Accelerating Innovations for Sickle Cell Disease with Real World Evidence
SCD Stakeholder Meeting

Welcome!
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<thead>
<tr>
<th>Time (EST)</th>
<th>Topic</th>
<th>Lead</th>
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<tbody>
<tr>
<td>12:00 PM</td>
<td>Welcome, Introductions, Objective of the Roundtable</td>
<td>Dr. Wood, Dr. Urnov</td>
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<tr>
<td>12:10 PM</td>
<td>The Future of Real-World Evidence for FDA Regulated Research</td>
<td>Dr. Marks</td>
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<tr>
<td>12:20 PM</td>
<td>Coordinated Registry Networks (CRN): A Possible Role for Sickle Cell Disease RWD Generation</td>
<td>Dr. Marinac-Dabic</td>
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<tr>
<td>12:35 PM</td>
<td>Real World Perspectives on Curative Therapies for Sickle Cell Disease</td>
<td>Ms. Woolford</td>
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<td>12:45 PM</td>
<td>The ASH Research Collaborative Data Hub SCD Program:</td>
<td>Dr. Wood</td>
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<td>Accelerating Research and Enhancing Care</td>
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<tr>
<td>1:05 PM</td>
<td>RWD Needs Related to Genomic Therapies Workgroup</td>
<td>Dr. Urnov</td>
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<td>• Opportunities and challenges</td>
<td>Dr. Neuberg</td>
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<td>• Proposed initial topics to be addressed</td>
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<td>• Process and Timeline</td>
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<tr>
<td>1:25 PM</td>
<td>Exploring the Use of Coordinated Registry Networks to Optimize the ASH RC Hematology Data Hub Workgroup</td>
<td>Dr. Pappas</td>
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<td>• Opportunities and challenges</td>
<td>Dr. Hankins</td>
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<td>• Process and Timeline</td>
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<tr>
<td>1:35 PM</td>
<td>Panel Discussion and Q&amp;A</td>
<td>Dr. Wood, Dr. Marinac-Dabic, Dr. Marks, Dr. Neuberg, Dr. Pappas, Dr. Urnov</td>
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<td></td>
<td>• Respond to questions Stakeholders submit during presentations</td>
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<tr>
<td>1:55 PM</td>
<td>Wrap Up and Next Steps</td>
<td>Dr. Wood</td>
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<td>2:00 PM</td>
<td>Adjourn</td>
<td>All</td>
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Why We’re Here

• The time is now
• We are the community
• We will live, learn, and work together as one body to create change in the real world
Roundtable Objectives

• Purpose of the SCD RWE Stakeholder project
• Role of real-world evidence (RWE) for monitoring safety and effectiveness
• ASH RC Data Hub and Clinical Trials Network
• Launch two workgroups

Exploring the Use of Coordinated Registry Networks to Optimize the ASH RC Data Hub Work Group

Real World Data Needs Related to Innovative Genetic and Genomic Therapies Work Group
Exploring the Use of Coordinated Registry Networks to Optimize the ASH RC Data Hub Work Group

- Coordinated Registry Network (CRN) models
- Inform Data Hub implementation
- Data, methods, and sustainability
- SCD case study
Real World Data Needs to Innovative Genetic and Genomic Therapies Work Group

- Gene therapy and genome editing technologies
- Off target effects
- Immunogenicity
- Production variables
- Development pipeline
Executive Committee

• Bill Wood, MD, MPH
• Fyodor Urnov, PhD
• Peter Marks, MD, PhD
• Ann Farrell, MD
• Danica Marinac-Dabic, MD, PhD
• Julie Panepinto, MD
• Jane Hankins, MD
• Alexis Thompson, MD
• Charles Abrams, MD

• Michelle McMurry-Heath, MD, PhD
• Donna Neuberg, ScD
• Jennelle Stephenson
• Carlton Haywood, Jr., PhD
• Vence L. Bonham Jr, JD
• Kathleen Hewitt, DNP, RN
• Greg Pappas, MD
• Ken Taymor, JD
Accelerating Innovations for Sickle Cell Disease with Real-World Evidence

- Co-led by ASH RC and IGI
- FDA collaboration
- What are the science, data and structural needs for the Data Hub to generate real-world data for FDA regulated research?
- White paper/publication
“Would you take a genomic therapy?”

Do I want to take something so risky vs just see how the disease will progress?

No – for now. If gene therapy were safer, I would consider it. ... I don’t want to risk dying while curing it.

BETTER QUALITY OF LIFE
Increasing value of data to give persons with SCD a better quality of life

1. **Clinical trials**
   Pre-set data collection points

2. **Real-world data 1**
   Persons receiving genomic therapies:
   long term, open ended record of patient experiences.

