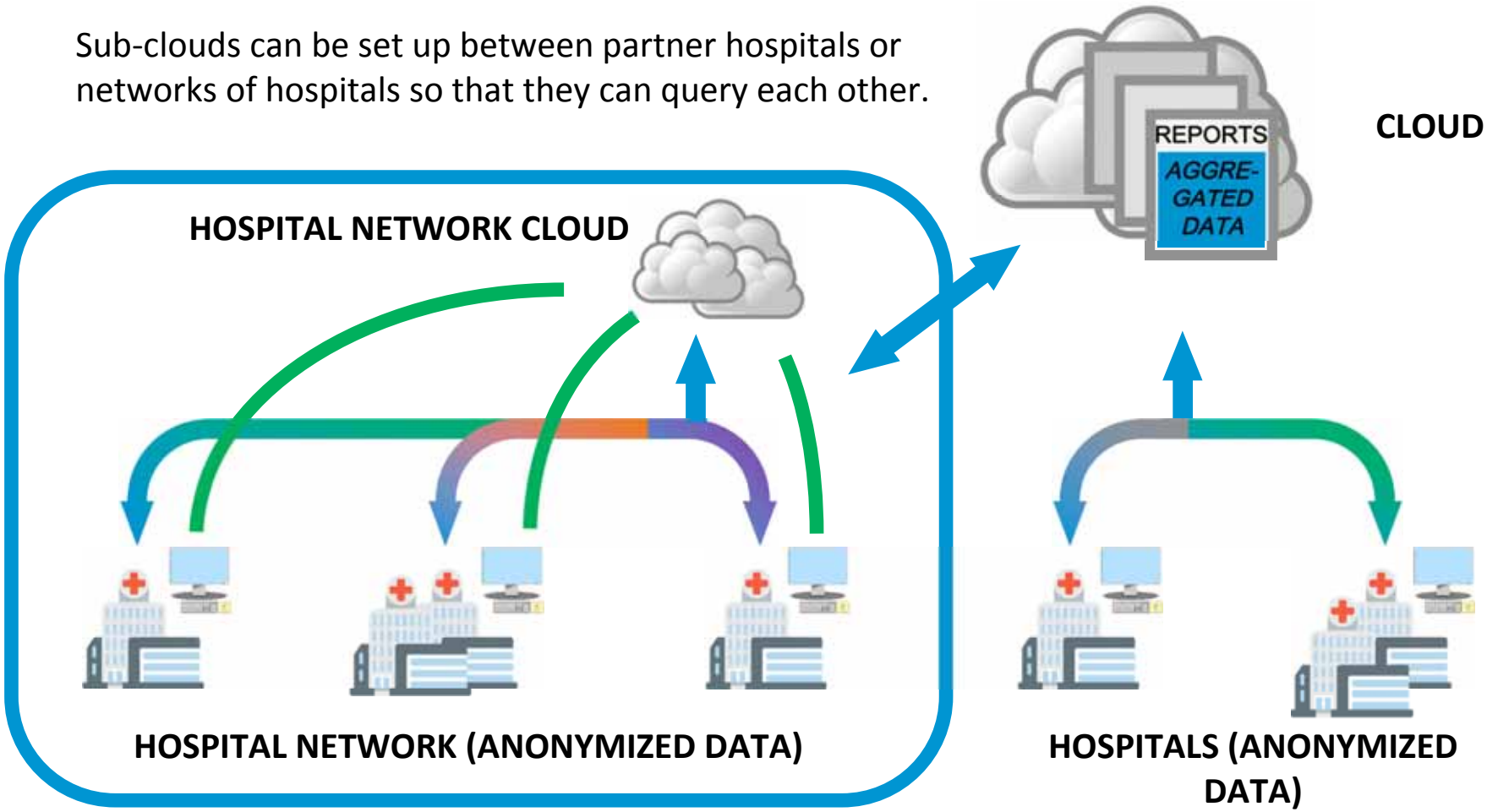
(2) Data assurance - Quality Control

Data quality control is essential for providing confidence in the reliability of RWD and RWE sources. RWD quality can generally be improved by following published recommendations concerning registries, such as those by the Agency for Health Care Quality, Patient-Centered Outcomes Research Institute,[27] the National Medical Device Registry Task Force,[21] and the Regulators Forum (IMDRF) Registry Working Group.[28] However, certain sources of RWD, such as some administrative and healthcare claims databases or EHRs, may not have established data quality control processes and may not be capable of fully implementing or following the above recommendations. When considering a source of RWD for regulatory purposes, it is important to consider any methods and systems used to help ensure sufficient data quality. Potential RWD sources should be evaluated in accordance with the data QA plan and procedures developed for the data source itself. Since evaluation of RWD sources may not always permit specific line item source verification, important factors for consideration include:

