U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Integration and Innovation Project Update

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U.S. Food and Drug Administration

Outline

- **Describe REMS Integration Use Case and prototype updates**
- Summarize January 2025 and 2026 Health Level 7 (HL7®) Fast Healthcare Interoperability Resources (FHIR®) Connectathons for REMS medications
- Summarize July 2025 NCPDP REMS pharmacy intermediary test event, and February 2026 colLAB / Work Group updates
- Discuss the US Medication REMS HL7 FHIR Implementation Guide (IG) and August 2025 updates
- Review REMS SPL submission updates
- Discuss future HL7® CodeX™ REMS integration pilots

REMS Modernization through Integration and Standardization

REMS – Current State

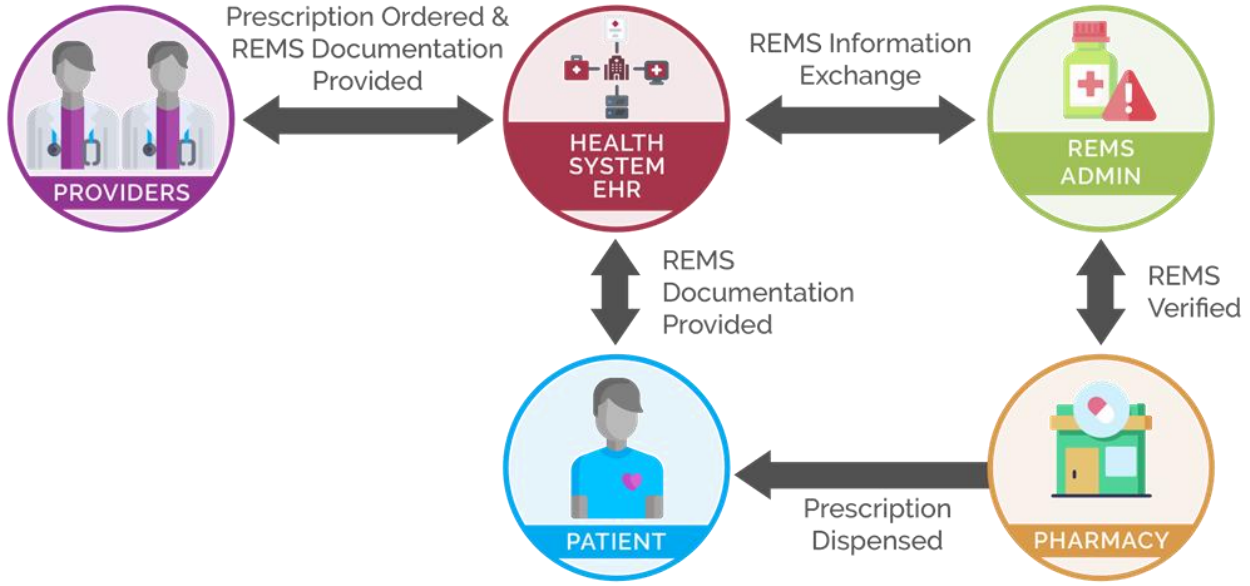
- Manual phone and fax implementation
- Not integrated into prescriber and pharmacist workflow
- Suboptimal patient engagement and transparency
- Lack of quality standardized data submission for feedback and evaluation
- No unified way to share data between REMS stakeholders
- Delays in therapy for patients

REMS – Future State

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

Proof-of-Concept Prototype

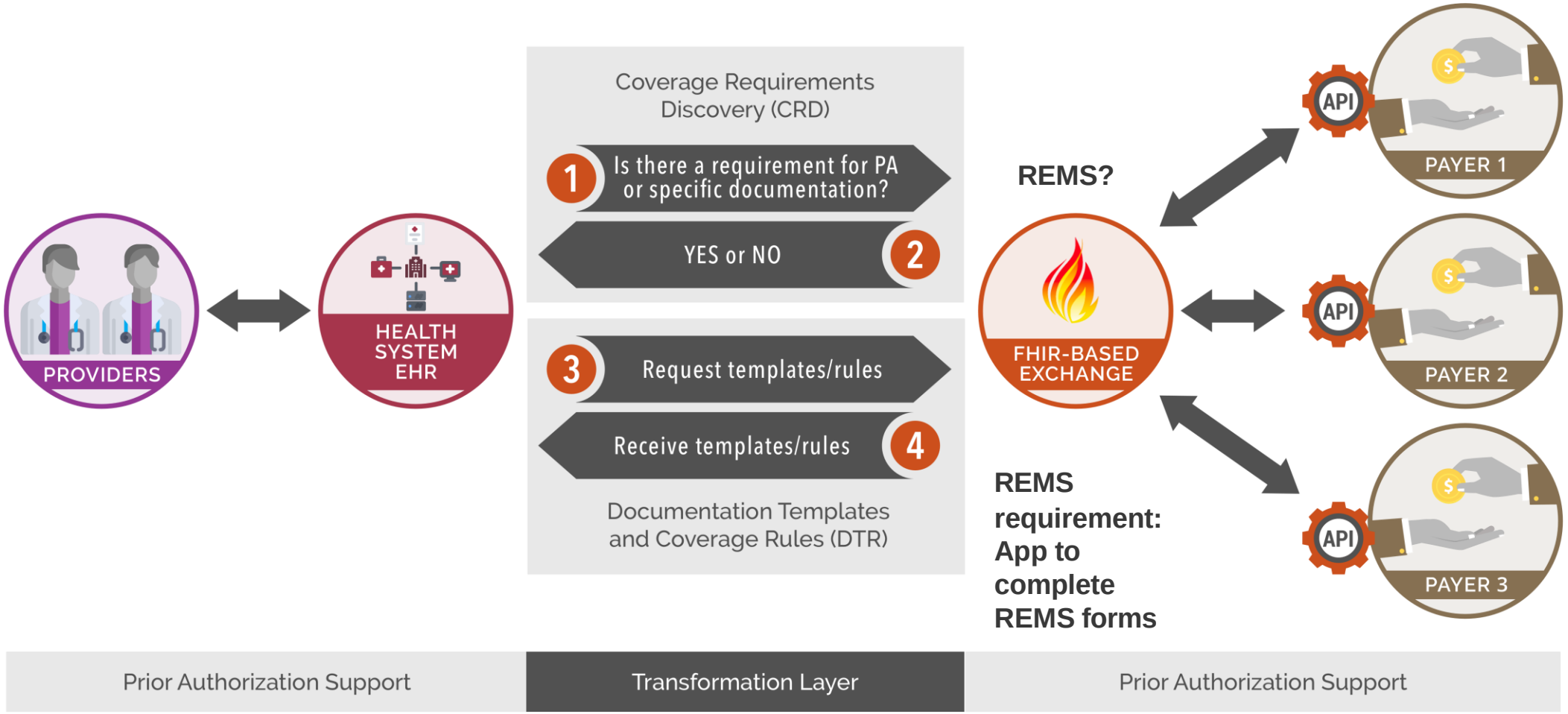
- MITRE and FDA are working together with REMS stakeholders under the HL7® CodeX™ FHIR Accelerator[1,2] to expand on an open-source proof-of-concept prototype that leverages data standards and technology to integrate REMS into the health care system
- Goal is to model data transactions and workflows 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



[1]HL7 FHIR – Health Level 7 Fast Healthcare Interoperability Resources

[2]CodeX: Member-driven HL7 FHIR Accelerator hosting a growing community working together to enable FHIR-based interoperability that drives substantial improvements around the most important challenges and opportunities in patient health.

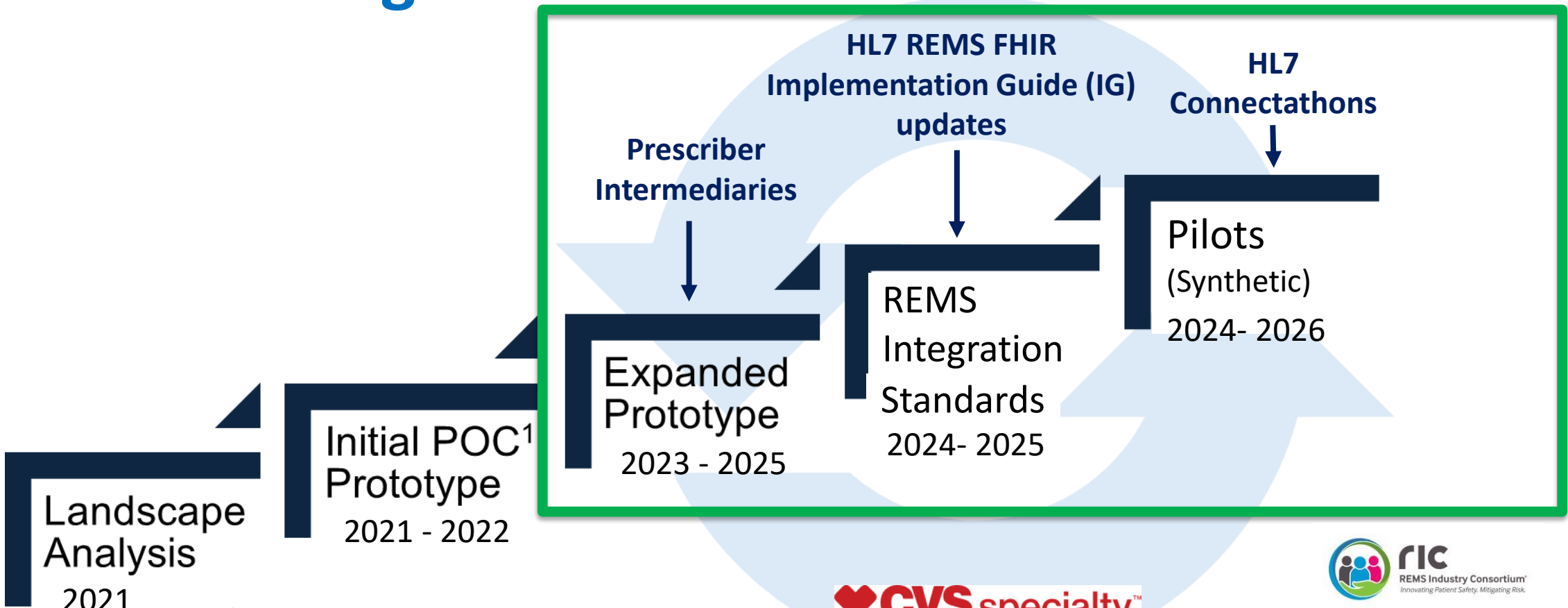
REMS Integration is Informed by Prior Authorization (PA)



Da Vinci Prior Authorization IGs and Supporting Comment: https://confluence.hl7.org/pages/viewpage.action?pageId=91980079