3. **Real-world data 2**
   All persons with SCD:
   long term, open ended record of the full range of individual experiences.
A unique moment in the history of genomic therapies for SCD

Progress to date

2014 – current:
- Gene therapy clinical trials, iterative improvements, clear clinical benefit for later cohorts.
- Feb ’21: SUSAR (AML) reported on lentiviral gene therapy trial (out of N=~40); two cases of MDS.
- 2018: Genome editing clinical trials initiated, promising early stage data.

Wealth of CT and RW data*

On the horizon

- Multiple new open INDs and open trials for distinct genome editing approaches.
- Both academia and industry.

Wealth of CT and RW data*

Data*?

Not harmonized.
- Preclinical and patient followup framework for genome editing / gene therapy emerged organically 1989-2015 and has not been upgraded.

Alignment – via stakeholder consensus – on CT and RW data points being collected will enhance the value of both as therapies roll out into larger populations.

1. What are the key data points?
2. Collection of these data from CT and RW experiences.
The Future of Real-World Evidence for FDA Regulated Research

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
Coordinated Registry Networks (CRN): A Possible Role for Sickle Cell Disease Real World Data Generation

Danica Marinac-Dabic, MD, PhD
Associate Director
Office of Clinical Evidence and Analysis
Food and Drug Administration
Outline

- Background and Context
- MDEPINET and CRNS
- Regulatory Impact
- Next Steps: Maturity Model and Beyond
No single data source has ‘device and procedural details, patient descriptors, or long-term outcomes’

Many ‘limitations could be mitigated through interoperability solutions that strategically link complementary registries and data sources’

There is a ‘recognition that many key elements in such networks (such as EHRs, administrative claims data, or mobile device outputs) are not registries per se’

Importantly ‘Creation of CRNs could encourage efficient “dual-purpose” leveraging of existing registries, EHRs, administrative data resources’
Strategically Coordinated Registry Network (CRN): What is it?

- CRN is a novel system that comprises of strategically partnered electronic health information systems serving one or more clinical areas.
- The key feature is a multi-stakeholder partnership.
- The CRN builds on the national/regional registry(ies) by strategic harmonization and linkage to comparable data across the systems (e.g., EHR, claims, patient generated data, etc.).
- In the device space, the registry(ies) within the CRNs adhere to the definition/attributes established by the International Medical Device Regulatory Forum (IMDRF) and US National Medical Device Registry Taskforce (NMDRTF).
CRNs Build on International Models and Standards

“Organized system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system)’ with a primary aim to improve the quality of patient care”.

The IMDRF definition approximates the definition of CRN.
CRNs Come in Different Shapes and Sizes

- CRNs consist of one registry or multiple registries (e.g., AUGS AQUIRE registry for stress urinary incontinence and pelvic organ prolapse forming one Urogynecological CRN)
- CRNs can form a larger CRN infrastructure (e.g., Women’s Health Technology CRN)
- CRNs often join international counterparts to form international consortia (e.g., ICVR – in vascular space)
- CRNs from diverse clinical areas can further be strategically coordinated to collect core minimum data sets in interoperable way through CRN Collaborative Learning Community (e.g., demographics, comorbidities etc.)
Role of FDA in CRN Development and RWE Use for Regulatory Decision Making

• Through series of cooperative agreements FDA collaborate with ecosystem partners to develop CRNs in 13 clinical areas and to form the CRN Collaborative Learning Community (CLC) – coordinated by MDEpiNet

• With the support from OS/ASPE PCORTF, FDA spearheaded the maturation of CRNs as a node within the National Evaluation System for health Technologies (NEST)

• Used the RWE from CRNs for regulatory decision making
11th Annual Meeting Series

Co-chairs
- Danica Marinac-Dabic, FDA
- Art Sedrakyan, WCM
- Michael Lauer, NIH
- Sandra Siami, NEST
- Richard Kuntz, Medtronic
- Scott Smith, HHS
- Meena Vythilingam, OASH

Panel

November 2020 –February 2021 Webinar Series: Focus on Advancing the CRNs

www.mdepinet.net
MDEpiNet: Intersections with FDA Strategic Initiatives and NEST
PCORTF CRN Maturity: Patient Input is Critical

**Maturity**

Advance 7 attributes
1. Patient Engagement
2. Device Identification
3. Data Quality
4. Efficiency
5. Governance
6. Sustainability
7. Total Product Life Cycle (TPLC)

**Interoperability**

Pilot test device-specific FHIR profiles (SMART on FHIR platform and the FHIR Structured Data Capture Initiative (SDC) the capture and exchange of data to inform of an HL7 FHIR profile

**PPI/PRO**

Develop a module for capturing patient generated information and the methodology to evaluate scientifically valid data regarding patient uncertainty in accepting a variety of benefit/risk tradeoffs

