Challenges and Opportunities for REMS Integration, Innovation, and Modernization

October 11, 2022 | 1:00-5:15 p.m. ET

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome & Introduction

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Agenda

Presentations:

Opening Remarks from FDA

FDA REMS Integration Project Overview

MITRE REMS Integration Prototype Demonstration

Panel Discussions:

Prescriber Perspectives

Pharmacy Perspectives

Health System Perspectives

Implementation Considerations & Next Steps

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Virtual Meeting Reminders

- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
- This meeting is being recorded, and the recording and slide deck will be posted on the Duke-Margolis event page in the weeks following the meeting.

Opening Remarks from FDA

Marta Sokolowska

U.S. Food and Drug Administration

Opening Remarks from FDA

Challenges and Opportunities for REMS Integration, Innovation, and Modernization

Marta Sokolowska, PhD
Deputy Center Director for Substance Use and Behavioral Health
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Introduction

- REMS, are required to ensure that the benefits of certain drugs outweigh their risks.
- REMS programs enable drugs that treat serious medical conditions to be approved that otherwise would not be available.
- In the recent public workshops, FDA and panelists discussed mandatory opioid prescriber education and REMS.
  - The first meeting, in October 2021, focused on the need for mandatory opioid prescriber education
  - The second meeting, in April 2022, focused on the content of an educational program for prescribers of opioid analgesics
  - These efforts are part of FDA's Opioid Overdose Prevention framework
- Neither of these meetings discussed the challenges with implementing such a REMS program.

Challenges with REMS Implementation

- There have been challenges associated with implementing different REMS across multiple therapeutic areas – not just opioid analgesics – leading to significant burden and suboptimal medication access and health outcomes.
- There is a timely opportunity to leverage Health Information Technology (HIT) to modernize REMS through standardization and integration into clinician workflow.

Emerging Opportunities

- Increasingly, the health care system is adopting and using the FHIR data standard to advance health data exchange and use in response to drivers such as the 21st Century Cures Act interoperability rules.
- Contemporary research is informing the use of standards and HIT to improve RWD for drug safety-effectiveness evaluation and safety surveillance, enable clinician education and decision support at the point of care, streamline prior authorization, and strengthen program evaluation.
- Standards-based HIT approaches align with:
  - FDA's regulatory science priorities, including optimizing use of RWE, empowering patients, and advancing digital health technologies.
  - FDA's overdose prevention strategy, including the ability to integrate education into workflow and, in the future, support prescribers at the point of care.

REMS Modernization through Integration and Standardization

REMS – Current State

- Manual phone and fax implementation
- Not integrated into prescriber and pharmacist workflow
- Suboptimal patient engagement and transparency
- Lack of quality standardized data for feedback and evaluation
- No unified way to share data between REMS stakeholders
- Delays in therapy for patients and suboptimal care for the patient

REMS – Future State

- Automated, low burden implementation
- Integrated into clinician workflow
- Patients complete requirements, report & monitor status through apps
- Standardized, quality data for timely feedback and more robust evaluations
- Reduced friction in exchange of REMS data
- Patients safely use their medications and achieve timely access to them

Summary

- FDA is championing a use case and working with MITRE and an open community of stakeholders to iterate a REMS integration prototype.
- We ask prescribers, pharmacists, patients, REMS administrators, sponsors, and other stakeholders to seize this opportunity to modernize REMS through piloting and iteration of the prototype.
- Standards-based REMS modernization can lay a foundation for future innovation and plug into the evolving health app and cloud-based environment.
- Working together we can create an efficient, effective, resilient, and learning REMS ecosystem and advance public health.

REMS Integration Project Overview

Edward Millikan & George Neyarapally

U.S. Food and Drug Administration

REMS Integration, Innovation, and Modernization

Ed Millikan, PharmD, RPh

George Neyarapally, PharmD, JD, MPH, RPh

Office of Surveillance and Epidemiology

CDER | US FDA

October 11, 2022

A Risk Evaluation and Mitigation Strategy (REMS)

- Is a drug safety program to help ensure the benefits of the medication outweigh its risks
- May include a number of interventions, including elements to assure safe use (ETASU), like labs and certification, to help reduce the occurrence and/or severity of a serious risks
- Designed to achieve specific goals to mitigate risks associated with use of a drug
- Our REMS authorities have allowed for the approval of drugs that would not have been approved or may have been removed from the market
- There are significant challenges in implementing and evaluating the effectiveness of REMS programs

REMS burden may be impacting patient access

- Each REMS is customized and uniquely designed and implemented by the drug manufacturer.
- When REMS with ETASU are not well-integrated into health system workflows or health information technology (HIT) systems, they create burdens for providers and pharmacists because they require them to step outside of their workflow.
- The additional burden placed on providers and healthcare systems seeking to comply with the REMS requirements may negatively affect patient access to REMS drugs.

"Thirty-four participants (54%) reported burdens accessing REMS-covered drugs unrelated to insurance coverage at some point during their course of treatment, ranging from additional but not prohibitive challenges to major obstacles."