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

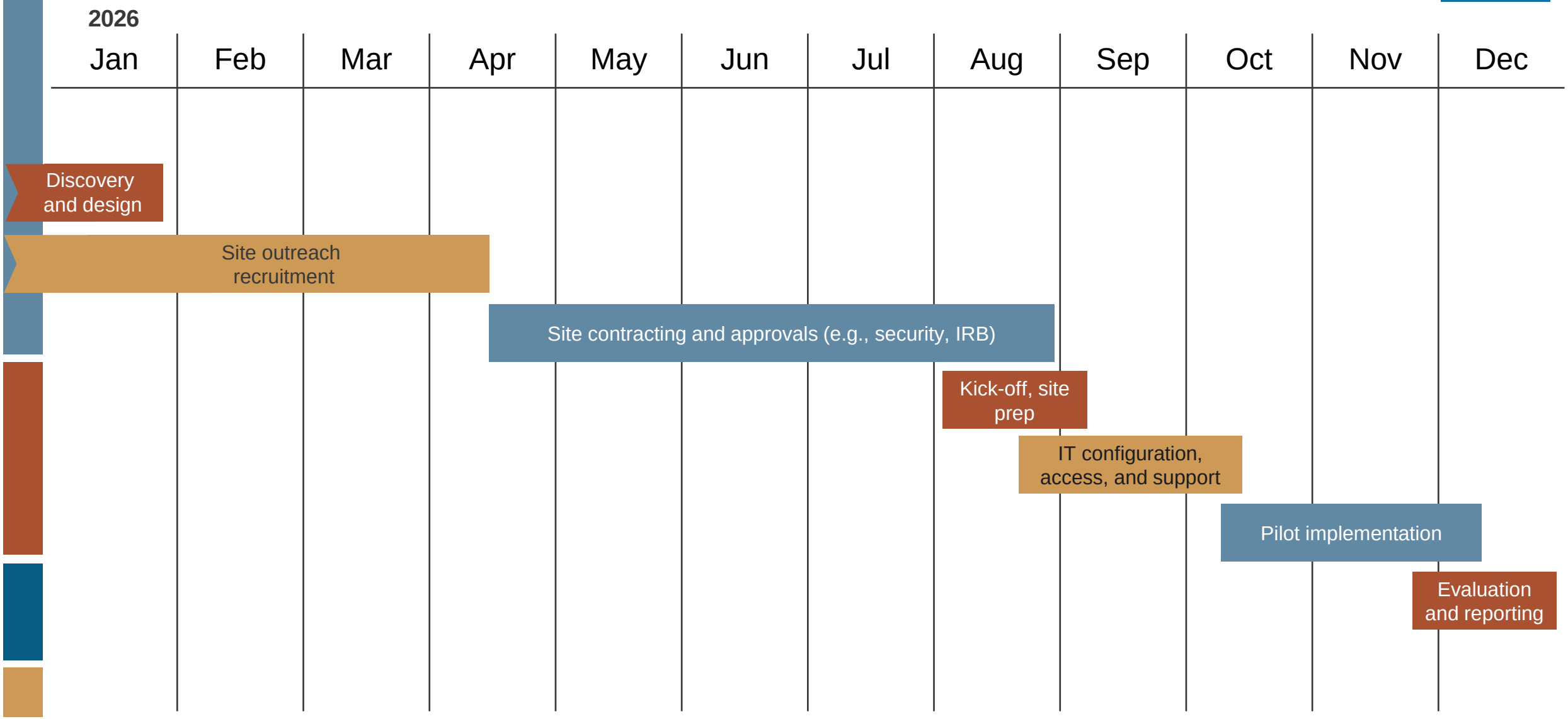
Iterative Pilots and Standards Development in CodeX REMS Integration Use Case



[1]POC = Proof of concept

Slide adapted from CodeX™ Pharmacovigilance and Risk Management Use Case Public Call on January 21, 2026.
See: https://confluence.hl7.org/spaces/COD/pages/413048123/01-20-2026+Pharmacovigilance+and+Risk+Management+Public+Call+Meeting+Minutes

Notional Timeline for REMS Integration Real-world Pilot



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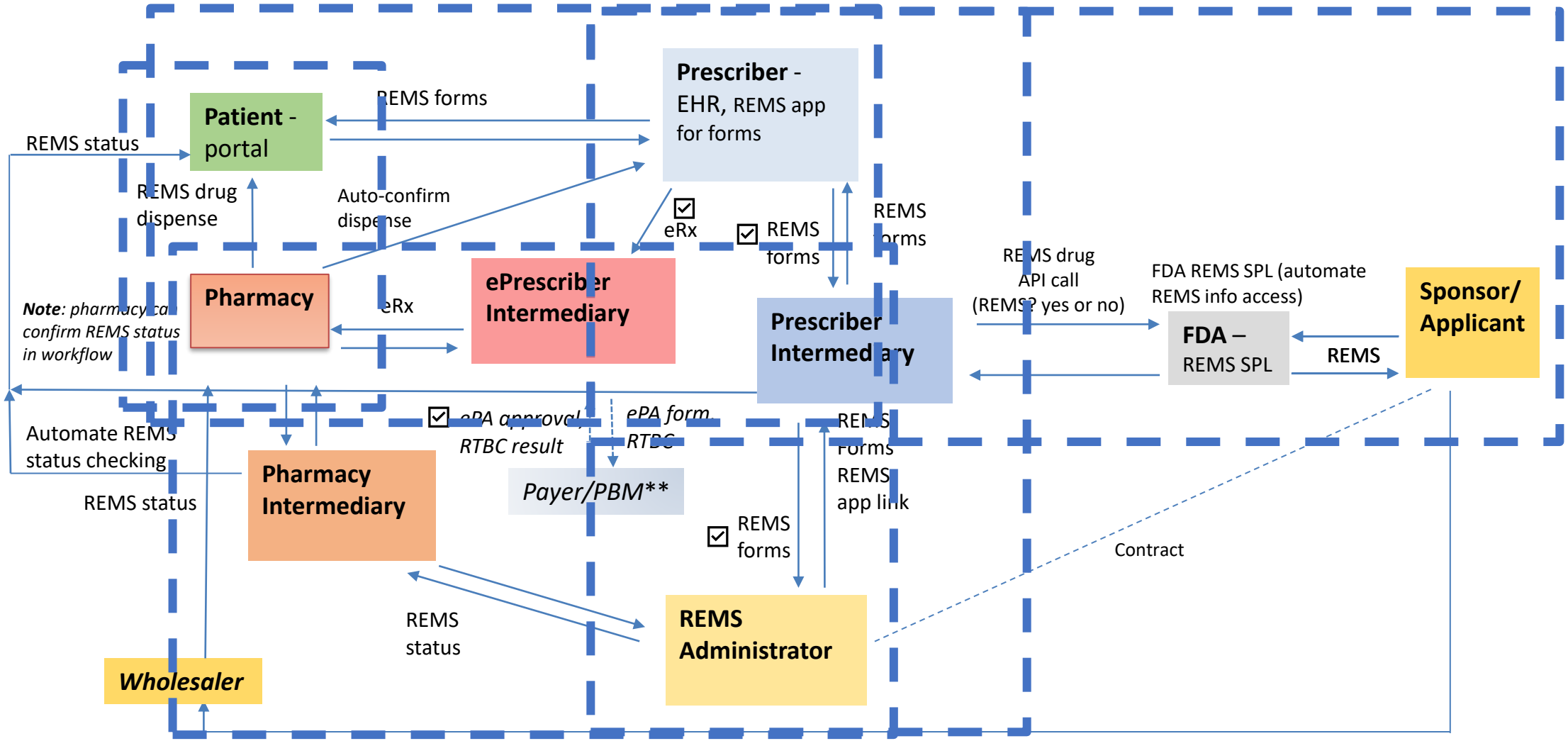
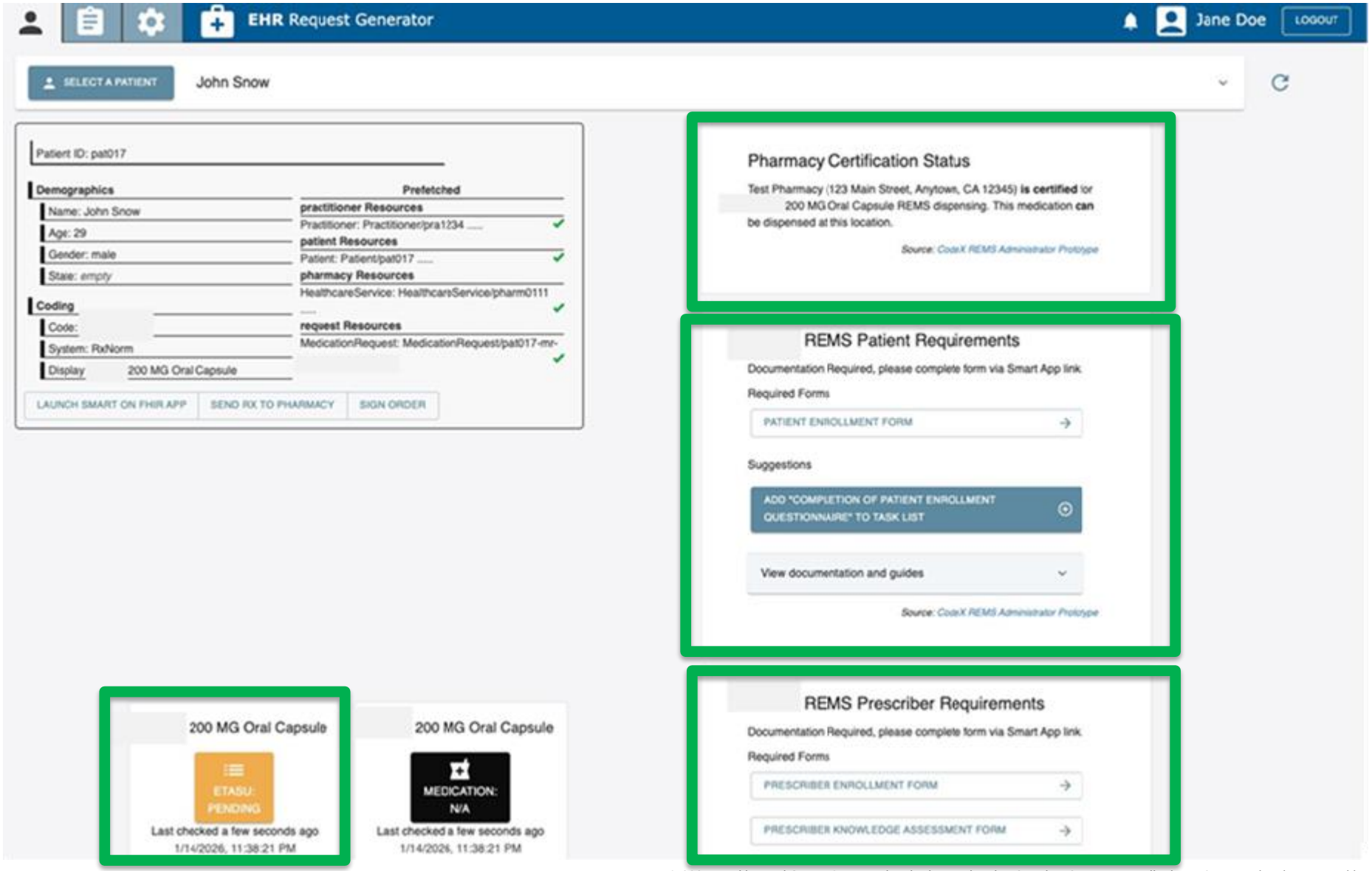
End-to-End REMS Integration Solution



Prototype EHR Screenshot



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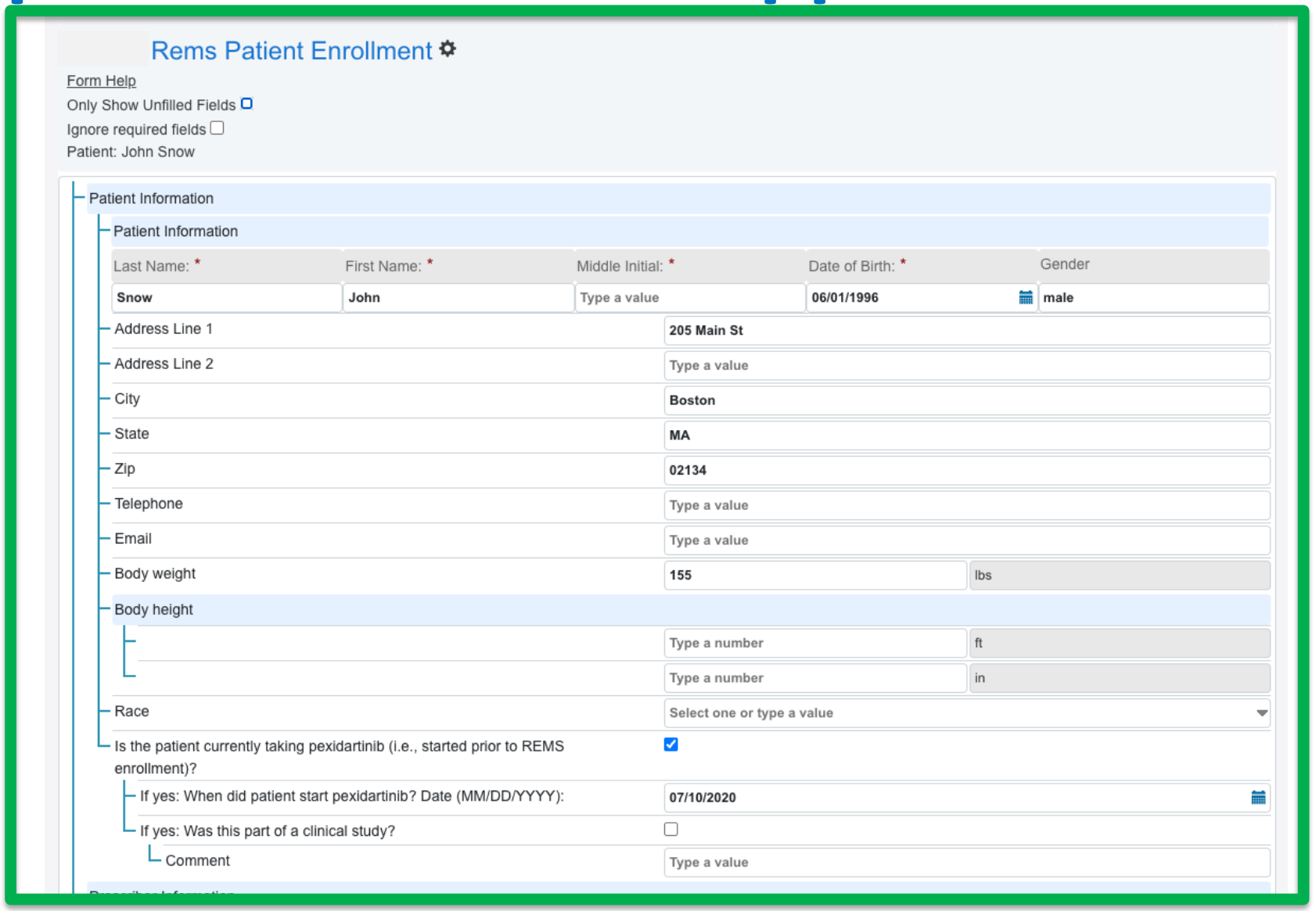
Prototype Shared SMART App Screenshot