- the quality of data element population (e.g., whether abstracted from a verifiable source to assess transcription errors or automatically populated through a data extraction algorithm);
- adherence to source verification procedures and data collection and recording procedures for completeness and consistency;
- completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including adjustment for confounding factors;
- data consistency across sites and over time;[29]

Technology Solution Architecture For Research Alliance

Sub-clouds can be set up between partner hospitals or networks of hospitals so that they can query each other.



Benefits of Research Alliance

- the network may access a larger pool of patients
- access to experts in a variety of fields and to facilities offering other treatment methodologies
- not every hospital's research department is funded well enough to be able to afford state-of-the-art equipment
- not every research institute has access to experts in every field required by the research topic
- resources and costs may be shared
- IT infrastructure solutions may also be shared

Case Study: Type 1 Diabetes

Protocol

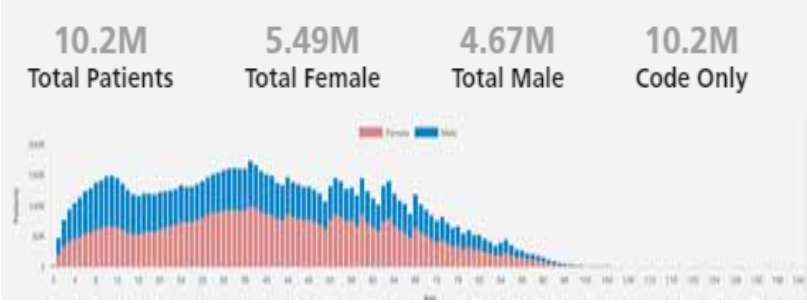
Inclusion Criteria

Exclusion Criteria

- Female patients aged between 40 and 75
- Diagnosed with Type 1 Diabetes Mellitus
- Documented unstable glycemic control within last 3 months
- Hospitalized within last 6 months
- Hepatitis B
- Hepatitis C

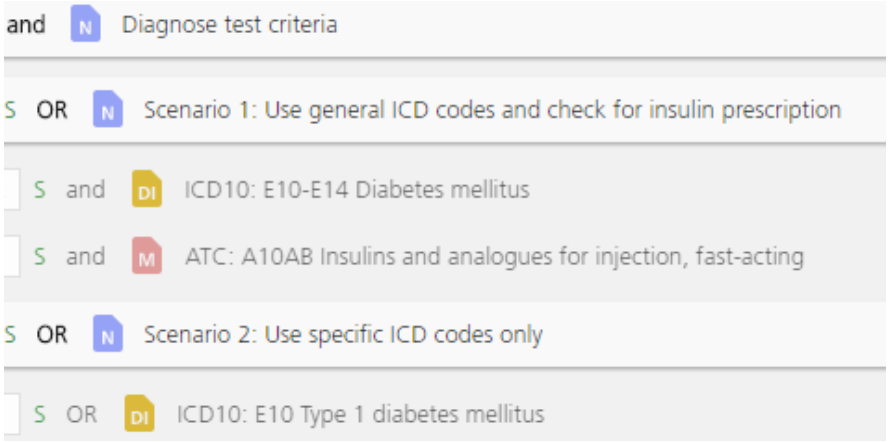
Case Study: Type 1 Diabetes

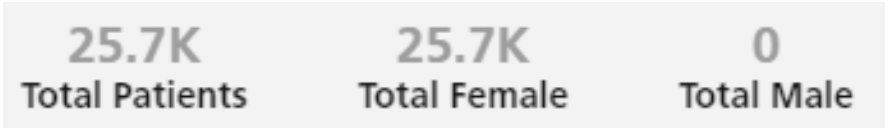
Total Patients in the EHR Network (Turkey)



Female patients aged between 40 and 75

Use general ICD codes and check for insulin prescription OR Use specific ICD codes only





Case Study: Type 1 Diabetes

Which strategy would you choose to code the eligibility criteria?