**Novel Methods**

Develop and apply novel methods
1. Linking heterogeneous data from multiple data sources comprising a CRN;
2. Novel analytical methods including NLP/ML/AI to CRN linked data sets
3. Novel ways of data integration

**Disparity**

Sex/gender specific outcome studies
Connecting Internal and External CRN Infrastructures

CDRH CRN Steering Committee (OPEQ, OST, OSEL, HOW)
Oversight, prioritization

- OHT I: TMJ CRN
- OHT II: VISION CRN
- OHT III: UGD, WHT-CRN, SPARED, ESRD, VANGUARD
- OHT IV: Robotic, NBIR, Abdominal Core
- OHT V: DAISI
- OHT VI: Ortho CRN
- OHT VII: SHIELD

MDEpiNetcc
Methods
CRN CLCs
UDI Adoption
HIVE
Blockchain
Informatics
Clinical International Claims
Mobile Apps
ROI

OCEA
RWE Policy Coordination Alignment
Lessons Learned Methods
PCORTF grant

MDEpiNet Exec. Ops. Committee
Typical Phases of CRN Development

- Core Data Elements
- DELPHI to finalize the CDE
- CDE Publication Socialization
- IG/HL7
- Implementation Pilots

Building trust, transparency, tools and infrastructure for translational science
Organizational Structure
Methodology Work: Data Linkage

The Coordinating Center supports the CRNs by developing and refining anonymous linkage algorithms to harness data resources including registries, claims data, and EHRs.

- Linkage with indirect identifiers is reliable, with high sensitivity and accuracy

Index procedure
Registry data

Long-term
Administrative
data

Short-term
Registry + Administrative data

Long-term Reintervention After Endovascular Abdominal Aortic Aneurysm Repair

Culombo, Jesse A., MD, MS; Martinez-Cambor, Pablo, PhD; O’Malley, Alistair James, PhD; Suckow, Bjoern D., MD, MS; Hol, Andrew W., MD; Stone, David H., MD; Schanzer, Andres MD; Schermerhorn, Marc L., MD; Sedrakyan, Art MD, PhD; Goodney, Philip R., MD, MS; on Behalf of the Society for Vascular Surgery’s Vascular Quality Initiative. Author Information ©

Annals of Surgery, July 8, 2019 - Volume Publish Ahead of Print - Issue -
doi: 10.1097/SLA.0000000000003446
MDEpiNet – HIVE Virtual Technology platform with Blockchain Integration

- MDEpiNet researcher
- Clinical data collected directly from physicians
- PRO collected directly from patients
- EMR collected directly from clinics
- Existing datasets

MDEpiNet Virtual/Federated technology platform:
- QC
- cleanup
- standardize
- forms

- federated ecosystem for archival
- federated ecosystem for AI, evolutionary, machine learning, probabilistic algorithms

- data ingestion
- data processing
- data/analytics use

- CMS
- distribution engine
- access portal

MDEpiNet Umbrella
Added Blockchain Capabilities to MDEpiNet

Integration between HIVE and CHIOS

Network of HIVE nodes
2.1. API to login/logout from the HIVE system as a service (not as end-user)
2.2. Common identity framework
2.3. API to upload content to HIVE
3.1. Data structure definition for retrieved encrypted hashes
3.2. API to submit contract and hashes during download
3.3. Common contract document structure
3.4. Format for downloaded content packaging

CHIOS Blockchain

Virtual File System
1.1. User permission system
1.2. Virtual folder for data upload
4.1. Virtual folder and file list operations
6.1. Virtual folder list
6.2. Virtual file read request

Medical data
Data administrator

MDEpiNet researcher

Elements that already are implemented on HIVE side
Elements in need of implementation on HIVE side
MDEpiNet Vascular (VISION) CRN encompasses data sets from national registry (VQI), claims data, NY State data (SPARCS), PCORNet, Mobile Apps and clinical trial data tailored for multiple uses.
The Vascular Implant Surveillance and Interventional Outcomes (VISION) Coordinated Registry Network: An effort to advance evidence evaluation for vascular devices

Greg Tsougrakis, BS,a,b,c Jens Eldrup-Jorgensen, MD,d Daniel Bertges, MD,e Marc Schermerhorn, MD,f Pablo Morales, MD,g Scott Williams, MS, RAC,h Roberta Bloss, MS,i Jessica Simons, MD, MPH,j Sarah E. Deery, MD, MPH,k Salvatore Scali, MD,l Graham Roche-Nagle, MD, MBA, ME,m Leilla Mureebe, MD, MPH, MMC,n,o Matthew Mell, MD,p Mahmood Malas, MD, MHS,q Brian Pullin, MS,r David H. Stone, MD,s,t Misti Malone, PhD,u Adam W. Beck, MD,v Grace Wang, MD, WS,t Danica Marinac-Dabic, MD, PhD,u Art Sedrakyan, MD, PhD,v, and Philip P. Goodney, MD, MS,a,b Lebanon and Hanover, NH; White River Junction and Burlington, VT; Portland, ME; Boston, Mass; Rockville, Md; Bloomington, Ind; Flagstaff, Ariz; Gainesville, Fla; Toronto, Ontario, Canada; Durham, NC; Davis, San Diego, Calif; Birmingham, Ala; Philadelphia, Pa; New York, NY