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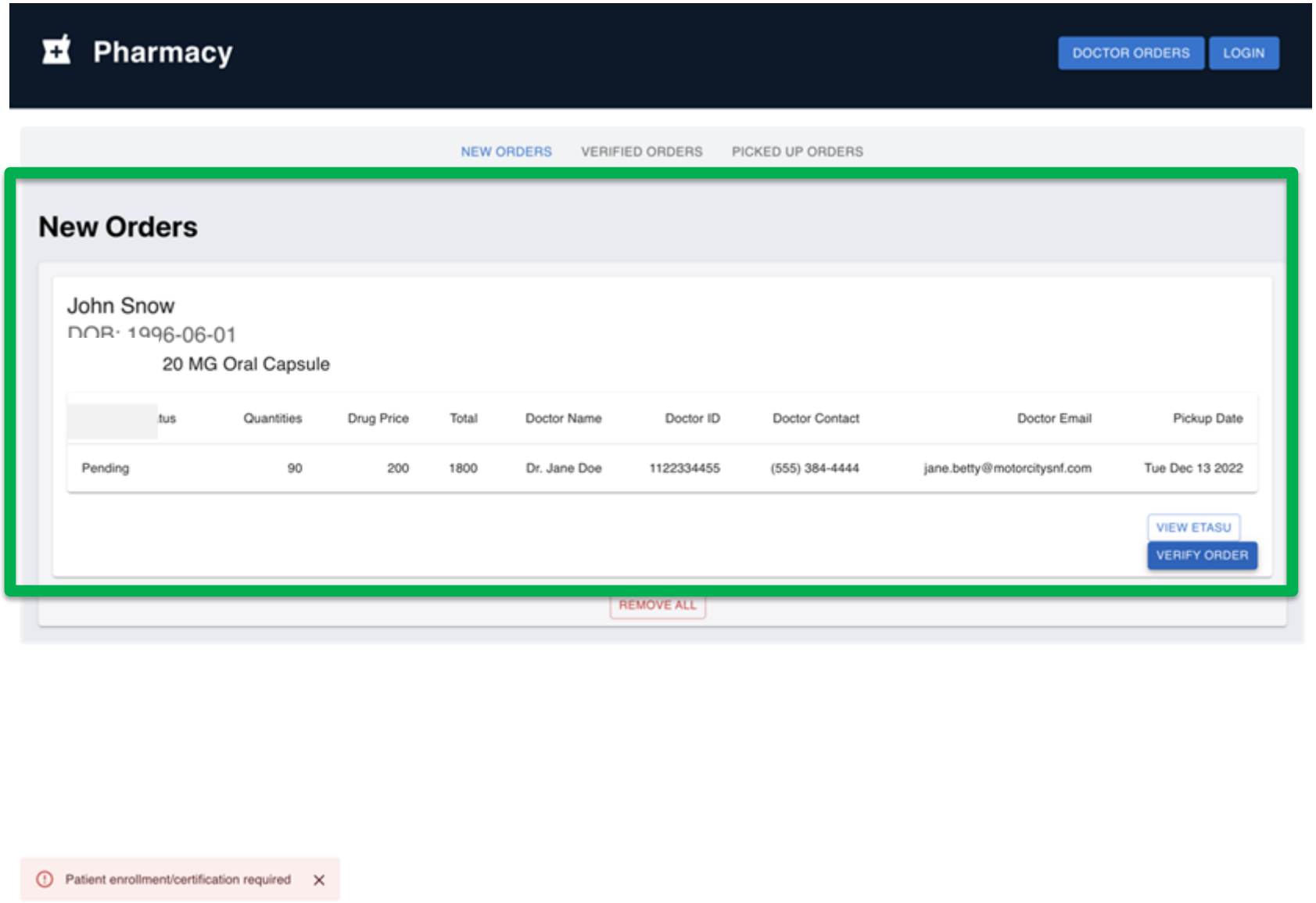
Prototype Pharmacy Screenshot



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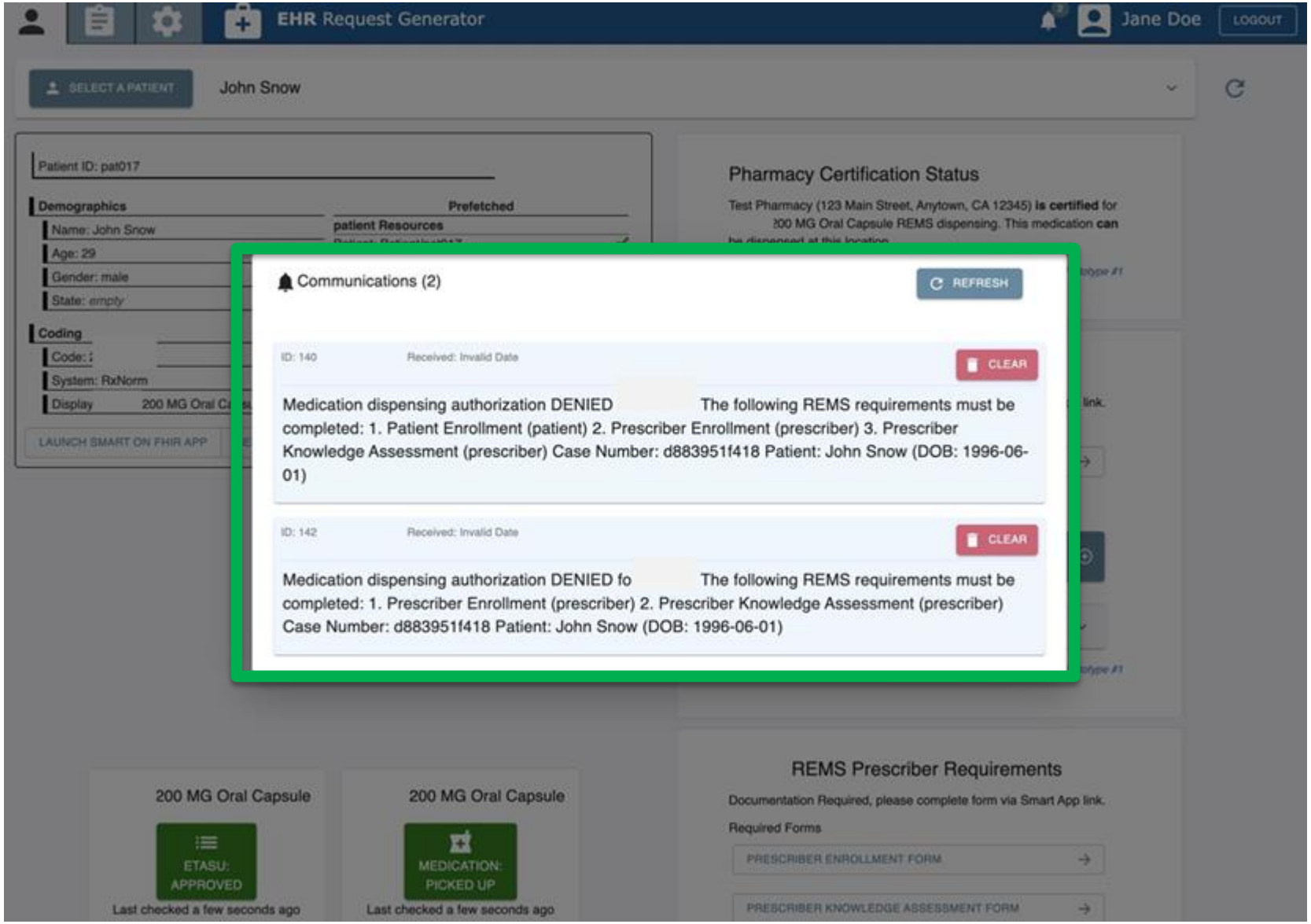
Prototype Improved EHR Communications



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Current REMS Integration Use Case Updates

- **January 2025 (HL7®)**:
  - Additional synthetic data pilots (2nd HL7® Connectathon); **REMS prescriber intermediaries for routing REMS via synthetic SPL FHIR endpoints**,
  - **Updated** the **HL7® FHIR[1] implementation guide** (integration of prescriber intermediaries), and
- **July 2025 (NCPDP)**
  - Expanded to **test integration into pharmacy workflow by connecting FHIR** (medical data/EHR) **and NCPDP SCRIPT[2]** (prescription drug data/e-prescribing) standards
- **January 2026 (HL7®)**:
  - Piloted (3rd HL7® Connectathon) test integration with the PACIO Project[3] for transitions of care from a health system to a skilled nursing facility

[1]HL7® FHIR – Health Level 7 Fast Healthcare Interoperability Resources
[2]NCPDP - National Council for Prescription Drug Programs
[3]PACIO - Post Acute Care InterOperability

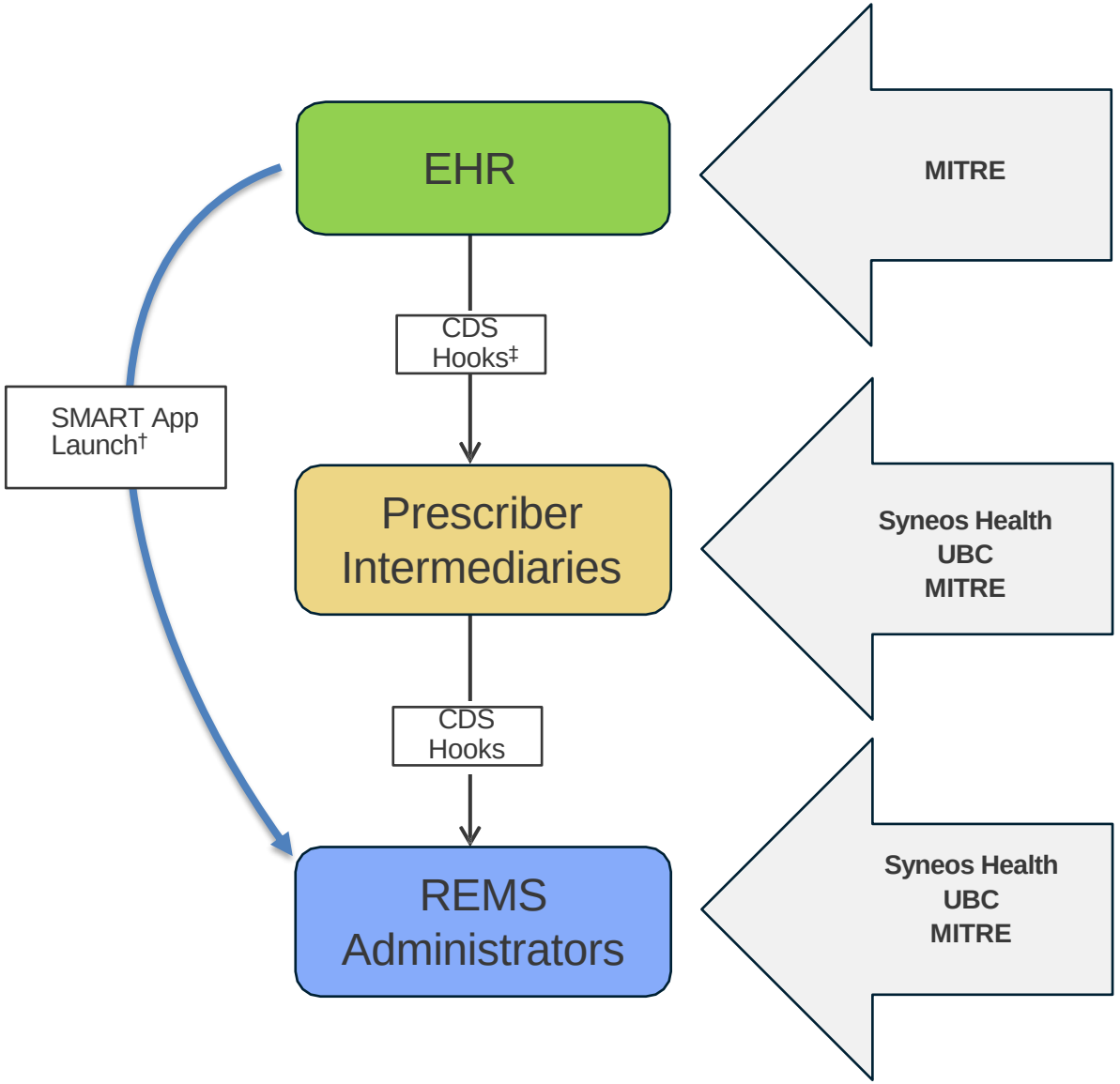
Improving Upon the IG for January 2025 Connectathon