Scenario 1:

glucose level
≥ 200 mg/dL

Scenario 2:

fructosamine level
≥ 285 µmol/L

Scenario 3:

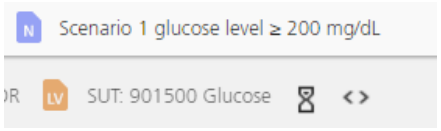
HbA1c level
≥ 11%

Case Study: Type 1 Diabetes

Documented unstable glycemic control within last 3 months

Scenario 1:

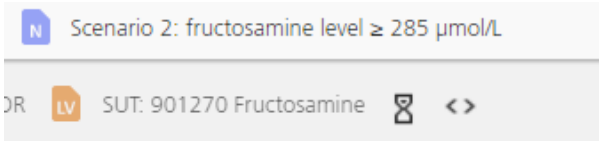
glucose level
≥ 200 mg/dL



614	614	0
Total Patients	Total Female	Total Male

Scenario 2:

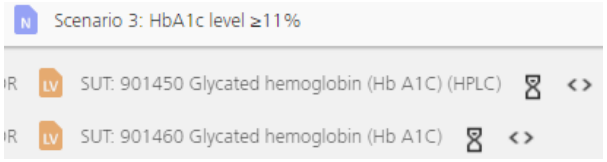
fructosamine level
≥ 285 µmol/L



7	7	0
Total Patients	Total Female	Total Male

Scenario 3:

HbA1c level
≥ 11%

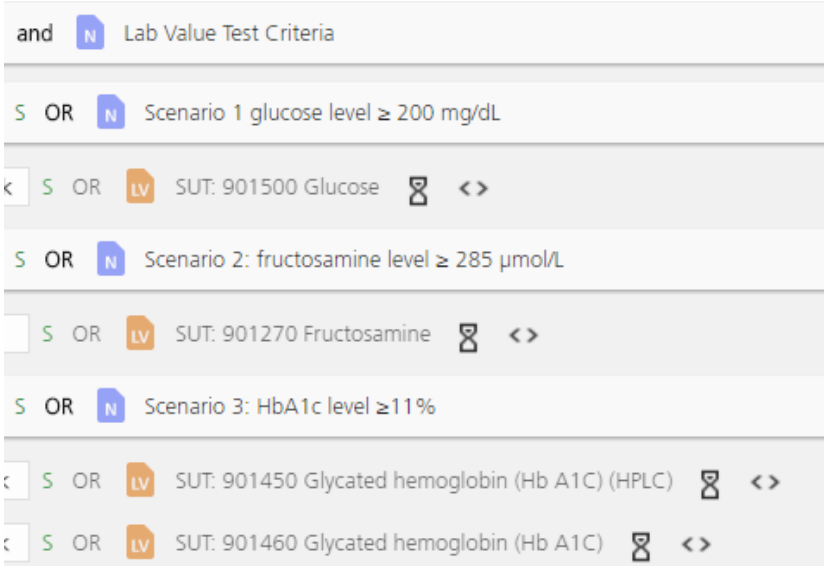


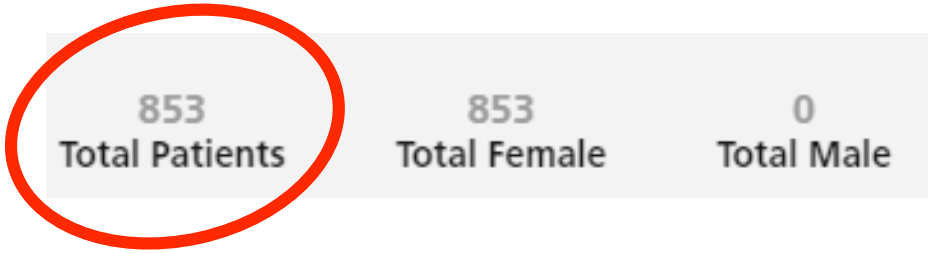
385	385	0
Total Patients	Total Female	Total Male