Sarpatwari, Ameet et al. "Patient and Caregiver Experiences With and Perceptions of Risk Evaluation and Mitigation Strategy Programs With Elements to Assure Safe Use." *JAMA network open* vol. 5,1 e2144386. 4 Jan. 2022, doi:10.1001/jamanetworkopen.2021.44386

Previous efforts to standardize and integrate REMS

- REMS Integration:
  - Enablement of REMS implementation by stakeholders within their respective workflows
- Primary steps to advance REMS integration to date:
  - FDA's Standardization of REMS documents supports integration
    - Format and Content of a REMS Document Guidance for Industry
    - Providing Regulatory Submissions in Electronic Format - Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling (SPL)
  - National Council for Prescription Drug Programs (NCPDP) SCRIPT REMS transactions

Structured Product Labeling† captures the essence of REMS documents

Data Element	Description	Examples
Stakeholder ("Who")	The party that must meet the REMS requirement	Prescriber, pharmacist, health care setting
Protocol ("When")	A particular "stage" in the treatment process around which REMS activities may occur	Certification, prescribing, pharmacy and administration
Requirement ("What")	A clinical or administrative activity that must be performed as part of the REMS	Counseling a patient, completing an enrollment form, lab testing
Material reference ("With what")	Reference to approved REMS material with which the requirement is carried out	Enrollment form, medication guide, educational pamphlet

† Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7®) and adopted by FDA as a mechanism for exchanging product, facility, and REMS information

Guidance for REMS SPL submissions to FDA‡

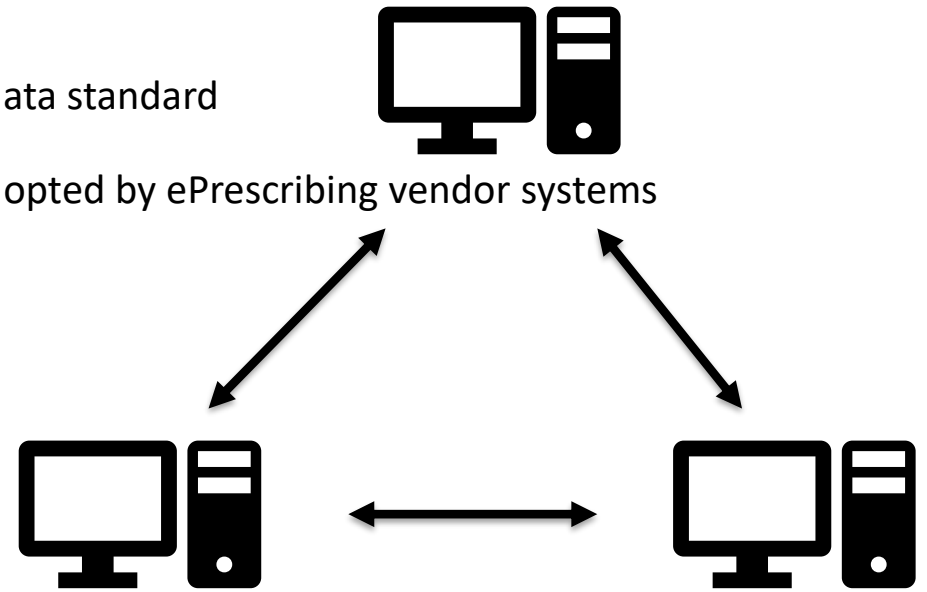
- **WHEN**:
  - December 28, 2022
- **WHO**:
  - Applicants must submit the content of their REMS document electronically using SPL
- **WHAT**:
  - All REMS documents submitted to FDA on or after December 28, 2022, must be in SPL format, which include:
    - REMS documents associated with a **new** REMS
    - REMS documents submitted as part of REMS **modifications**
    - REMS documents that are **already in SPL format** must remain in SPL format
  - Components of a REMS required to be filed in SPL format:

Component of a REMS Submission	Submitted in SPL Format?
REMS document	Yes
REMS supporting document	No
REMS materials	Referenced in SPL file (see Structured Product Labeling Implementation Guide with Validation Procedures at https://www.fda.gov/media/84201/download)

‡ Providing Regulatory Submissions in Electronic Format -- Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling

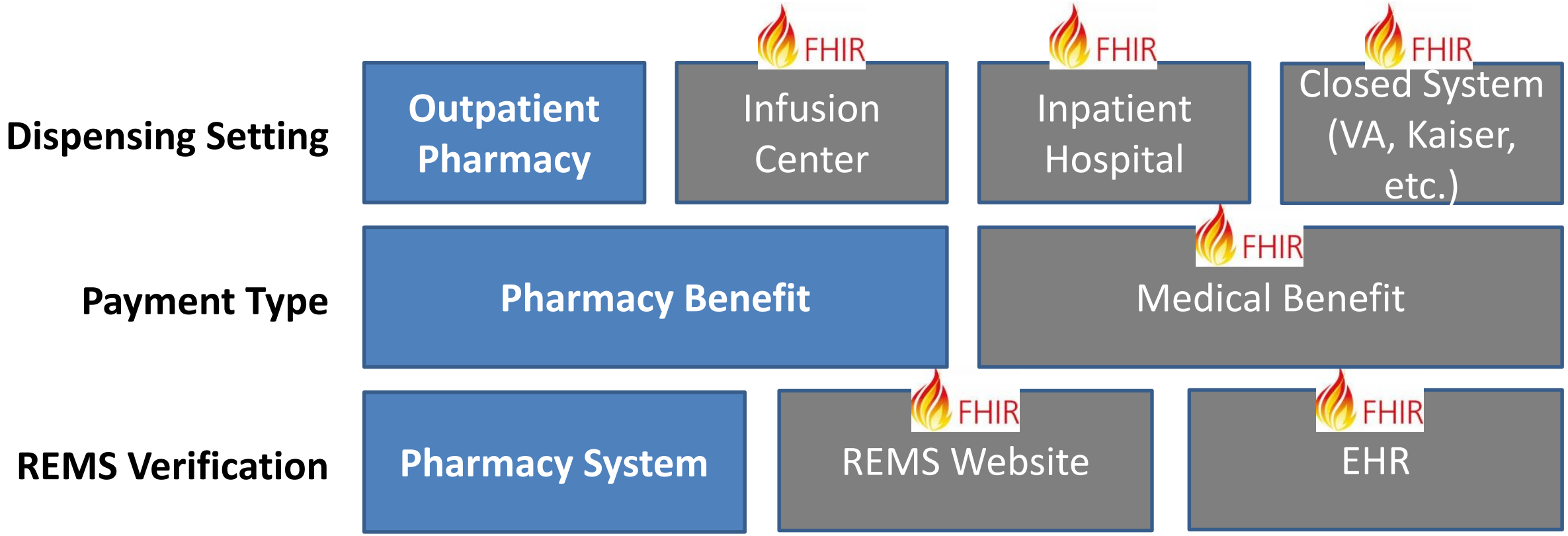
Role of health data standards in REMS Integration