ABSTRACT

The Vascular Implant Surveillance and Interventional Outcomes Network (VISION) is a Coordinated Registry Network (CRN) a member of Medical Device Epidemiology Network, a U.S. Food and Drug Administration (FDA) supported global public-private partnership that seeks to advance the collection and use of real-world data to improve patient outcomes. The VISION CRN began in September 2015 and held its first strategic meeting on September 10, 2018, at the FDA headquarters in Silver Spring, Maryland. VISION is a collaboration of the Vascular Quality Initiative (VQI), the FDA, and other stakeholders. At this annual meeting, leaders from the FDA, VQI, industry representatives, population health researchers, and regulatory science experts gathered to discuss strategic goals and opportunities for VISION. One of the key focus areas for VISION is linkage of VQI registry data to Medicare, longitudinal data sources maintained by various states, and other relevant data sources, as a model for efficient, cost-saving, and effective evidence generation and appraisal. This would provide the means to expand data collection, assess long-term procedural outcomes across the carotid, lower extremity, aortic, and venous intervention datasets, and execute registry-based trials through the CRN structure in an efficient, cost-effective manner. Looking forward, VISION strives to validate long-term outcome data in the VQI using industry datasets, in hopes of
Device type: gore aort

Would you recommend someone else to use this Web-Application?
- yes
- no

Please score your overall experience on a 1(worst)-10(best) scale.

How can we improve the web-application?

Where there any gaps noted in the outcomes that you consider as important?

Do you find the survey
Connecting Internal and External CRN Infrastructures

CDRH CRN Steering Committee (OPEQ, OST, OSEL, HOW)
Oversight, prioritization

OHT I
OHT II
OHT III
OHT IV
OHT V
OHT VI
OHT VII

TMJ CRN
VISION CRN
UGD, WHT-CRN, SPARED, ESRD, VANGUARD
Robotic, NBIR, Abdominal Core
DAISI
Ortho CRN
SHIELD

MDEpiNetcc
- Methods
- CRN CLCs
- UDI Adoption
- HIVE
- Blockchain
- Informatics
- Clinical
- International
- Claims
- Mobile Apps
- ROI

MDEpiNet Exec. Ops. Committee

PCORTF grant

Lessons Learned
Alignment
Coordination
RWE Policy

OCEA

Exec. Ops. Committee

CDRH CRN Steering Committee
(OPEQ, OST, OSEL, HOW)
Oversight, prioritization
Labeling Expansion
Registry data regarding safety and effectiveness of unapproved use may support expansion of FDA-approved indications for use

Control Group
Concurrent control group derived from RWD to support premarket decision

RWE Use Examples

Post-Approval Surveillance
Earlier device approval made possible by the use of RWE
RWE supplemented IDE helps FDA come to appropriate regulatory decisions faster

Supplementary Data
Leveraging CRNs for Regulatory Decisions

• Active Surveillance pilots (report to Congress under FDARA section # 708) (e.g., cardiovascular, orthopedics, women’s health)
• International study for label updates (e.g., ruptured AAA in ICVR)
• Signal discernment (e.g., paclitaxel pathways initiative) using VISION CRN
• Produced ROI analyses demonstrating value of CRN approach (e.g., TVT, VQI/VISION)
• Developed Objective Performance Criteria (OPCs) (e.g., peripheral vascular devices; hips and knee arthroplasty devices)
U.S. 42nd Country to Approve a 1st Generation TAVR Device

TVT Registry Established at Time of Device Approval

CMS NCD FDA Approval of Subsequent Indications Automatically Covered

TVT Registry Used to Support Approval of Subsequent Indications and Device Generations

3rd Generation TAVR for Intermediate Risk 18 Days After CE Mark for Similar Device

Mitral Valve-in-Valve 1st in World

Transcatheter Heart Valves
The Road from 42nd
Transcatheter Heart Valves
The Road from 42nd

U.S. 42nd Country to Approve a 1st Generation TAVR Device

TVT Registry Established at Time of Device Approval

CMS NCD
FDA approval of Subsequent Indications Automatically Covered

TVT Registry Used to Support Approval of Subsequent Indications and Device Generations