- Created Prescriber Intermediary – To utilize the REMS medication implementation guide (IG) to send to a **Prescriber Intermediary** so that we can have information sent to the **correct REMS administrator**
- Once sent to **pharmacy**, create a **check point to make sure all REMS data are complete** before prescription adjudication (solution while waiting for NCPDP Foundation Grant for Pharmacy Intermediary[1])

[1] See NCPDP Foundation Funds New Project to Streamline REMS Process for the Industry at: https://ncpdpfoundation.org/pdf/NCPDPFoundationREMSGrantInfoWerks.pdf

Slide adapted from CodeX™ REMS Integration Use Case Public Call on November 20, 2024. See: https://confluence.hl7.org/download/attachments/288396005/REMS%20Nov%202024%20Public%20Call.pdf?version=1&modificationDate=1732145107549&api=v2

January 2025 HL7® Connectathon Summary



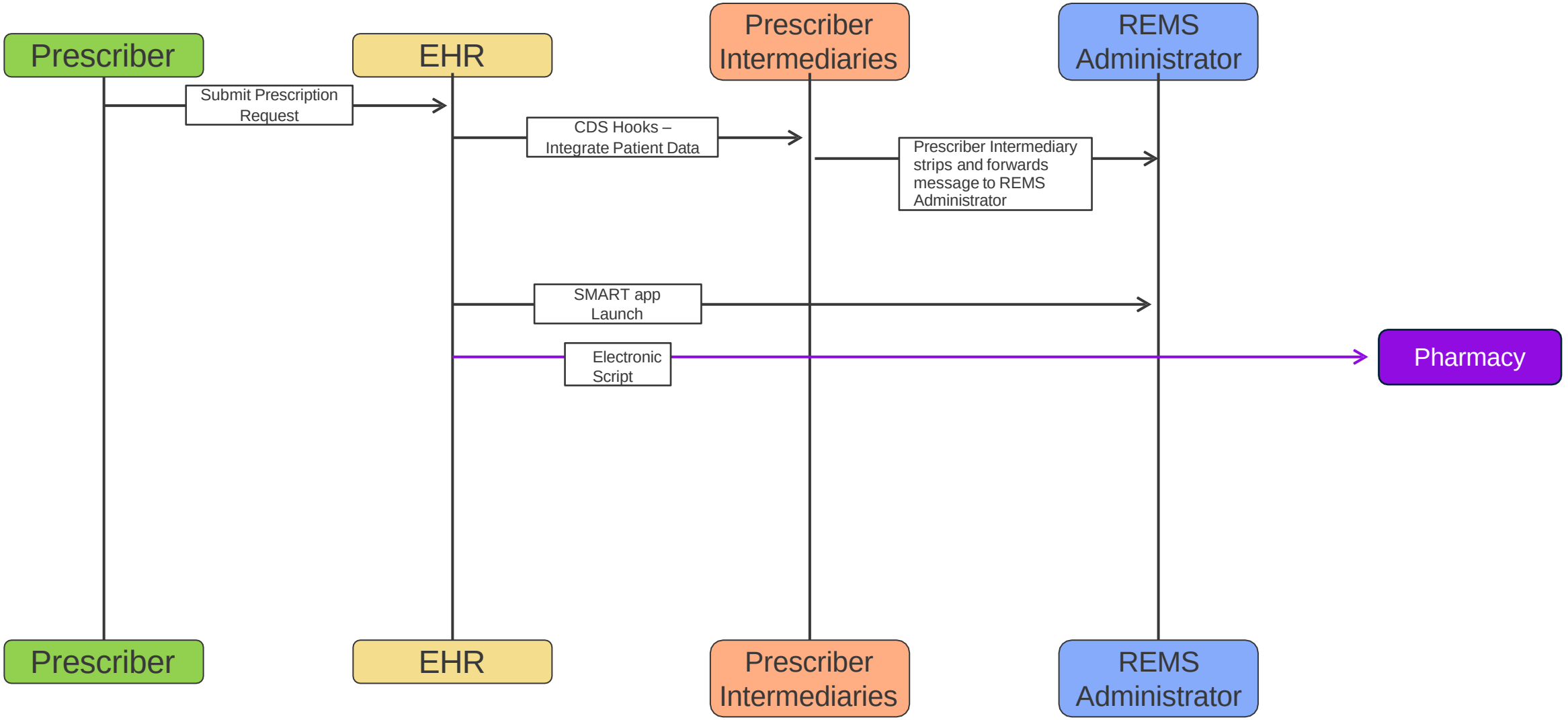
† Substitutable Medical Apps, Reusable Technology (SMART) App Launch is a framework for user-facing apps that connect to EHRs and health portals

‡ Clinical Decision Support (CDS) Hooks is a specification that describes a "hook"-based pattern for invoking decision support from within a clinician's workflow

Slide adapted from CodeX™ REMS Integration Use Case Public Call on November 20, 2024. See: https://confluence.hl7.org/download/attachments/288396005/REMS%20Nov%202024%20Public%20Call.pdf?version=1&modificationDate=1732145107549&api=v2

January 2025 HL7® Connectathon

- Processes to Implement



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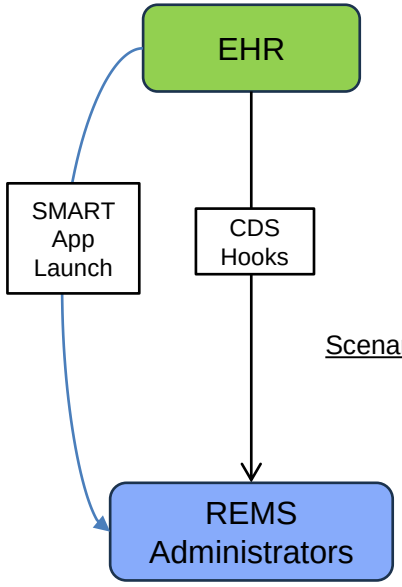
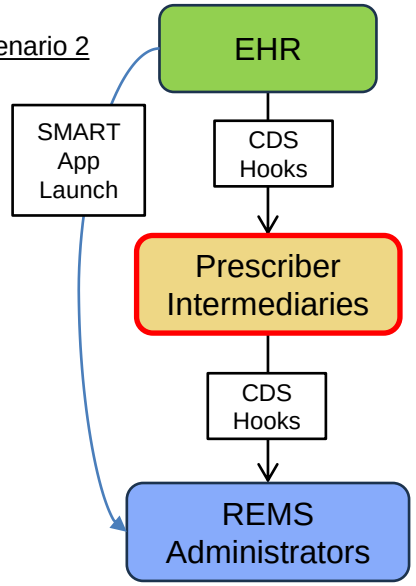
January 2025 HL7® Connectathon Test Scenarios

- Validating the Approach Within Stakeholder Systems

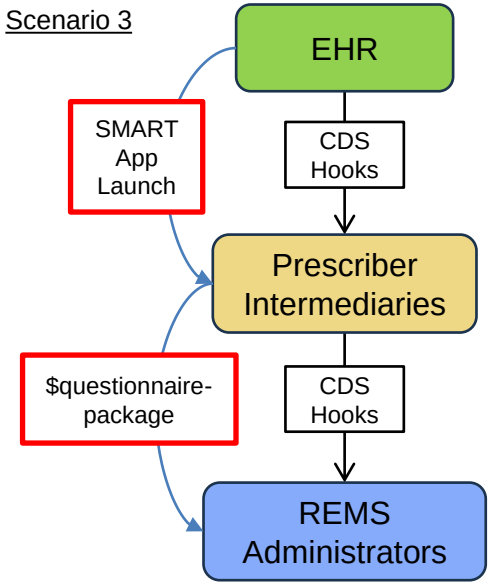


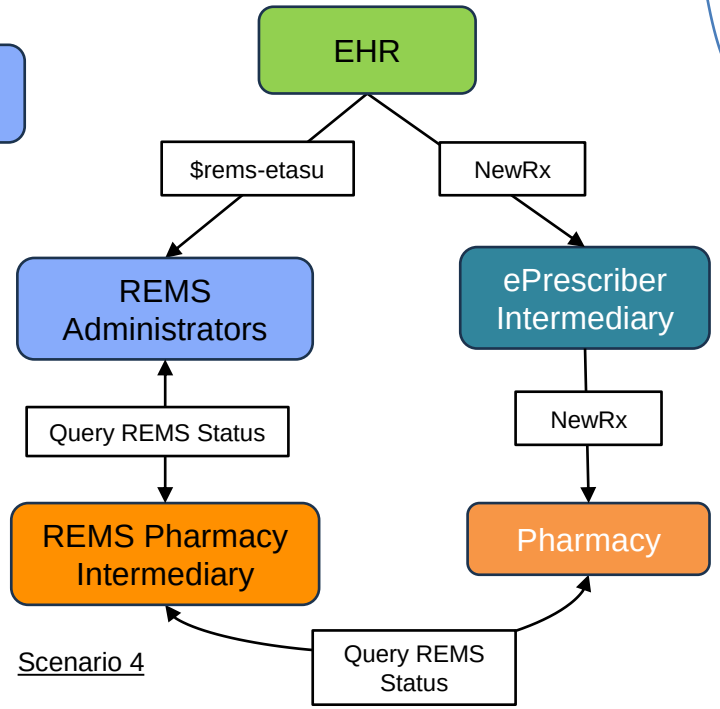
Scenario 1

Scenario 2

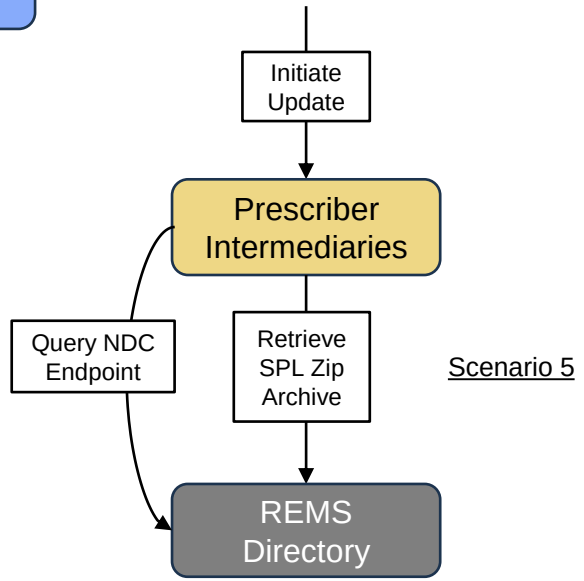


Scenario 3





Scenario 4



Scenario 5

January 2025 HL7® Connectathon - What Worked

Five Scenarios, One Goal: Seamless, Standards-Based REMS Compliance

Scenario	What It Demonstrated
1. Direct Prescriber ↔ REMS Admin	A prescriber can **discover** REMS requirements and **launch** a REMS application
2. Intermediary Forwarding	An intermediary can **route** requests from multiple prescribers to multiple REMS admins
3. Shared SMART App	A **single app** can be used for multiple REMS admins using **standardized** questionnaires
4. Full Pharmacy Flow	REMS **status** can be requested and used to drive **dispensing decisions**
5. Admin Directory	**Standard** software interfaces can support REMS **admin discovery** and registration