- Automated interoperable exchange of standardized REMS data is a key component
- FDA works with established standards development organizations (SDOs)
- Health data standards currently in place in health care are developed by SDOs, including groups such as:
  - National Council for Prescription Drug Programs (NCPDP)
    - SCRIPT version 2017071 adopted by CMS as the US ePrescribing data standard
    - SCRIPT allows for 4 REMS transactions, but they have not been adopted by ePrescribing vendor systems
  - Health Level 7 (HL7®) International
    - REMS SPL data standard
    - Fast Healthcare Interoperability Resources (FHIR®)



HL7® FHIR® can address gaps in current REMS standards

(Potential future state)

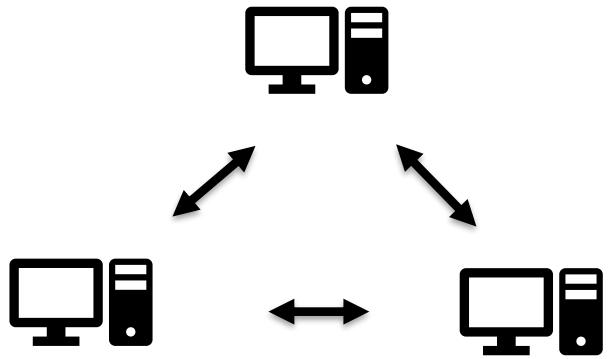


Blue boxes show the workflow addressed by current NCPDP Standards (Telecommunication, SCRIPT)

Slide from MITRE's, "FDA CDER Risk Evaluation and Mitigation Strategies (REMS) Proof of Concept Landscape Analysis."

Challenges and Opportunities in REMS integration

- Previous standardization efforts (NCPDP SCRIPT, SPL) have not been enough to integrate REMS into electronic health care processes
- More work must be done to promote the use of electronic health data standards for REMS integration within stakeholder workflow
- Coevolution between health data standards like NCPDP SCRIPT and HL7® FHIR® is key to moving forward and better supporting REMS integration and interoperability
  - NCPDP SCRIPT
    - Focused more on the pharmacy side
  - HL7® FHIR®
    - Needed for other EHR data and information from the prescriber side
    - Being broadly adopted due to ONC and CMS requirement for certified EHRs by the end of 2022



Background/Definitions

HL7: Health data standards development organization (SDO)

Contemporary health data exchange standard

HL7 FHIR-based cancer data standard (a “lingua franca” for cancer care/research/public health purposes)

Collaborative, stakeholder driven initiatives focused on solving health problems with FHIR-based solutions

CodeX: HL7 FHIR Accelerator building a community around mCODE to solve problems through stakeholder-driven use cases

HL7® FHIR Data Standard

F – Fast (to design & implement)
H – Healthcare
I – Interoperability
R – Resources (building blocks)

Fast, Efficient, & Flexible

- Uses 80/20 Rule: 20% of the requirements satisfy 80% of the needs
- **FREE** to use
- Uses mainstream web technology
- Solutions built from modular components called "Resources"
- Option to develop custom extensions

FHIR® is a standard for exchanging healthcare information electronically

- Standards establish a common language and process for all health information technology (IT) systems to communicate, allowing information to be shared seamlessly and efficiently
- FHIR® can be used as a stand-alone data exchange standard or with existing standards

Slide adapted from CodeX Community of Practice Presentation, "Introduction to FHIR," by MITRE on July 30, 2021.

What is a FHIR Accelerator?

".. designed to assist communities .. across the global health care spectrum in the creation and adoption of high quality FHIR Implementation Guides .. to move toward the realization of global health data interoperability"

https://www.hl7.org/about/fhir-accelerator/

HL7 FHIR Accelerators

HL7 FHIR ARGONAUT PROJECT

DA VINCI HL7 FHIR

CodeX™

HELIOS

carin
Creating Access to Real-time Information Now through Consumer-Directed Exchange

gravity PROJECT

VULCAN HL7 FHIR

FAST
FHIR AT SCALE TASKFORCE

Slide adapted from the CodeX™ Master Slide Deck titled, "Introduction to mCODE™ and the CodeX™ HL7® FHIR® Accelerator" available on the CodeX™ Confluence page.