3rd Generation TAVR for Intermediate Risk
18 Days After CE Mark for Similar Device

Mitral Valve-in-Valve 1st in World

Return on Investment (ROI)
3 companies invested total of $25M
23 Decisions: Studies would have cost ~$134M
ROI > 500%
CRN Maturity: Key Domains

Unique device identification (UDI): precise identification of medical devices and their attributes is essential to evaluation

Engaging patients and measuring patient reported outcomes: Evaluate preferences and measure general and disease specific PROs

Data Quality: Coverage, completeness of enrollment & records at both baseline and follow-up, and periodic audits
CRN Maturity: Key Domains

**Improving data collection efficiency:** use of mobile apps, structured data capture and automation with interoperability solutions

**Governance and Sustainability:** Engage major stakeholders: societies, payers, various states. Obtain major & diverse funding

**Healthcare Quality Improvement:** Device technologies require continuous evaluation: Feedback, benchmarking and outlier assessments

**Total Product Life Cycle:** Registries can serve as an infrastructure for conducting both clinical research and device surveillance at different stages of device evaluation. Important role for data linkages
Continued Modernization of MDEpiNet & CRNs

- Ensuring security of integrated cloud-based CRN infrastructure
  - E-consent integration
  - Smart contracting engine
  - Data provenance tracking
  - Integrating smart audits

- CRN architecture improvements and novel methods
  - Telemedicine/remote monitoring
  - Patient- and clinician-facing portals (e.g. PRO, PPI)
  - Interoperable "Lean" and "Smart" architecture implemented in EHR
  - Digital tool (e.g. sensors) & imaging data
  - Adding “Trusted AI/ML features” in cloud-based virtual environment

- Developing New CRN
  - Robotic Surgery

- Across all CRNs
  - Implementing Maturity Model
  - Adding COVID 19 modules

- Transforming legacy registry data collection
  - Routinely capturing cost data as foundation for future CRN ROI and value studies
  - Routinely conducting gender/sex, race/ethnicity CRN studies of disparity and outcomes
Lessons learned

- Registries are low hanging fruit; when linked to other data sources can produce RWE
- Value is created by **re-use of data**, achieved by coordinating multiple stakeholders (data producers and data users)
- MDEpiNet, as a public private partnership, has developed trust among the partners, which is critical in these networks contributing data to NEST
- Building a CRN through Collaborative Learning Communities promotes communication of best practices/lessons learned and collaboration
- FDA plays a critical role in the creation of RWE by arbitrating the utility of data (quality and fit for purpose) essential to the ecosystem
  - Ensuring proper variables are used and of regulatory grade, validation of endpoints, evaluation of methods.
Thank You!

danica.marinac-dabic@fda.hhs.gov
Real World Perspectives on Curative Therapies for Sickle Cell Disease

Teonna Woolford
CEO, Sickle Cell
Reproductive Health Education Directive
The ASH Research Collaborative Data Hub SCD Program: Accelerating Research and Enhancing Care

Bill Wood, MD, MPH
Chair, Data Hub Oversight Group
Senior Medical Advisor, ASH RC
What is the ASH Research Collaborative?

Background

• Established in 2018
• Non-profit organization
• American Society of Hematology

Our Goal

• Foster collaborative partnerships
• Accelerate progress in hematology
• Improve lives of people affected by blood diseases
The Need

- 4 FDA approved SCD therapies
- Unprecedented & deep SCD therapeutic pipeline
  - 40+ therapeutics in development for SCD
  - Difficulty getting patients interested in participating in clinical trials
SCD Clinical Trials Network

Community-Centered
- Overcome barriers to clinical trial participation
- Prioritize research areas of interest to the SCD community
- Improve enrollment, design, and execution of trials
- Community Advisory Boards

Real-World Data
- Utilizing the Data Hub to identify cohorts for research
- Natural history studies
- Contemporaneous control group

Research Ready
- Assembly of sites with a culture of collaboration and research
- Matching sponsors with sites
- Ensuring an efficient and coordinated approach to trials
- Centralized IRB and contracting
CTN Sites

25 Consortia
- 25 Clinical Trial Units
- 118 Clinical Research Sites

Represents ~50,000 individuals living with SCD
CTN Rapid Study Start Up

Geographically Diverse
~26 CTUs with 118 CRSs SQVs

GCP Training (CITI)
Site personnel associate their CITI accounts with ASH RC training requirements
CTU Coordinator

Single IRB Review Process
WCG IRB – protocol, ICF and associated documents
Study specific reliance Agreements
Single Invoicing

Electronic Trial Master File
Collect essential documents through trial activation
Review of study specific operations guide
Veeva Vault

PI Protocol review
Feasibility questionnaire
Data Hub Cohort Analysis
Study Feasibility Assessments

Master Agreements with CTUs
Sponsor studies through separate task orders
Single Contracting

Guidance Docs for Local Community Advisory Boards
Tools and Templates Continuous Patient Engagement

Opportunity for stakeholders and PI to meet
Annual ASH RC Summit

Trial Operations and Study Execution
SCD Community Engagement

Community-Centered Approaches

• Overcome barriers to clinical trial participation
• Prioritize research areas of interest to the SCD Community
• Improve enrollment, design, and execution of clinical trials
• Community Advisory Boards (CABs)
The Data Hub

- Sickle Cell Disease
- SCD Learning Network
- Multiple Myeloma
- COVID-19 Registry
Responding to a Need...