Case Study: Type 1 Diabetes

Documented unstable glycemic control within last 3 months

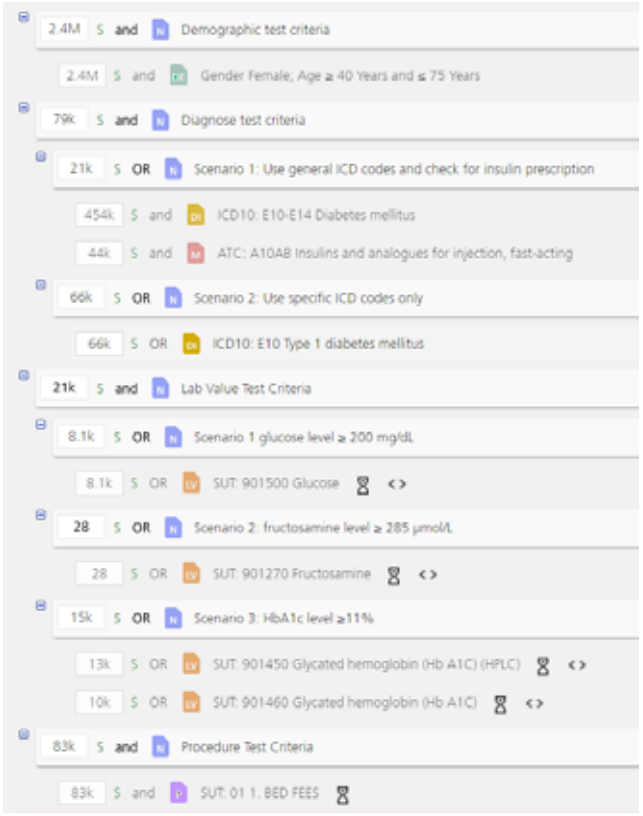
Scenario 4: Combine Scenarios 1, 2 and 3