All scenarios successfully executed with real software across vendors and roles

January 2026 HL7® Connectathon

Transition to Pharmacovigilance and Risk Management Use Case

REMS (Risk Evaluation and Mitigation Strategies) are drug safety programs that the FDA requires for certain medications with potential for serious adverse effects to help ensure the benefits of the medication outweigh its risks

This track is part of the REMS / Pharmacovigilance and Risk Management Use Case, which aims to

- reduce REMS implementation burden
- improve the quality of REMS data for feedback and evaluation, and
- optimize safe medication use and health outcomes

The use case is part of GenomeX within the CodeX FHIR accelerator

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January 2026 HL7® Connectathon Goal Summary

- Focus on the prescriber, patient, and pharmacy REMS interactions
- Discover REMS Requirements using existing standards
  - Connect several REMS Administrators to an EHR using the REMS IG using:
    - CDS Hooks
    - SMART App Launch (Shared)
- Demonstrate connectivity using Intermediaries
- Educate on IG capabilities
- **Explore use case beyond Connectathon**
- **Build towards a real-world pilot**

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Post-Acute Care InterOperability (PACIO) Project

- Collaborative effort to advance interoperable health data exchange between post-acute care (PAC) and other providers, patients, and key stakeholders across health care
- Promote health data exchange in collaboration with policy makers, standards organizations, and industry through a consensus-based, use case-driven approach.
- Sponsored by the Centers for Medicare & Medicaid Services (CMS) and led by The MITRE Corporation
- For more information see: https://pacioproject.org/

January 2026 HL7® Connectathon

Track Roles and Systems (HL7 FHIR)

- **EHR**
  - Send CDS Hooks
  - Receive and process card
  - SMART App Launch
  - Send $rems-etasu FHIR Operation
  - *Receive FHIR Communication Resource*
  - *Query and parse PACIO[1] Transitions of Care (ToC) Bundle*
- **Prescriber Intermediary**
  - Forward CDS Hooks
  - Receive and return card to client
  - Forward $rems-etasu FHIR Operation
  - Host Shared SMART on FHIR App
    - Retrieve $questionnaire-package
    - Render Questionnaire and execute CQL
    - Send completed QuestionnaireResponse
  - Query SPL and ndc.json endpoint to add/update REMS Administrator
- **REMS Administrator**
  - Respond to CDS Hooks
  - Host SMART App
  - Support $rems-etasu FHIR Operation
    - Include REMS Case Number (if available)
  - Support $questionnaire-package FHIR Operation
  - Receive QuestionnaireResponse
  - *Send FHIR Questionnaire Resource*
- **REMS Directory**
  - Host SPL Zip File
  - Support ndc.json endpoint
- **PACIO FHIR Server**
  - *Host Transitions of Care (ToC) FHIR Bundle*

[1]**PACIO** – Post-Acute Care InterOperability

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January 2026 HL7® Connectathon

Track Roles and Systems (NCPDP SCRIPT)

- **EHR**
  - Send NCPDP SCRIPT NewRx
  - *Receive NCPDP SCRIPT RxFill*
- **Pharmacy**
  - Receive NCPDP SCRIPT NewRx
  - Verify REMS requirements met
    - Send Message to REMS Pharmacy Intermediary
  - *Send NCPDP SCRIPT RxFill*
- **REMS Pharmacy Intermediary**
  - Forward REMS requests from Pharmacy to REMS Administrator
  - Return response from REMS Administrator to Pharmacy
- **REMS Administrator**
  - Communicate with Pharmacy Intermediary
    - Receive REMS Inquiry
    - Send response (dispense authorization or reject)
  - *Receive NCPDP SCRIPT RxFill*

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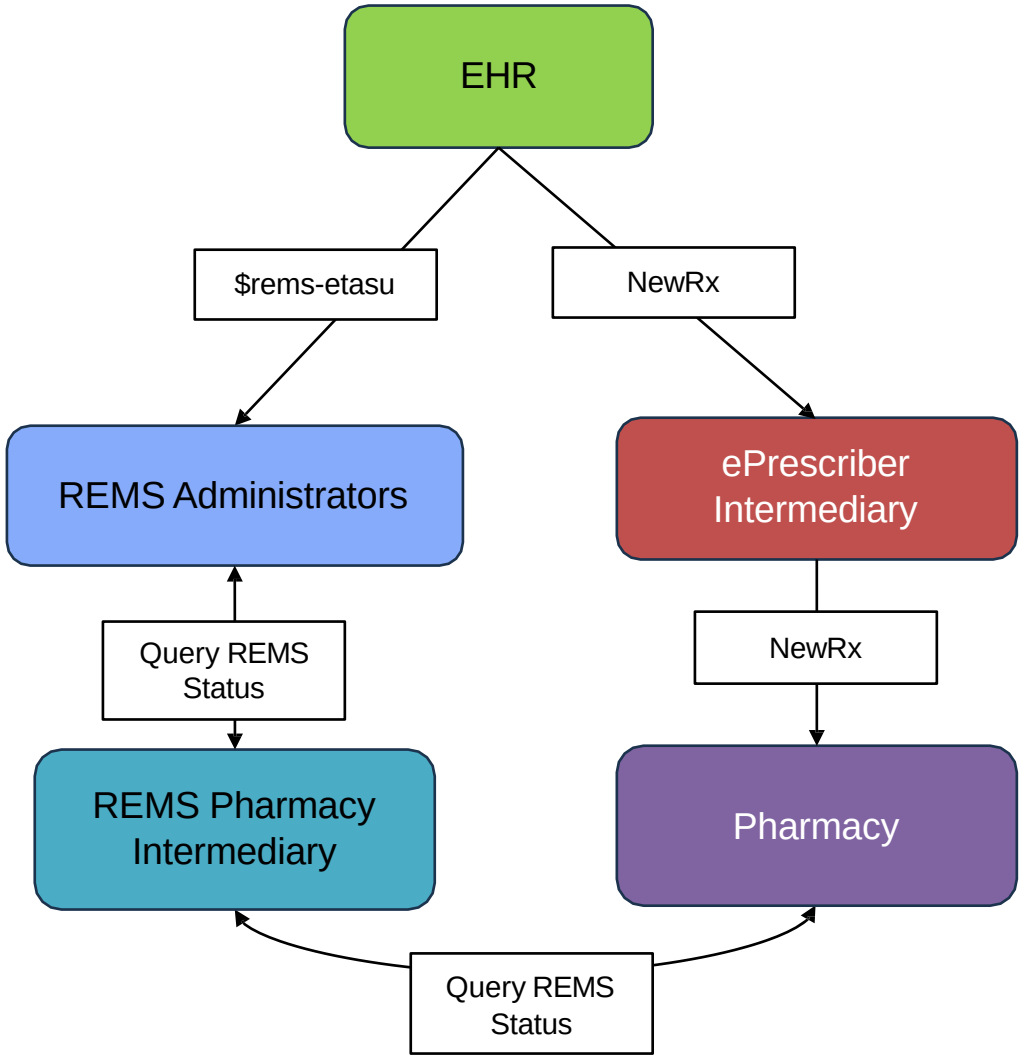
Scenario 1 – Pharmacy Success



- **REMS Pharmacy Intermediary** forwards request to **REMS Administrator**
- **REMS Administrator** responds with *Dispense Authorization*
- **REMS Pharmacy Intermediary** forwards response to **Pharmacy**
- **Pharmacy** dispenses medication to **Patient**
- **Pharmacy** sends *RxFill* to **EHR** **and** **REMS Administrator**

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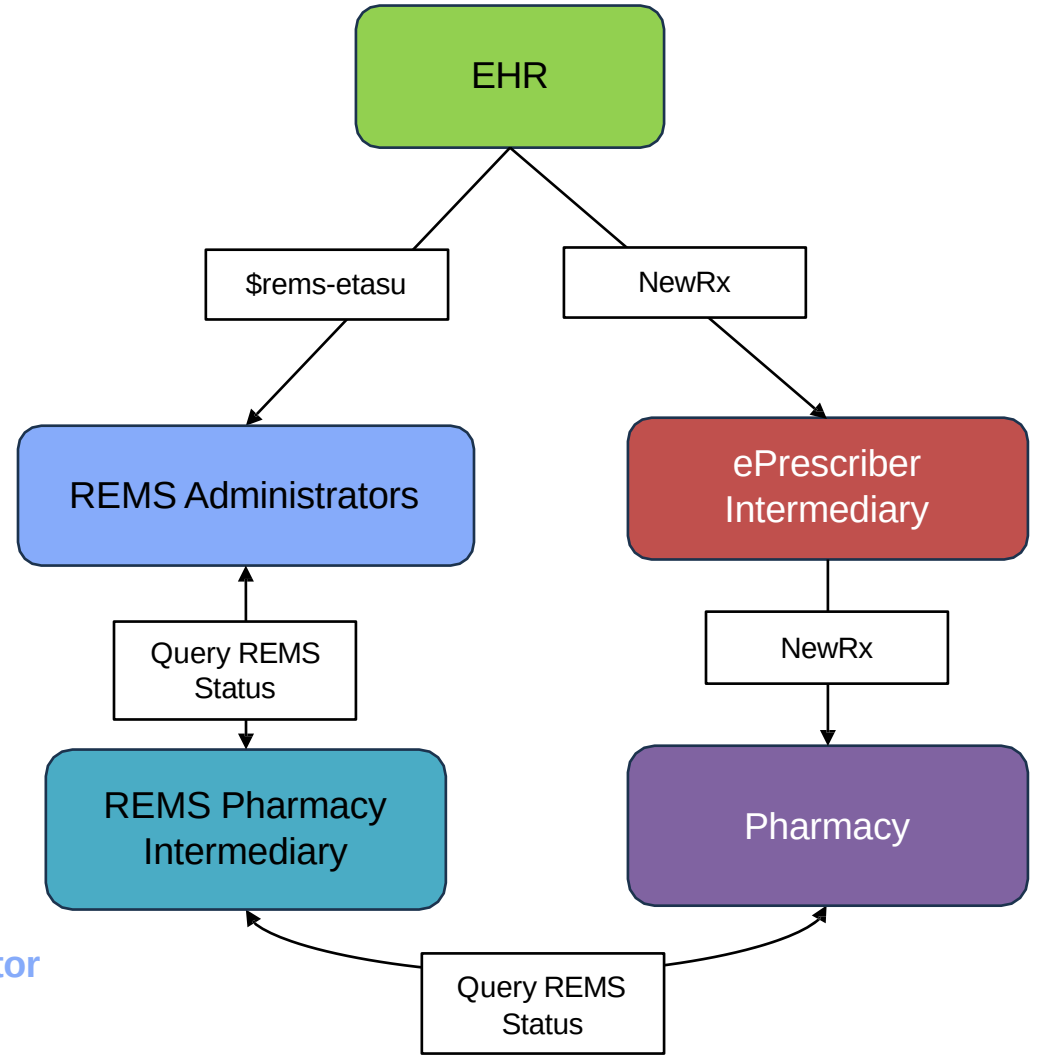
Scenario 2 – Pharmacy Rejection



- **REMS Pharmacy Intermediary** forwards request to **REMS Administrator**
- **REMS Administrator** responds with *Reject Code*
- **REMS Pharmacy Intermediary** forwards response to **Pharmacy**
- **REMS Administrator** sends FHIR *Communication* to **EHR**
- **Pharmacy** sends *RxFill* to **EHR** **and** **REMS Administrator**