- Facilitate capture and sharing of benign and malignant hematologic data
- Support scientific inquiry and discovery
- Be the largest real world data information resource within the global hematology community
A Centralized Real-World and Research Data Hub

**Data Inputs**
- EHR
- Public Health Surveillance Data
- Claims
- Clinical Trial Data
- Genomics

**Data Hub**

**Data Analytics**
- Clinical/Quality Metrics
- Research

**Outcome**

**Enhance Clinical Care**
- Insights on current practice
- Quality Improvement
- Personalization of care

**Accelerate Research**
- Pre-Market Research
- Post-Market Research
- Academic Research
Data Hub SCD Program Update

- 12 sites enrolled
- Site Portal / Dashboard launching 2021 Q2
- Adult eConsent launching 2021 Q3

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<tr>
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<th>Adult F</th>
<th>Adult M</th>
<th>TOTAL</th>
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<td>1,919</td>
<td>1,953</td>
<td>1,746</td>
<td>1,531</td>
<td>7,149</td>
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Consenting patients submit full PHI; non-consenting patients submit a limited dataset (LDS). Patient-level EMR data is automatically uploaded using OMOP or FHIR abstraction data standards. Industry closed clinical trials and other data sources (e.g., payer, genomic, laboratory, etc.) are uploaded using an individualized dataset converter solution.

Data is validated for completeness and integrity. Data Quality Reports are provided to Sites to enhance data completeness. Data is cataloged and sent to the Data Hub for secure storage.

Validated data is securely stored in an agile Data Hub for reuse.

Validated data is organized by patient population and includes data from DH sites and, when available, other data sources.

Data included in the data model of a given patient population is used to create patient population-specific datasets.

Patient population datasets are used to create user-specific Data Marts for use in:
- Site Portals (to enhance care)
- Research
Data Capture and Reporting Process

Data Capture and Transmission

1. Consent - Full PHI
2. No consent – LDS

OMOP or FHIR

Data Hub Participating “Site”

- eCRF, completed trials, genomic, claims, lab, etc.
- Other Dataset Converter

Validation

OMOP or FHIR

Data Quality Report

Data Hub Warehouse of all data

Other Data Sources

- OMOP or FHIR
- DH Site
- EMR

Validation

- Data is validated for completeness and integrity.
- Data Quality Reports are provided to Sites to enhance data completeness.
- Data is cataloged and sent to the Data Hub for secure storage.

Data Preparation

SCD Data Model

SCD Harmonizer (all SCD data)

MM Data Model

MM Harmonizer (all MM data)

DX Data Model

DX Harmonizer (all "Disease X" data)

Data Request

SCD Site Portal

- SCD Site Portal

MM Site Portal

- MM Site Portal

Custom DX Data Mart

End-user Utilization

- Data included in the data model of a given patient population is used to create patient population-specific datasets.
- Patient population datasets are used to create user-specific Data Marts for use in: Site Portals (to enhance care) Research

- SCD Patient Dataset
- MM Patient Dataset
- DX Dataset

- SCD Custom Analytic/Research Data Mart
- MM Custom Analytic/Research Data Mart
Data Capture and Reporting Process

Data Hub Participating “Site”

1. Consent - Full PHI
   - EMR
   - DH Site
   - OMOP
   - FHIR
   - Upload Data for Validation

2. DH Site Data Quality Report
   - Data Validation
   - Data Hub Warehouse of all data

3. Other Dataset Converter
   - eCRF, completed trials, genomic, claims, lab, etc.

Other Data Sources

- Consenting patients submit full PHI; non-consenting patients submit a limited dataset (LDS).
- Patient-level EMR data is automatically uploaded using OMOP or FHIR EHR abstraction data standards.
- Industry closed clinical trials and other data sources (e.g., payer, genomic, laboratory, etc.) are uploaded using an individualized dataset converter solution.
- Data is validated for completeness and integrity.
- Data Quality Reports are provided to Sites to enhance data completeness.
- Data is cataloged and sent to the Data Hub for secure storage.

• Validated data is securely stored in an agile Data Hub for reuse.