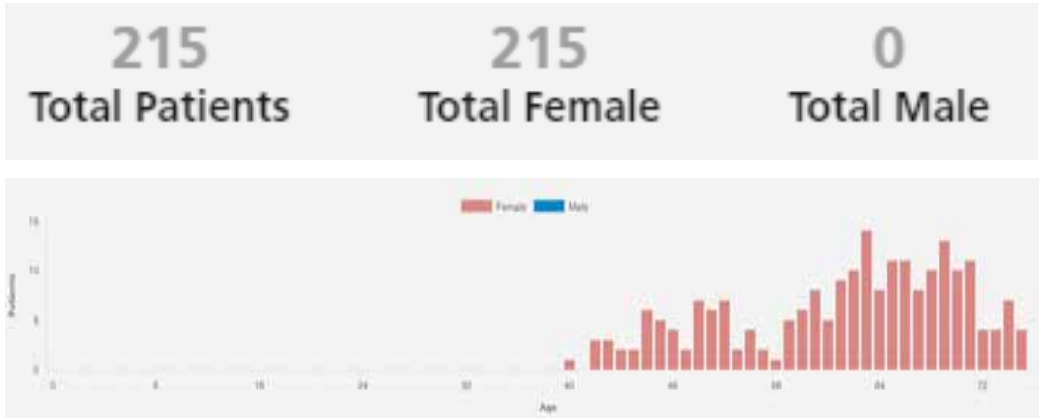




Case Study: Type 1 Diabetes

Hospitalized within last 6 months





Case Study: Type 1 Diabetes

Exclusion Criteria

Hepatitis B

203	203	0
Total Patients	Total Female	Total Male

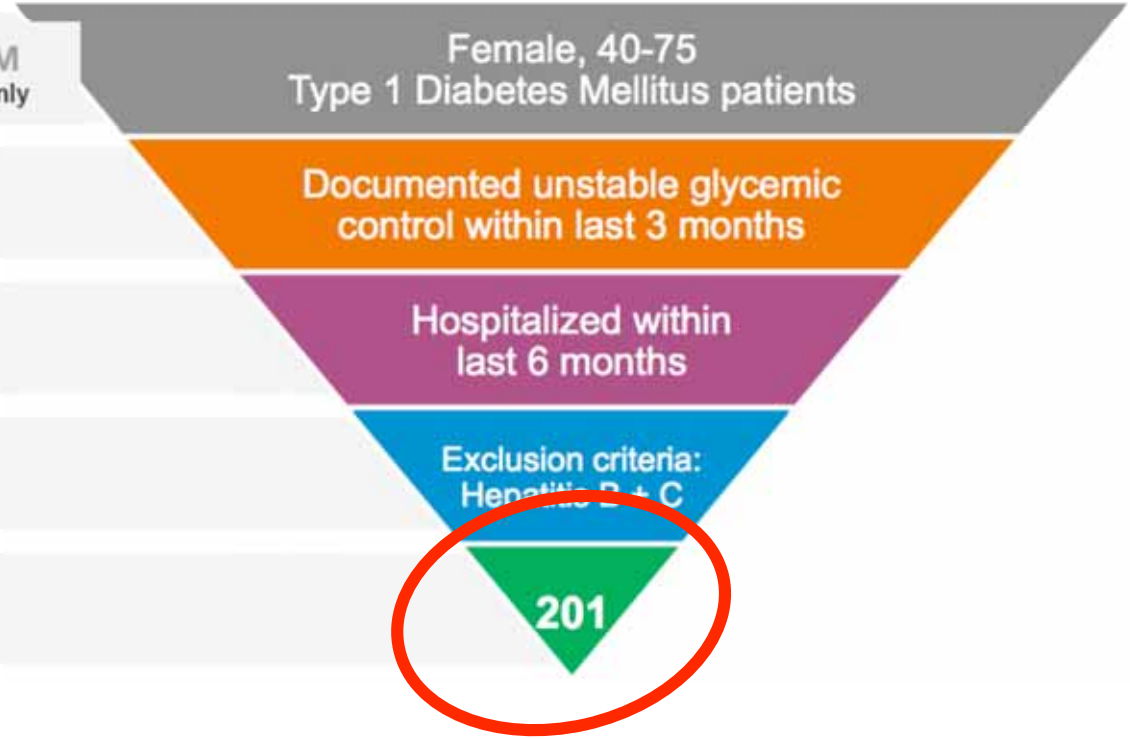
Hepatitis C

201	201	0
Total Patients	Total Female	Total Male

Case Study: Type 1 Diabetes

Optimal data driven planning and design / feasibility

10.2M Total Patients	5.49M Total Female	4.67M Total Male	10.2M Code Only
2.44M Total Patients	2.44M Total Female	0 Total Male	5.51M Code Only
25.7K Total Patients	25.7K Total Female	0 Total Male	
853 Total Patients	853 Total Female	0 Total Male	
215 Total Patients	215 Total Female	0 Total Male	
201 Total Patients	201 Total Female	0 Total Male	

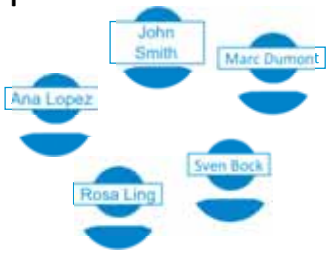


Anonymized Identification Technology

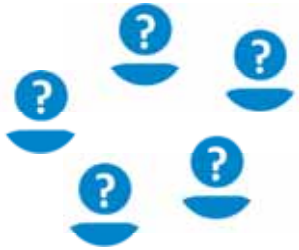
1. Patient records are anonymized and then synchronized to a separate server inside hospital's infrastructure.

How does it work?

Original hospital patient records



Anonymized patient records



2. Query is created in cloud based on protocol parameters.

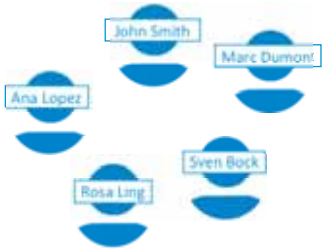
Protocol 1

Anonymized Identification Technology

How does it work?

3. User sends query to all local sites which allow queries. Query runs on the anonymized patient data to evaluate number and location of eligible candidates.

Original hospital patient records



ANONYMIZED

Anonymized patient records

Protocol 1

Two matches

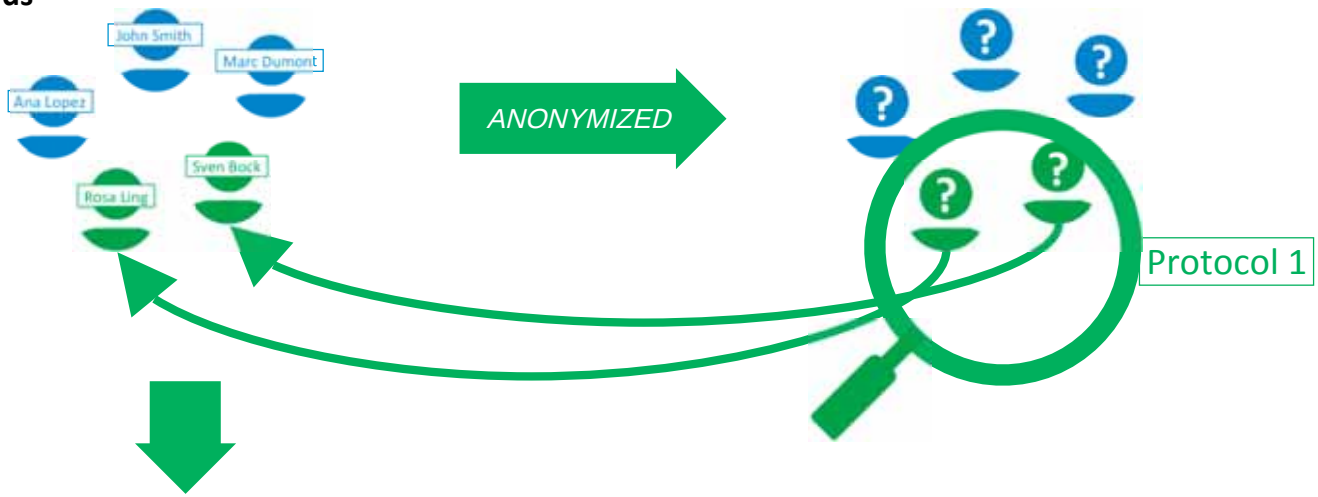
4. Query returns a COUNT of patients matching the protocol criteria at each site which has allowed its database to be queried.