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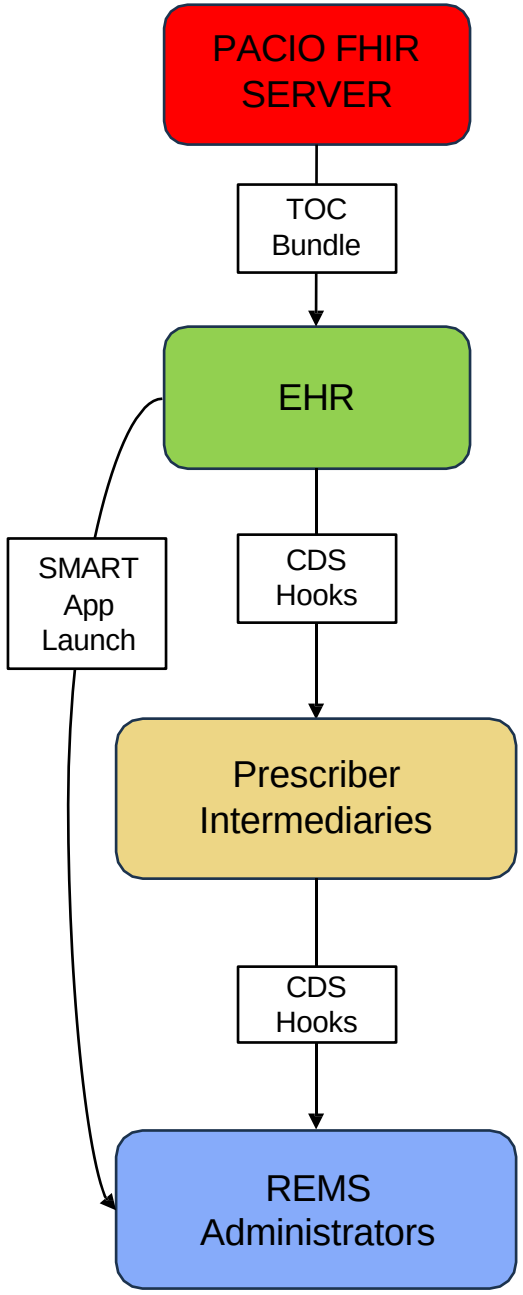
Scenario 3 – PACIO[1]



[1]**PACIO** – Post-Acute Care InterOperability

January 2026 HL7® Connectathon PACIO REMS vignette demo: https://www.youtube.com/watch?v=2szzF53IlZU

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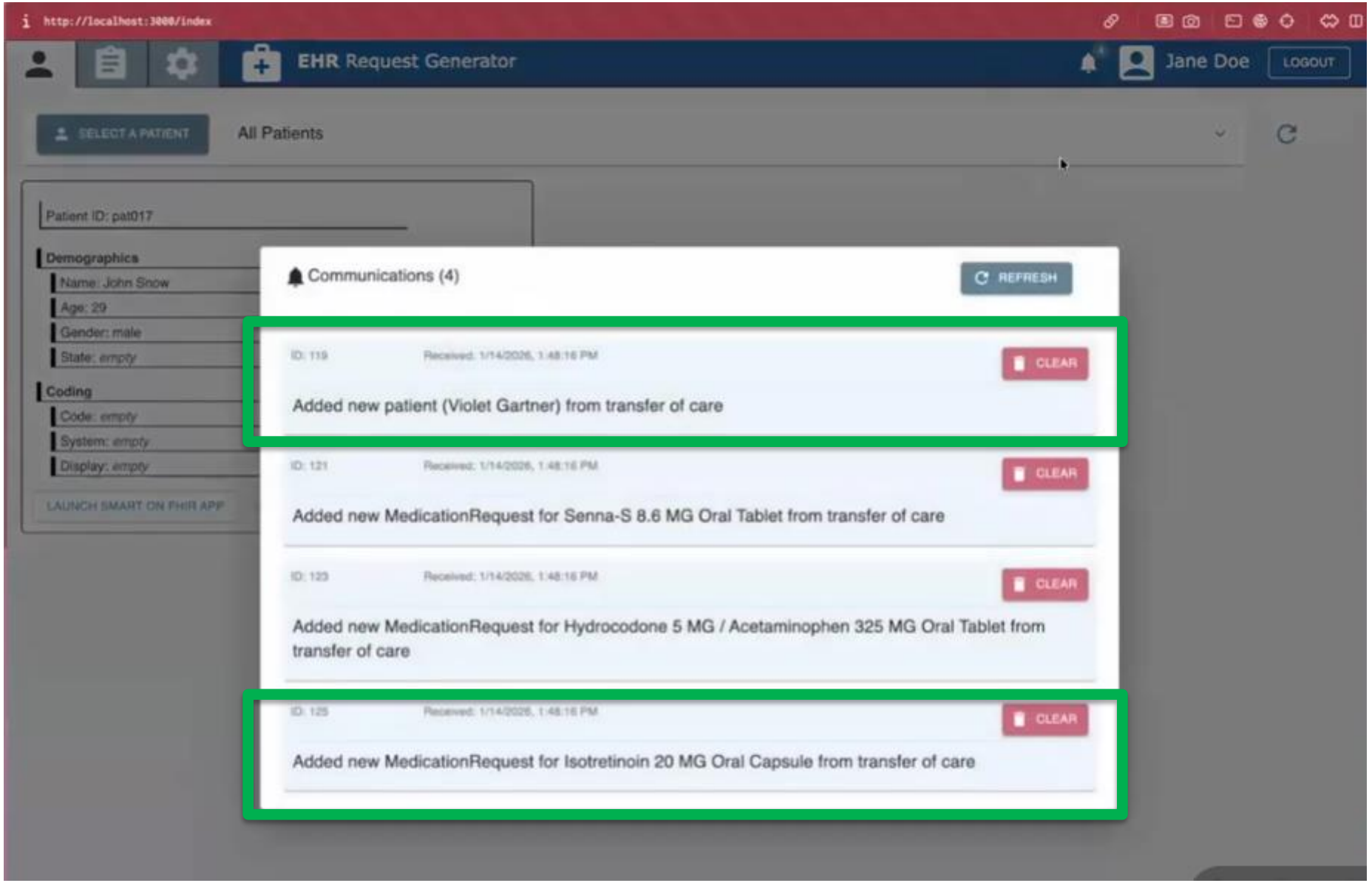
PACIO[1] REMS Vignette

Skilled nursing facility EHR receives information on a new patient on a REMS drug

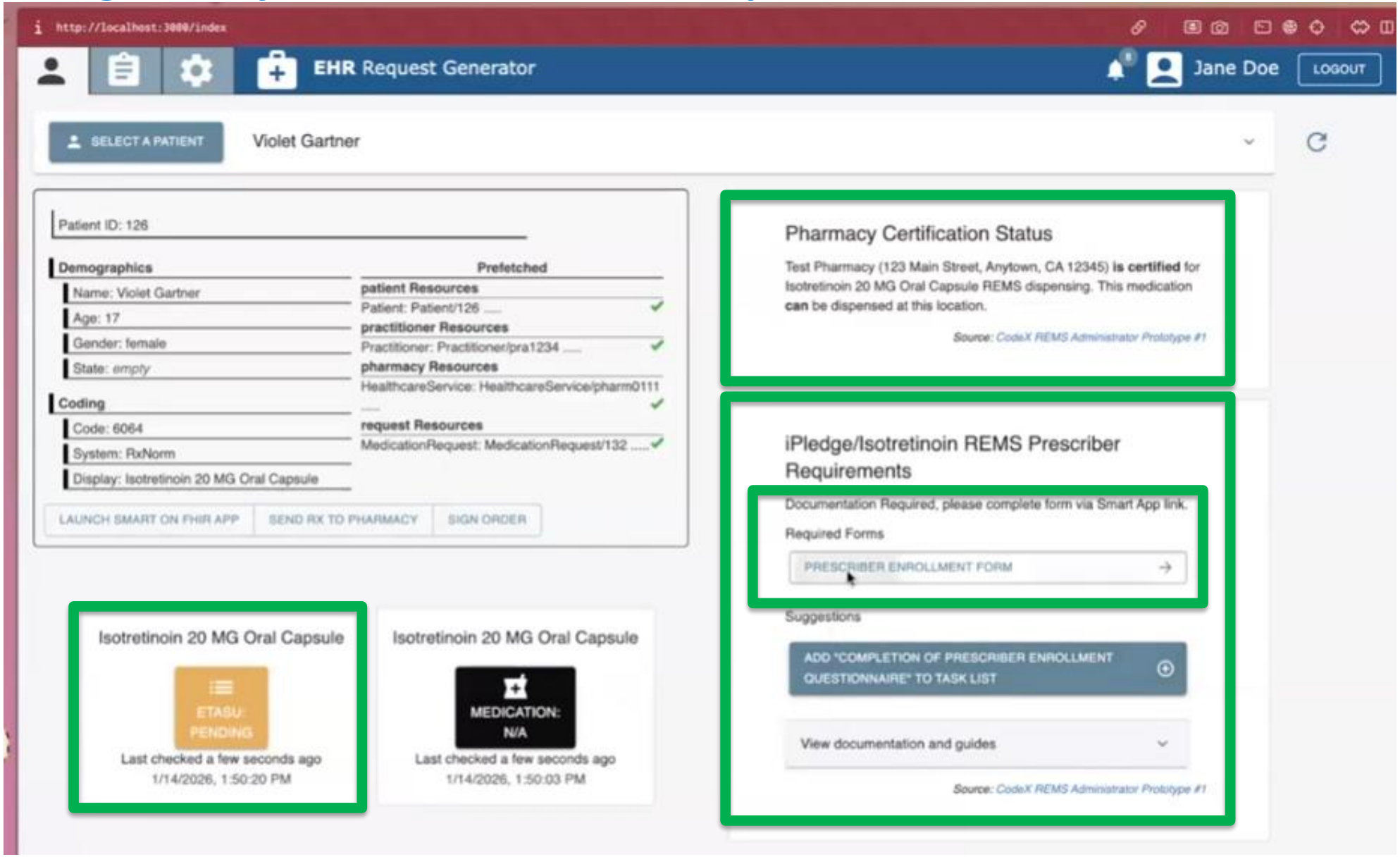


[1]PACIO – Post-Acute Care InterOperability

January 2026 HL7® Connectathon PACIO REMS vignette demo: https://www.youtube.com/watch?v=2szzF53IlZU

PACIO[1] REMS Vignette

Skilled nursing facility EHR checks REMS requirements status



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January 2026 HL7® Connectathon

List of Participants

- Demonstrating Software
  - MITRE: EHR, Intermediary, REMS Administrator
- Other Participants
  - FDA
  - Synerio
  - InfoWerks
  - Epidaurus Health

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January 2026 HL7® Connectathon

Notable Achievements

- Successfully able to test all scenarios
  - REMS requirements discoverable through CDS Hooks
  - Intermediaries able to forward requests to different REMS Administrators based on Medication
  - Applications launched returned cards were able to access FHIR resources on EHR using SMART App Launch
  - NCPDP SCRIPT messages used to verify REMS in pharmacy
  - Cross-over demonstrations with Post-Acute Care InterOperability (PACIO) track
- Demonstrations
  - Demo recordings of all scenarios available on the use case confluence page
    - https://confluence.hl7.org/spaces/COD/pages/358886982/GenomeX+-+Pharmacovigilance+and+Risk+Management
  - Epidaurus Health gave a prior authorization AI demonstration
- Held discussions on the state of the use case and continued testing

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Now What?