CodeX™ Members (September 2022)

CodeX Founders ★

PREMIER

AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE ★
ASTRO AMERICAN SOCIETY FOR RADIATION ONCOLOGY ★
HL7 International ★
Pfizer ★
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY ★
MITRE ★
EVERNORTH℠
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UnitedHealthcare® ★

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Cancer Action Network℠ American Cancer Society ★
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TEMPUS
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CDC CENTERS FOR DISEASE CONTROL AND PREVENTION ★
FDA U.S. FOOD & DRUG ADMINISTRATION
University of Nebraska Medical Center BREAKTHROUGHS FOR LIFE.®
MCSP MICHIGAN CANCER SURVEILLANCE PROGRAM

SPONSORED MEMBER

AMGEN®
ONS® Oncology Nursing Society
LEARNING HEALTH COMMUNITY
COMP Canadian Organization of Medical Physicists
OCPM Organisation canadienne des physiciens médicaux
NRG ONCOLOGY Advancing Research. Improving Lives.℠
SIIM

DEVELOPER/IMPLEMENTER

Cancer Insights
elimu informatics
MASSIVEBIO
mcg
Mettle SOLUTIONS
Navigate Oncology
NeuralFrame
Oncora MEDICAL
patientlink Better Patient Connection · Better Data Collection
PHENOTIPS
PRINCIPIA HEALTH SCIENCES
QL HC Quantum Leap Healthcare Collaborative
storyhealth
Wemedoo Clinical Information Specialists

Slide adapted from the CodeX™ Master Slide Deck titled, "Introduction to mCODE™ and the CodeX™ HL7® FHIR® Accelerator" available on the CodeX™ Confluence page.

CodeX™ Community of Practice

A group of health systems, specialty societies, government agencies, pharmaceutical manufacturers, researchers, EHRs and supporting organizations, participating in a monthly public forum focused on real-world applications of mCODE.

Latest developments on mCODE, CodeX, and cancer data exchange

Ask questions and learn from the experience of other community participants

Develop and share best practices for clinical workflows, data modeling, and exchange