End-user Utilization

- Pre-Market Research
- Post-Market Research
- Academic Research

Clinical/Quality Metrics

Enhance Clinical Care
- Insights on current practice
- Quality Improvement
- Personalize Care

Research

Accelerate Research
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<th># Coverage</th>
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Cohort Analyzer
Real World Data Needs Related to Genomic Therapies
Workgroup

Fyodor Urnov, PhD
Professor of Molecular and Cell Biology
University of California, Berkeley

Donna Neuberg, ScD
Workgroup Co-Chair
Biostatistician
Dana Farber Cancer Institute
Genetic engineering for SCD: synergies and acceleration of progress

Number of subjects with SCD dosed in the clinic will grow nonlinearly in next 5 years
CT and real-world evidence are the biggest drivers of efficacy / safety improvements in the gene therapy and gene editing field:

the path to better genomic therapies for SCD is also through clinic and RW evidence
Our field has a 30 yr history of learning from clinical trial and RW data.

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

Knowledge sharing and harmonization are not built into the system.
Genome editing 2009-2015: safety, efficacy, and subject followup

An important opportunity for a “rising tide lifts all boats” effort
## Data related to efficacy / safety in genome editing clinical trials for SCD

### The subject
- Genome sequence and:
  - ease of mobilization
  - on/off target effects
  - response to editing
  - HbF control
- Epigenome in target cell population.
- Pre-existing immunity to the genome editing machinery

### The cell product
- At target:
  - Efficiency
  - Spectrum
- At off-targets:
  - Biological nature
  - Spectrum
  - Genomic stability

### Subject + product
- At the target and off-target sites, timecourse of:
  - Efficiency
  - Spectrum
- Acquired immunity to the genome editing machinery.
- Genome sequence(s).

### Relationship to biomarkers and clinical outcome?
Data typically available publicly in genome editing clinical trials for SCD

1. **The subject**
   - Genome sequence and:
     - ease of mobilization
     - on/off target effects
     - response to editing
     - HbF control
   - Epigenome in target cell population.
   - Pre-existing immunity to the genome editing machinery.

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   - At target:
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     - Spectrum
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     - Spectrum
     - Genomic stability

3. **Subject + product**
   - At the target and off-target sites, timecourse of:
     - Efficiency
     - Spectrum
   - Acquired immunity to the genome editing machinery.
   - Genome sequence(s).
Data related to efficacy / safety in gene therapy clinical trials for SCD

1. The subject
   - Genome sequence and:
     - ease of mobilization
     - Transduction eff’cy
     - IS distribution
   - Epigenome in target cell population.

2. The cell product
   - Cell dose
   - Vector
   - M.O.I.
   - Vector copy number overall and per cell.
   - Biological nature of integration sites (IS)
   - IS diversity/distribution in the genome overall and per cell.

3. Subject + product
   - Timecourse of:
     - Overall marking
     - Cell-type-specific marking
     - Transgene expression overall
     - Cell-type-specific transgene expression
     - IS diversity/distribution in the genome overall and per cell.
     - Genome sequences

RELATIONSHIP TO BIOMARKERS AND CLINICAL OUTCOME?
Genomic therapies for SCD and RWE

1. Mount a customized framework on a neutral platform to address "known unknowns" in genomic therapies, including issues such as off-target effects and immunogenicity.

2. Use the Coordinated Registry Network in SCD, based on EHR data, to generate control data for patients receiving genome-directed therapies on single arm studies.
“A rising tide lifts all boats” – JFK 1963

Why build a dam in Arkansas?