- Further exploration of collaborations with other use cases
- Expand to new uses within new Pharmacovigilance and Risk Management Use Case
- Real-world pilot
  - Synthetic patient data
  - Real patient data

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NCPDP® & HL7® FHIR® Cross-Pollination

Legend	
* Existing NCPDP Standard	[4] Supported by SCRIPT, Telecom & Pharmacist eCare Plan Standards
[1] Supported by Telecom & SCRIPT Standards	[5] Supported by Billing Unit, Product Identifiers, SCRIPT, Telecom, F&B, RTPB & Benefit Integration Standards
[2] Supported by SCRIPT, Telecom, & UPI Standards	[6] Separate standards developed jointly between NCPDP and HL7
[3] Supported by SCRIPT Standard	

NCPDP® STANDARDS & INITIATIVES

HL7® FHIR® ACCELERATORS

Cancer Care & Research

REMS[1], PGx, VBA[4], & ePA[3] Alignment

Pharmacy eCare Plan*, Post Adjucation* Pharmacy/ePrescribing Functional Profiles[6], ePA[3], F&B*, RTPB*, & VBA[4], Alignment

RTPB*, Digital Health[5] & UPI*, Post Adjudication* Alignment

National Facilitator Model[2]

VBA[4] & EHR Alignment

API & JSON Alignment

Digital Health[5] & UPI* Alignment

Payers/Providers

Consumers

Public Health

Social Determinants of Health

Providers

Clinical Research

CodeX Project

Da Vinci Project

CARIN Project

Helios Project

Gravity Project

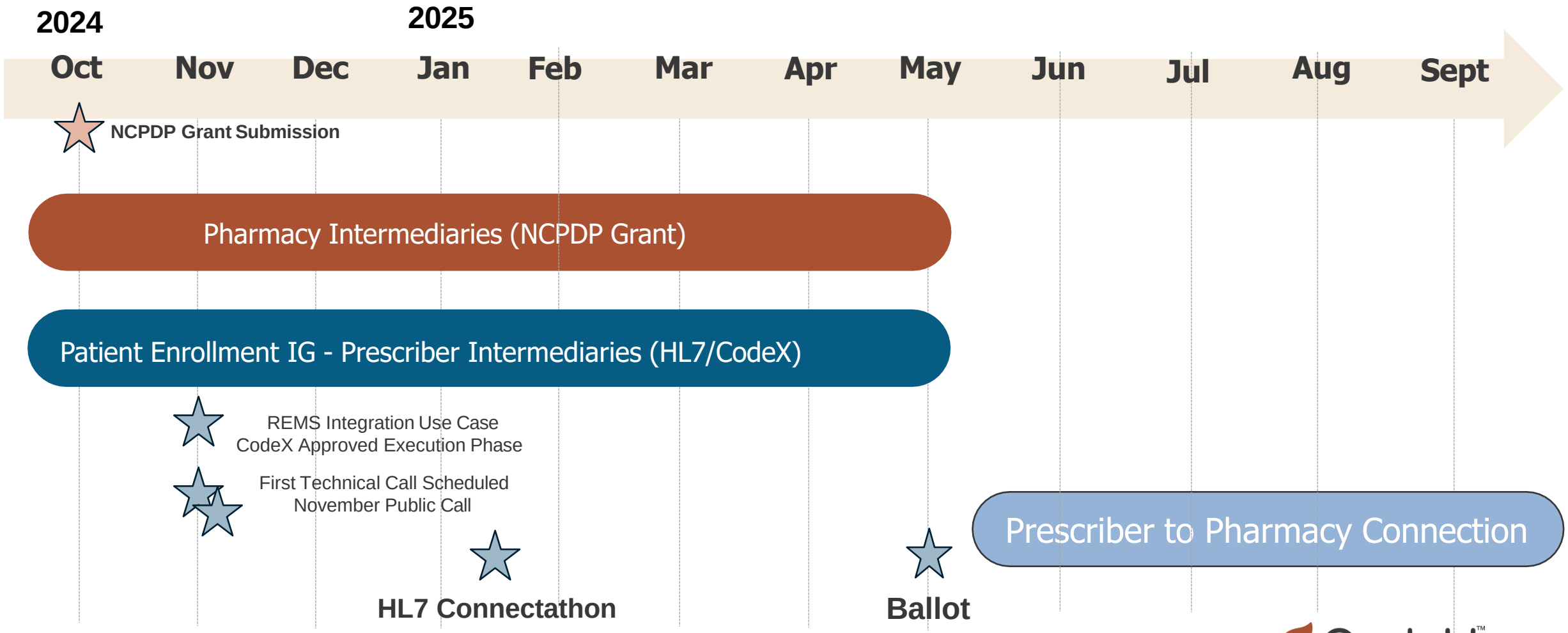
Argonaut Project

Vulcan Project

Slide adapted from CodeX™ REMS Integration Use Case Public Call Presentation, "CodeX™ REMS Integration Use Case," by POCP on February 14, 2023.

REMS Integration Use Case 2024-2025 Timeline

Building interoperabilty between HL7® FHIR® and NCPDP REMS integration data standards through intermediaries.



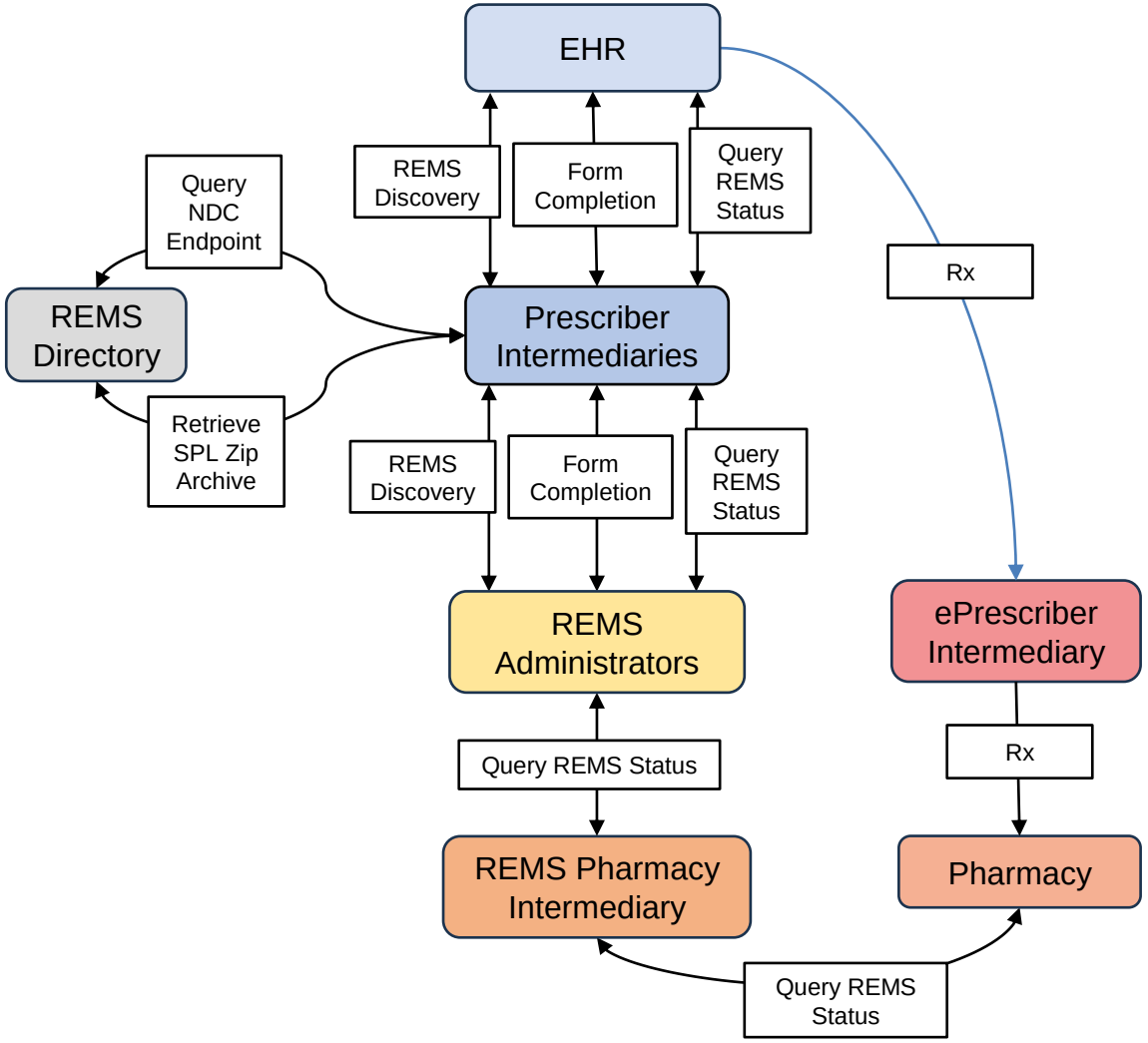
NCPDP = National Council for Prescription Drug Programs

Slide adapted from CodeX™ REMS Integration Use Case Public Call on November 20, 2024. See: https://confluence.hl7.org/download/attachments/288396005/REMS%20Nov%202024%20Public%20Call.pdf?version=1&modificationDate=1732145107549&api=v2

Test Events

Validating the Approach Within Stakeholder Systems

- HL7® January Connectathon
  - January 2025
    - REMS EHR → Prescriber Intermediary → REMS Administrator Interactions
      - Discovery
      - Form Completion
- NCPDP Proof of Concept Workshop
  - July 2025
    - EHR → Pharmacy → REMS Administrator Interactions
      - Prescription Submission
      - Query REMS Status
    - Automatic REMS Administrator Registration



NCPDP February 2026 colLAB[1] Test Event and Work Group Updates

- **What is colLAB?**
  - A **free** place for the healthcare industry to connect, collaborate, innovate and explore real-world use of NCPDP standards, pharmacy and provider workflows and innovations happening around pharmacy technology.
  - Use cases are predetermined by NCPDP member leaders and focus on a patient story to show how the patient goes through the system to get the healthcare they need.
  - The event includes open discussion and dialogue about standards and workflow, demonstrations from vendors and brainstorming on innovative solutions to solve any gaps that may be discovered during the day.
- **February 2026 Use Cases:**
  - Pharmacy Product Locator
  - Electronic Prior Authorization (ePA), and
  - Real-Time Benefit Check (RTBC)