55 Health Systems

7 Payers

10 Pharma

85 EHRs and other tech companies

12 Medical Societies and Consortia

14 Government Agencies

12 Research Organizations

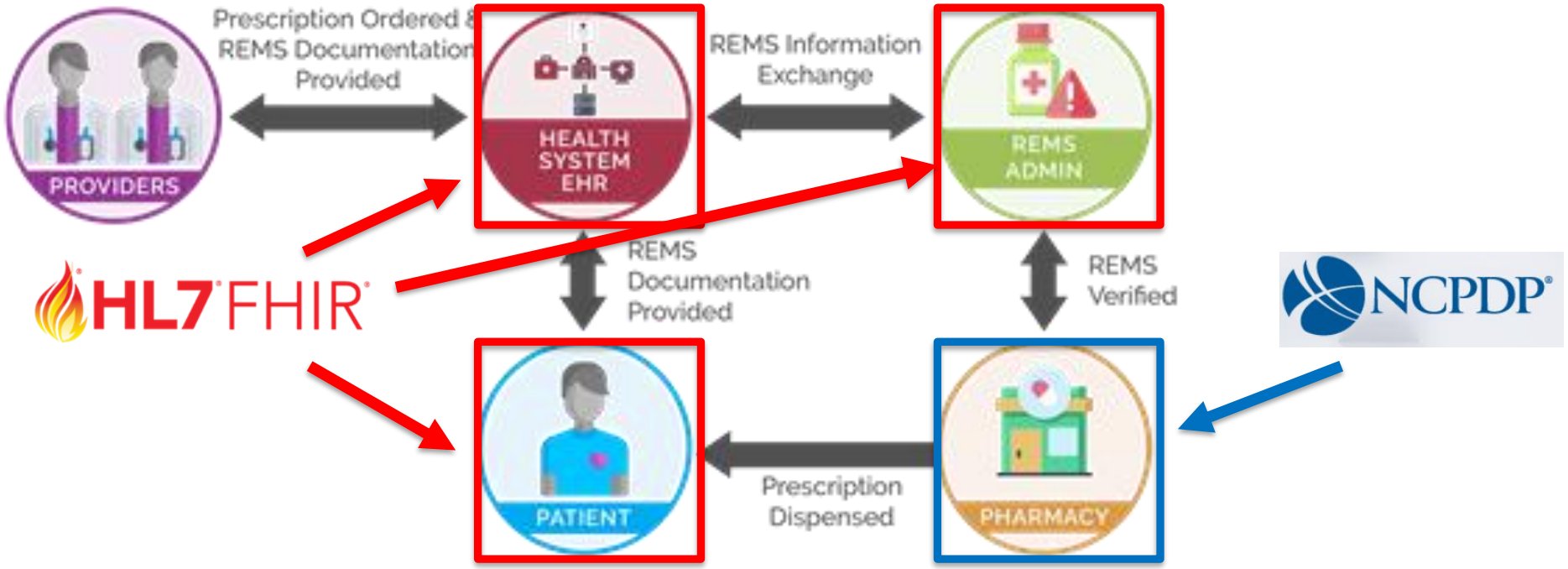
7 Nonprofits/ Foundations

2 Patient Advocacy Organizations

https://confluence.hl7.org/display/COD/mCODE+Community+of+Practice

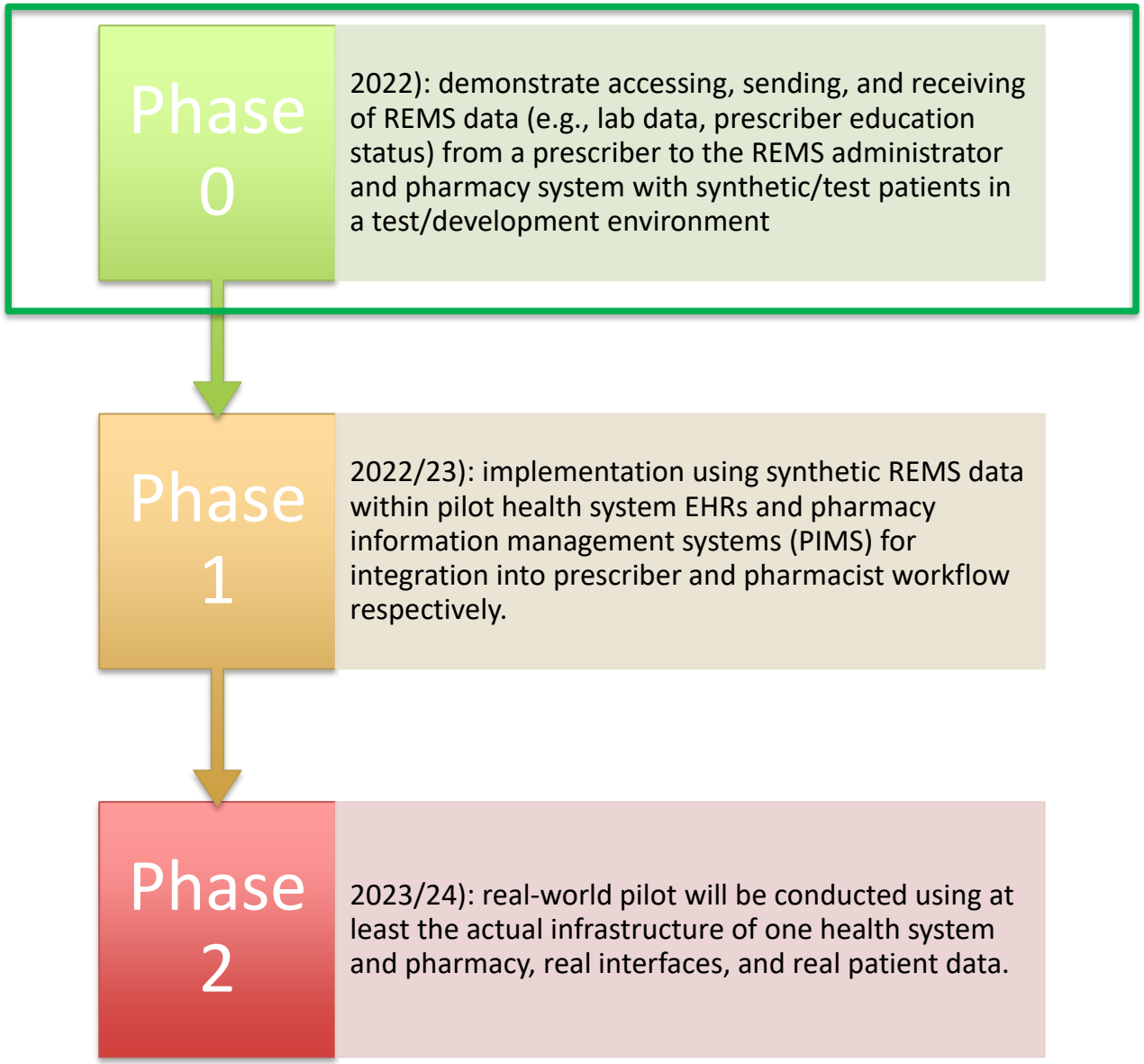
Slide adapted from the CodeX™ Master Slide Deck titled, "Introduction to mCODE™ and the CodeX™ HL7® FHIR® Accelerator" available on the CodeX™ Confluence page.

REMS Integration Proof-of-Concept/CodeX Use Case



https://confluence.hl7.org/display/COD/Risk+Evaluation+and+Mitigation+Strategies+-+REMS

Planned CodeX™ REMS Integration Use Case Phases



HL7 FHIR

CodeX™
Common Oncology Data Elements eXtensions

Scalable, standards-based solution for REMS integration & optimization

* These phases do not include the development of a REMS data hub/platform or database for prescriber education and REMS data and information. This will need to be developed in the future.

REMS Integration Prototype Demonstration

Lauren DiCristofaro, Sahil Malhotra, and Nicole Ng

MITRE

REMS Integration Prototype

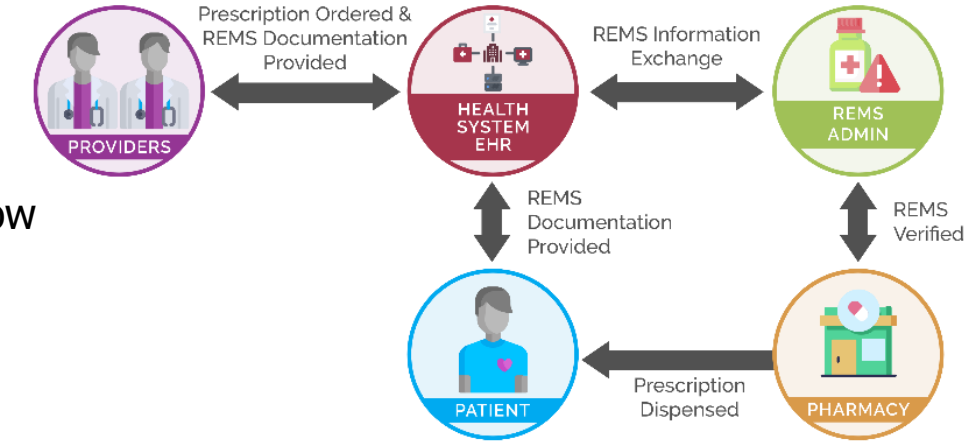
October 11, 2022

Nicole Ng, Sahil Malhotra, Lauren DiCristofaro

Proof-of-Concept Prototype

- MITRE and FDA are working together to develop an open-source proof-of-concept prototype that leverages data standards and technology to integrate REMS into the health care system