“These projects produce wealth, they bring industry, they bring jobs, and the wealth they bring brings wealth to other sections of the United States. This State had about 200,000 cars in 1929. It has a million cars now. They weren't built in this State. They were built in Detroit. As this State's income rises, so does the income of Michigan. As the income of Michigan rises, so does the income of the United States. A rising tide lifts all the boats and as Arkansas becomes more prosperous so does the United States.”
Real World Data Needs Related to Genomic Therapies: Working Group Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Type</th>
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<tbody>
<tr>
<td>Charles Abrams, MD</td>
<td>ASH RC SCD CTN</td>
<td>academia</td>
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<tr>
<td>Cindy Dunbar, MD</td>
<td>ASH, NHLBI</td>
<td>academia</td>
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<tr>
<td>Daniel Bauer, MD PhD</td>
<td>Boston Children’s</td>
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<td>Donna Neuberg, ScD</td>
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<td>IGI</td>
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<td>Hans-Peter Kiem, MD, PhD</td>
<td>ASGCT, FHCRC</td>
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<td>John Tisdale, MD</td>
<td>NHLBI</td>
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<td>Lea Witkowski, PhD</td>
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<td>Mark Walters, MD</td>
<td>UCSF Children’s</td>
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<td>Matthew Porteus, MD PhD</td>
<td>Stanford</td>
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<td>St Jude’s</td>
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<td>Punam Malik, MD</td>
<td>Cincinnati Children’s</td>
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<tr>
<td>Shengdar Tsai, PhD</td>
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<td>Chrystal Louis, MD, MPH</td>
<td>CRISPR Tx</td>
<td>industry</td>
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<tr>
<td>Jason Fontenot, PhD</td>
<td>Sangamo</td>
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<tr>
<td>Lisa Michaels, MD</td>
<td>Editas</td>
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<td>Philip Gregory, D. Phil.</td>
<td>bluebird bio</td>
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<td>Sean Burns, MD</td>
<td>Intellia</td>
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<tr>
<td>Larissa Lapteva, MD, MBA</td>
<td>OTAT, CBER, FDA</td>
<td>government</td>
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<tr>
<td>Samantha Maragh, PhD</td>
<td>NIST</td>
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- Comprehensive cross-functional expertise
- Direct experience developing and deploying genomic therapies for SCD
- Preclinical leads, CT PIs, and sponsors of open INDs / CTs
Exploring the Use of Coordinated Registry Networks to Optimize the ASH Research Collaborative Data Hub Work Group

Greg Pappas, MD, PhD
Work Group Co-Chair
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration

Jane Hankins, MD, MS
Work Group Co-Chair
Associate Member
St. Jude’s Children’s Research Hospital
CRN Work Group Members (Invited)

- Jane Hankins, MD, MS – Co-Chair
- Gregory Pappas, MD, PhD – Co-Chair
- Ken Anderson, MD
- Angelo DeClaro, MD
- Payal Desai, MD
- Marcus Droegge, PhD, MBA
- Ann Farrell, MD
- Bindu George, MD
- Nicole Gormley, MD
- Ajai Chari, MD
- Kathleen Hewitt, DNP, RN
- Allison King, MD, MPH, PhD
- Danica Marinac-Dabic, MD, PhD, MMSc, FISPE
- Julie Panepinto, MD, MSPH, FAAP
- Art Sedrakyan, MD, PhD
- Charles Quinn, MD, MS
- Alexis Thompson, MD, MPH
- Emily Tucker, MS
- Saad Usmani, MD
- Fyodor Urnov, PhD
- Bill Wood, MD, MPH
Building on Dr. Marinac-Dabic’s presentation

- Coordinated Registry Networks are a way to create evidence for many stakeholders
- Collect data once; use many times – is the key to success
- Linkage is critical to utility of the data; many of our familiar data sets have limited utility when used alone
- For example, registries alone have limited use to understand care longitudinally; when linked to other data sources (e.g., claims), the utility increases
- The essence of the CRN is to bring many databases together to answer questions
Objectives:

- Explore the concept of Coordinated Registry Networks
- Use the example of SCD
- Inform ASH RC Data Hub
- Support generation of real-world evidence (RWE)
- Produce a report with recommendations for the Executive Committee of these Roundtables and ASH RC consideration
Methodology

• **Review work of Coordinated Registry Networks (CRN) in other areas**
• Explore emerging data resources that may serve CRN in the future
  • Explore development of All Payer Claims Data
  • Explore mobile health solutions
  • Explore data standardization efforts
• Explore tools and approaches development that will improve efficiency of operation of the Data Hub (e.g., BAIT Taskforce)
• Explore institutional context that will support development
  • MDEpiNet Community of Practice
• Within a context of improved utility, efficiency and sustainability for the Data Hub
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Value created by the CRN: RWE that is “better, faster, and cheaper”
Over 29 post approval studies, label expansions, and compliance studies*

Registries provide the cohorts in data on intervention.
This data was linked with CMS claims data that provided outcomes data.

Lessons Learned from ROI Literature

• CRN creates value by reducing time and money to collect evidence and evidence may be improved upon traditional sources -- “better, faster, cheaper”

• About half of the ROI of a mature CRN comes from the registry and the other half from linkages

• Value should drive the development of the CRN and that value can be measured and evaluated
  • Value to our patients is a critical view
Possible Framework (Adopted from MDEpiNet)

- **Data**
  - Fit for use
  - Data Quality
  - Data Governance
  - Data Access

- **Methods**
  - Nested Studies
  - Statistical Methods
  - Linkage/matching

- **Sustainability**
  - Stakeholder Adoption
  - Measures or ROI
Thank you
Panel Discussion
Next Steps

• Launch workgroups
• Community input
• Reconvene in the Spring
• Stay engaged
How To Stay Engaged

• New Website
• Workgroup Surveys
• Attend the Spring Roundtable

• Sign up to be contacted and share with others
  tinyurl.com/SCD-RWE