NEW Anonymized Identification (ANID) Technology

5. Query is sent back to the individual hospital. Authorized hospital staff at the hospital run the query again on their own local anonymized database.

Original hospital patient records

Anonymized patient records



How does it work?

Two matching patients are IDENTIFIED.

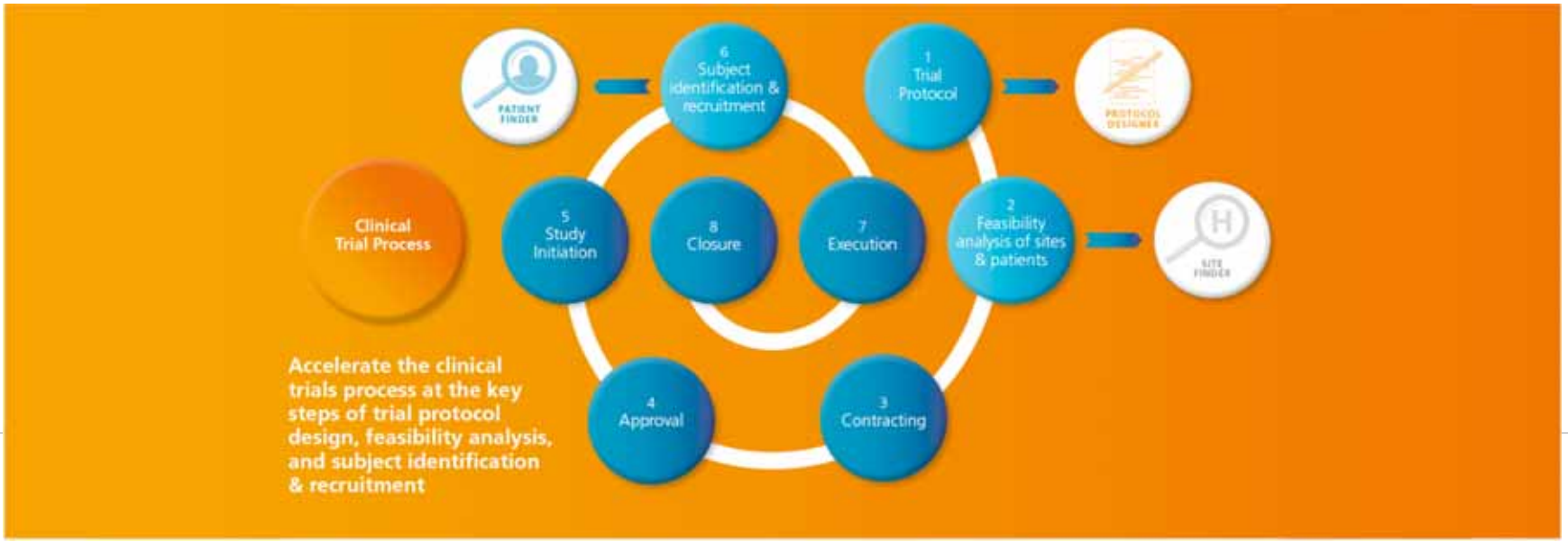
6. Query results are matched locally by authorized hospital staff.

Benefits For The Industry

- Make the protocol more relevant and realistic.
- Improve site strategy: fewer sites with more patients.
- Reduce delays and save resources.

Speed up the whole process!

Professional Research Units



- Competition starts at sites!
- We need Professional Sites with automated processes.

Thank you!

Barış Erdoğan, PhD

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