- Goal is to model data transactions and workflows to demonstrate the art of the possible
  - Aims not to develop an interface for users but instead focus on how data can be exchanged and used
  - Used to engage the broader REMS community to help drive conversations around opportunities to enhance REMS



Demo

REMS Phase 1 – What's Next?

- **Community Engagement**
  - Work with the CodeX stakeholder community to guide prototype development
  - Leveraging community engagement and previous notes from CodeX calls to prioritize tasking
- **Pilot Definition and Implementation**
  - Define the scope of a pilot definition of the prototype
  - Identify community members to integrate with the REMS prototype in a mock workflow setting using synthetic data
  - Initiate implementation of a pilot, using synthetic data, in at least one health or prescriber system and one pharmacy system, with a REMS administrator
- **Implementation Guide Development**
  - Work with CodeX community members to start defining a FHIR Standard Specification for REMS

CodeX REMS Integration Use Case: Call to Action

Explore how the REMS community can harness the FHIR standard to develop open-source, interoperable REMS solutions that reduce stakeholder burden and address your needs.

Contribute your real-world expertise to REMS prototype development.

Consider opportunities to leverage this work in pilots to drive adoption in real-world healthcare settings.

- **Join other upcoming REMS Public Calls**
  Registration information is available on the REMS confluence page:
  https://confluence.hl7.org/display/COD/Risk+Evaluation+and+Mitigation+Strategies+%28REMS%29+Integration
- **Share your REMS implementation experiences and recommendations**
  Champion a CodeX REMS Integration Use Case Pilot
- **Spread the word to friends and colleagues and encourage them to participate**
- **Ensure a stakeholder-focused workflow**
  Examine prescriber and pharmacist workflows to identify and address gaps in reference implementation resources
- **Email Kelee Petzelt (kelee.petzelt@pocp.com) with any ideas, requests, or to join**

CodeX™

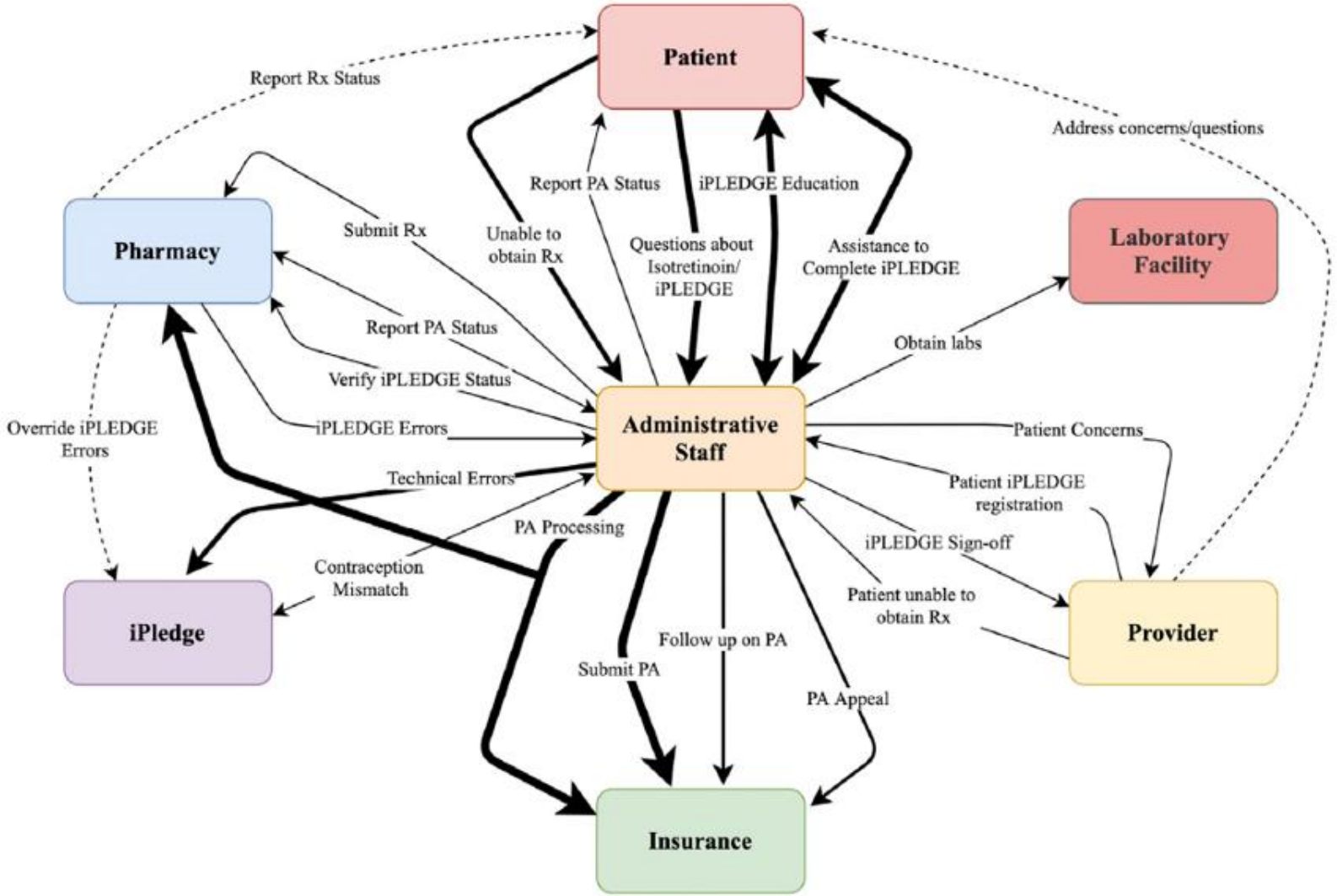
Prescriber Perspectives

Moderator: **Mark McClellan**, Duke-Margolis Center for Health Policy

Panelists:

- **Lane Abernathy,** Patient Advocate
- **Robert Cotes,** American Psychiatric Association
- **Ilona Frieden,** American Academy of Dermatology

Logistical Burdens of iPLEDGE REMS program



From Shah et al. The administrative burden of prescribing and treating with isotretinoin. J Am Acad Dermatol; 2022:86:1165-7

Burden of iPLEDGE program for **144 patients** (typically over 7 month period)

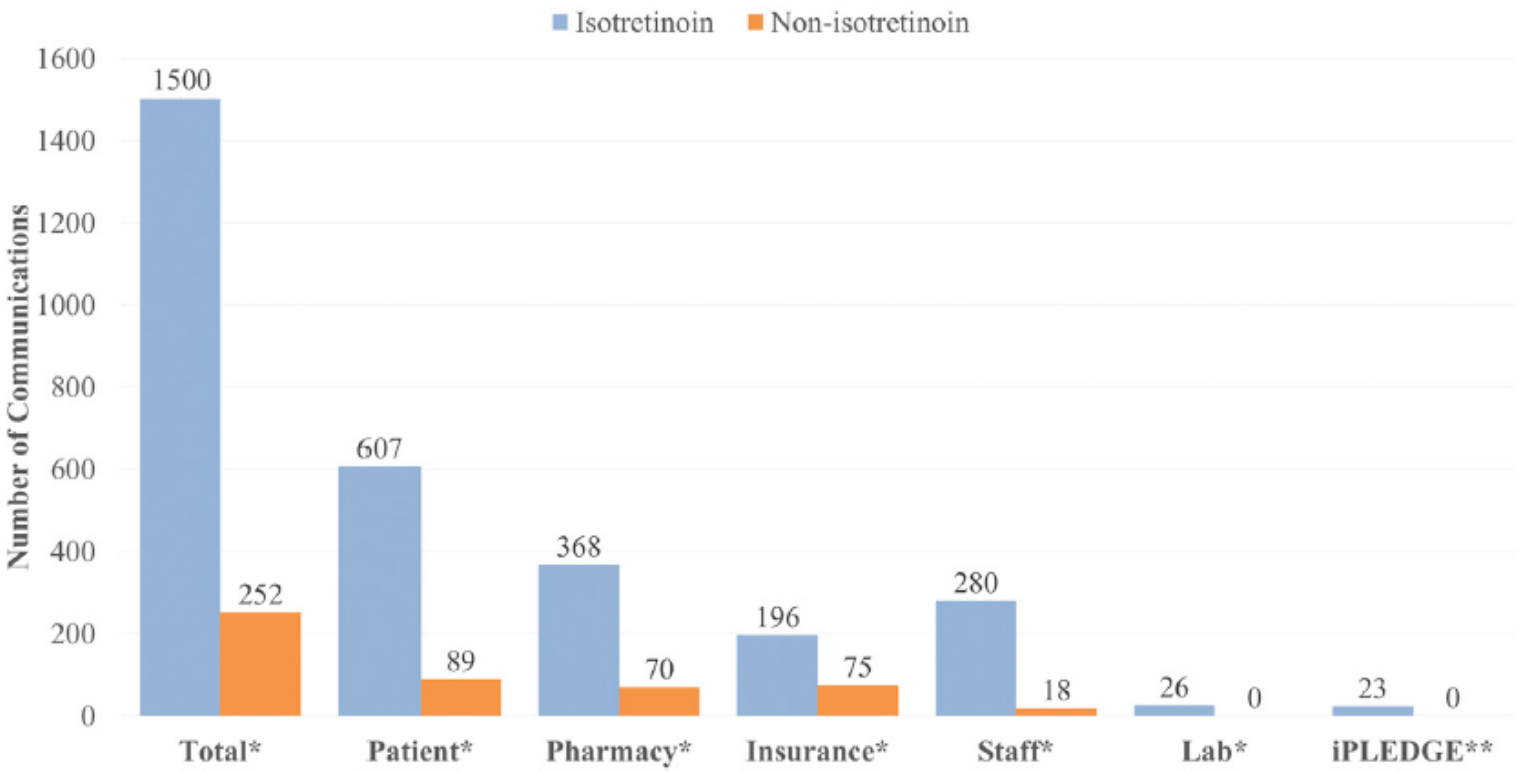


Fig 1. The number of communications by category and medication. *Difference in communications between isotretinoin and non-isotretinoin medication is statistically significant ($P < .001$); **Comparison not applicable.

From Shah et al. The administrative burden of prescribing and treating with isotretinoin. J Am Acad Dermatol; 2022:86:1165-7

Table 1. Comparison of FDA REMS Programs for Teratogenicity

Medication	Isotretinoin	Ambrisentan	Bosentan	Macitentan	Riociguat	Thalidomide, Lenalidomide Pomalidomide	Mycophenolate	Phentermine and Topiramate
Approval date	2010	2019	2019	2021	2013	2021	2012	2012
Indication for use	Acne	Pulmonary arterial hypertension	Pulmonary arterial hypertension	Pulmonary arterial hypertension	Chronic thromboembolic pulmonary hypertension, Pulmonary arterial hypertension	Multiple myeloma, Kaposi sarcoma (P), Myelodysplastic syndrome (L), Lymphoma (L)	Sold organ transplant immunosuppression	Weight loss
REMS type	Shared system (iPLEDGE)	Shared system	Shared system (Fetal and liver toxicity)	Shared system	Single provider	Shared system	Shared system	Single provider
Attestation for patients who can become pregnant	Monthly	At start	Monthly	At start	At start	At start, q6 months	No	No
Provider attestation for patients who can become pregnant	Monthly	At start	Monthly	At start	At start	Monthly	At start	No^
Inclusion of patients who cannot become pregnant	Yes	Only female	Yes	No	Only female	Yes	No	No
Provider attestation for patients who cannot become pregnant	Monthly	Yearly	Yearly	No	Yearly	Monthly (male, child), 6 months (adult female)	No	No
Waiting period to start	Yes (30day)	No	No	No	No	Yes (10-14d); requires contraception 4 wk	No	No
7-day window	Yes	No	No	No	No	Yes (repeat HCG)	No	No
19-day waiting period for missed window	Yes	No	No	No	No	No	No	No
Two forms of contraception for LARC	Yes	No	No	No	No	Yes (LARC included with hormonal contraception)	No	No

Courtesy of Andrea Zaenglein M.D.

Discussion Questions

1. How might integrating REMS within your clinical workflow using contemporary health data standards alleviate challenges you currently experience when prescribing REMS drugs?
2. Do you think there are any drawbacks to this approach? Are there clinical workflow issues associated with prescribing REMS drugs that are not addressed by the prototype?
3. Based on your experience with REMS, how could integrating REMS into a patient friendly app, similar to your patient health record or web portal, benefit patients? Do you think there are any potential drawbacks with this approach?
4. Can you think of additional functions or features that could be added to the prototype to further streamline the prescribing process?

Break

We will reconvene at 2:55 p.m. ET for the next panel discussion.

Pharmacy Perspectives

Moderator: **Dure Kim,** Duke-Margolis Center for Health Policy

Panelists:

- **John Simon,** Patient Advocate
- **Michelle Kershaw,** CVS
- **Michele Kidd,** Accredo
- **Jennifer Martin,** U.S. Department of Veterans Affairs

Discussion Questions

1. How might integrating REMS within your pharmacy workflow using contemporary health data standards alleviate challenges you currently experience when verifying and dispensing REMS drugs?
2. Do you think there are any drawbacks to this approach? Are there key issues associated with dispensing REMS drugs that are not addressed by the prototype?
3. What other aspects of the retail and specialty pharmacy experience could be addressed with this type of solution (building on this initial proof of concept work)?
4. Have you experienced delays in care or other issues in obtaining your REMS drug? How might REMS integration help patients get timely access to their REMS medication in safe manner?

Health System Perspectives

Moderator: **Rachele Hendricks Sturrup,** Duke-Margolis Center for Health Policy

Panelists:

- **Laurie Adami,** Patient Advocate
- **A.J. Burnett,** Intermountain Health
- **Ann McGee,** Duke University
- **Diana Schreier,** Mayo Clinic

Discussion Questions

1. How could integrating REMS within your health system's electronic health record (EHR) using contemporary health data standards help with transitions of care between outpatient and inpatient settings?
2. How can REMS integration help with pharmacy dispensing and specialty drug management in a hospital or health system?
3. Prescriber and pharmacy: What health data infrastructure currently supports prescribing and dispensing of REMS drugs in your health system? What challenges might arise with implementing the prototype into those systems?
4. What can be done to streamline the path to piloting or adopting the prototype for health systems?
5. How can REMS integration facilitate better interactions and experiences while navigating steps to get care within a health system?

Implementation Considerations & Next Steps

Moderator: **Mark McClellan**, Duke-Margolis Center for Health Policy

Panelists:

- **Danielle Boyce,** Patient Advocate
- **Cathy Graeff,** National Association of Chain Drug Stores
- **Jason Leedy,** Examoto
- **Sean Mackey,** Stanford Health Care

Discussion Questions

1. What recommendations do you have and what issues should be considered for piloting the prototype?
2. What additional steps could promote adoption of the prototype among prescribers, pharmacists, and health systems? What support might stakeholders need to smooth the implementation process?
3. In the long term, how could this prototype support iterative improvements to REMS systems beyond prescribing and dispensing interactions to promote access and improve time to therapy for patients?
    a) How might standardized data collection through the prototype enhance workflows for prescribers and pharmacists and reduce barriers to access for patients? What other REMS system benefits might this enable?

Closing Remarks

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

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