[1] See NCPDP colLAB Events page: https://www.ncpdp.org/colLAB

Outline

- Describe REMS Integration Use Case and prototype updates
- Summarize January 2025 and 2026 Health Level 7 (HL7®) Fast Healthcare Interoperability Resources (FHIR®) Connectathons for REMS medications
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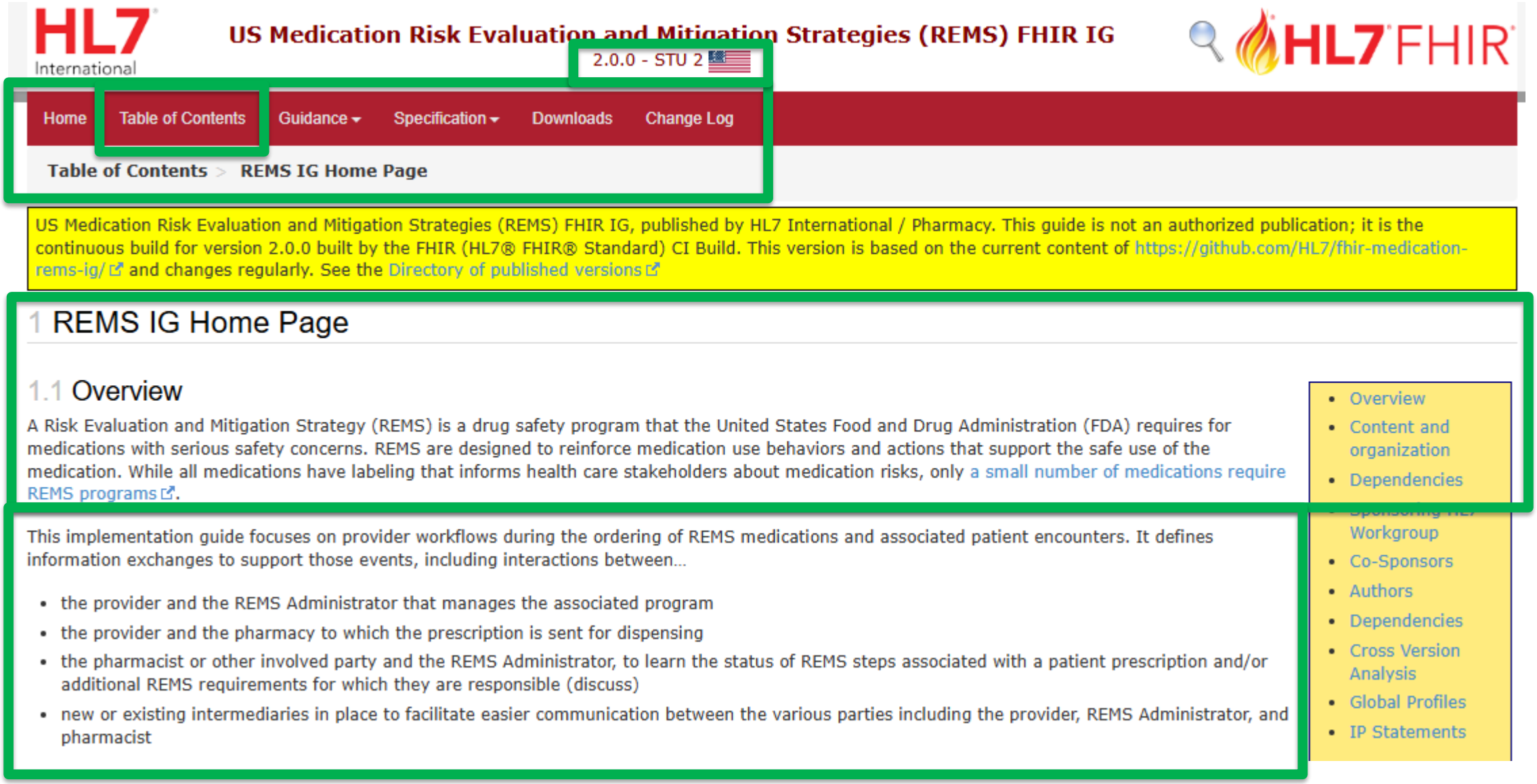
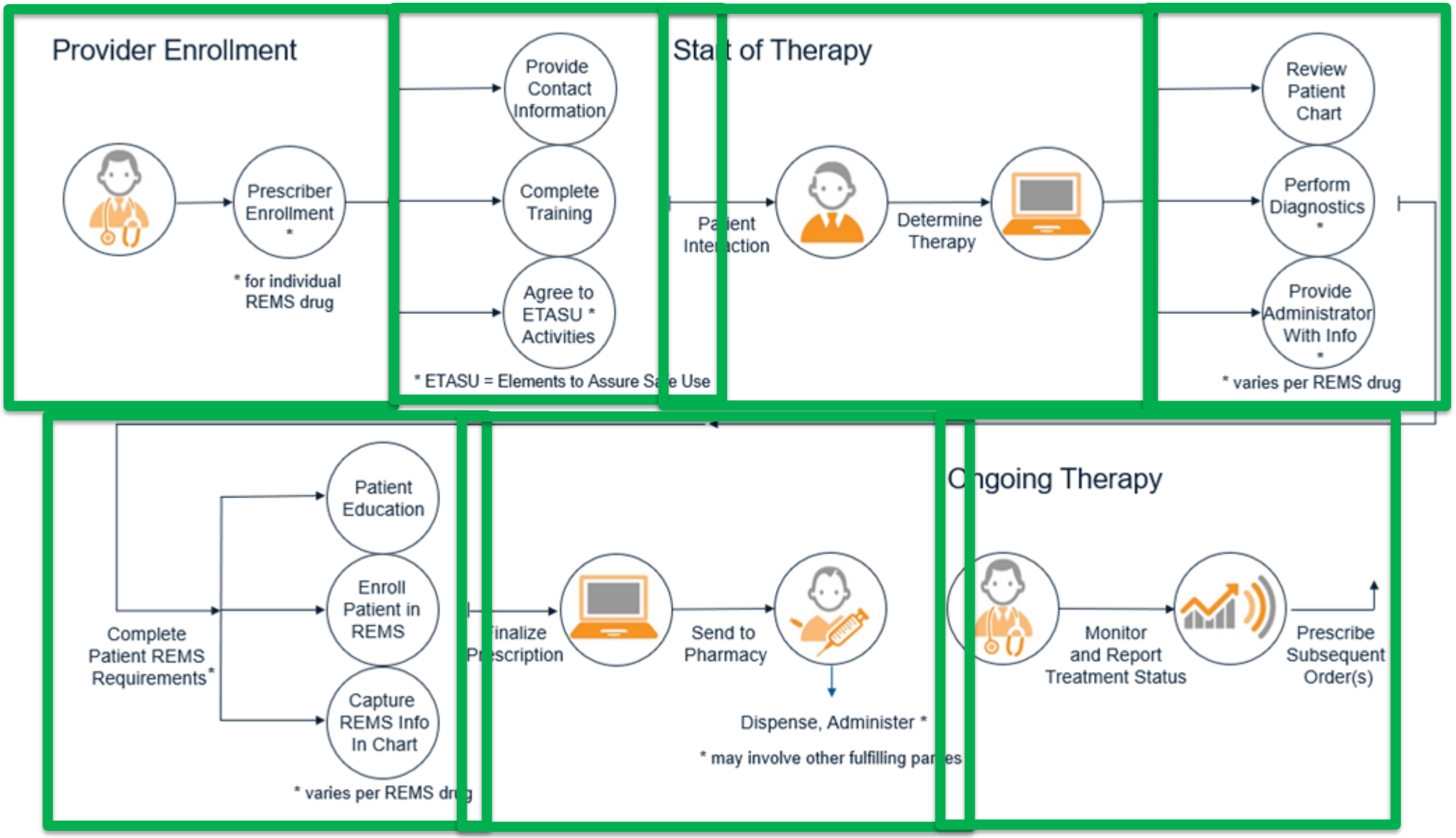
- **Discuss the US Medication REMS HL7 FHIR Implementation Guide (IG) and August 2025 updates**
- Review REMS SPL submission updates
- Discuss future HL7® CodeX™ REMS integration pilots

US Medication REMS FHIR Implementation Guide (IG)



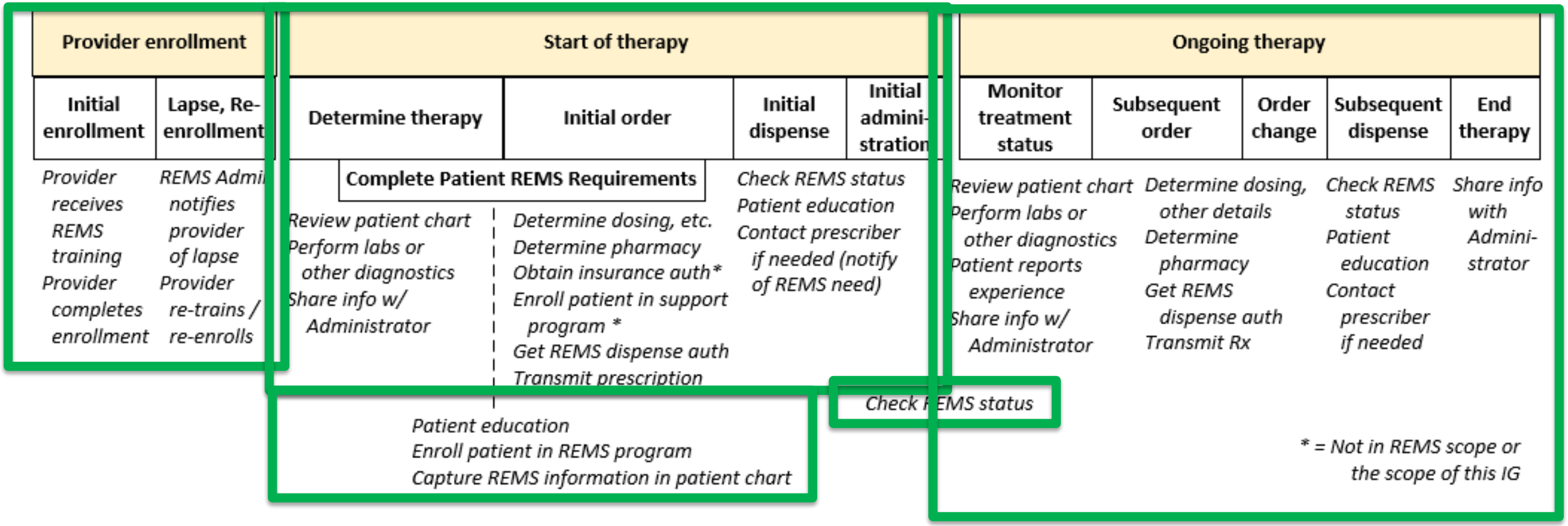
REMS IG Home Page - US Medication Risk Evaluation and Mitigation Strategies (REMS) FHIR IG v2.0.0 available at: https://build.fhir.org/ig/HL7/fhir-medication-rems-ig/index.html

Generalized REMS Process Flow



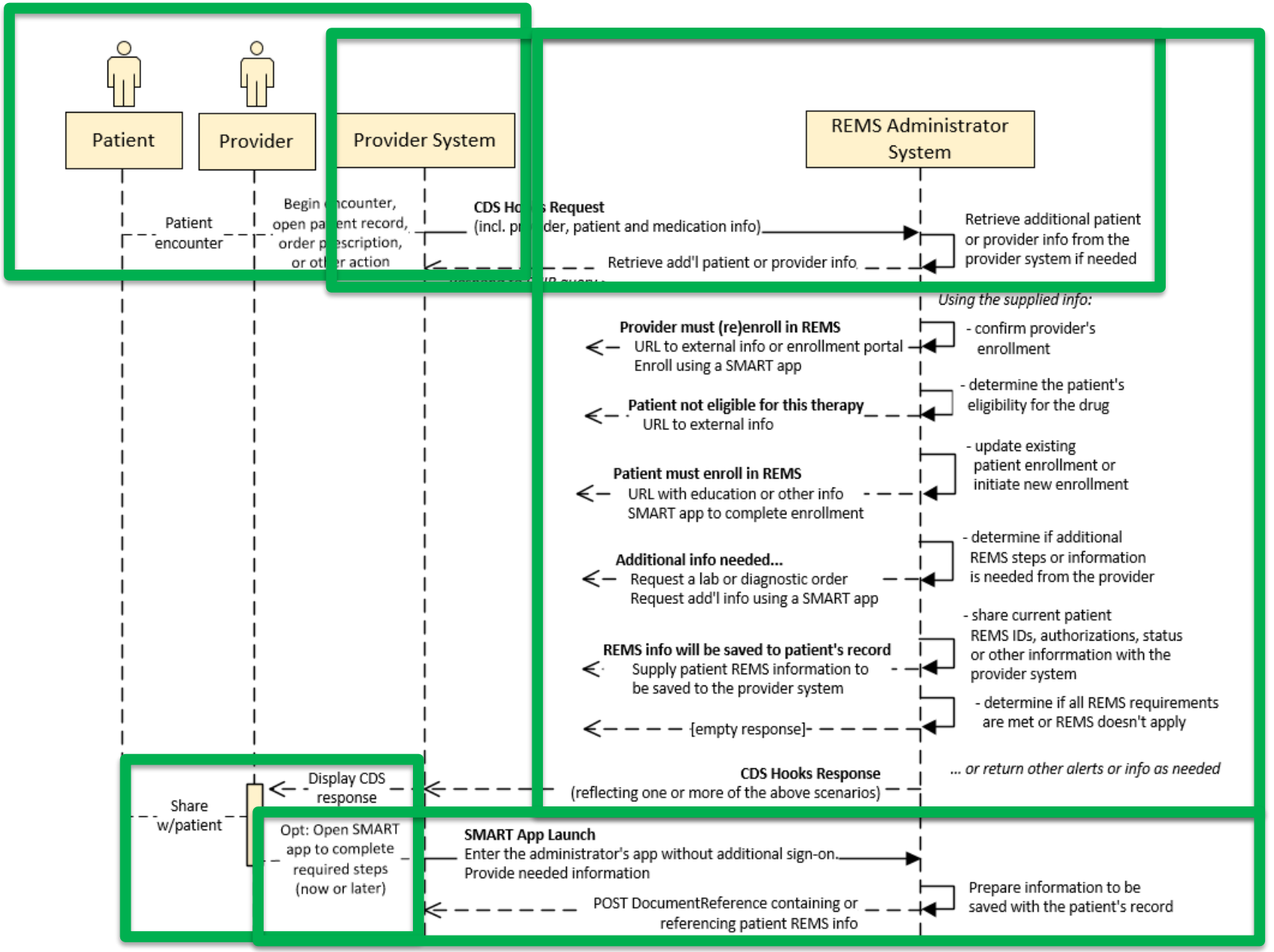
REMS Steps and Terminology - US Medication Risk Evaluation and Mitigation Strategies (REMS) FHIR IG v2.0.0 available at: https://build.fhir.org/ig/HL7/fhir-medication-rems-ig/process.html

REMS Process Activities



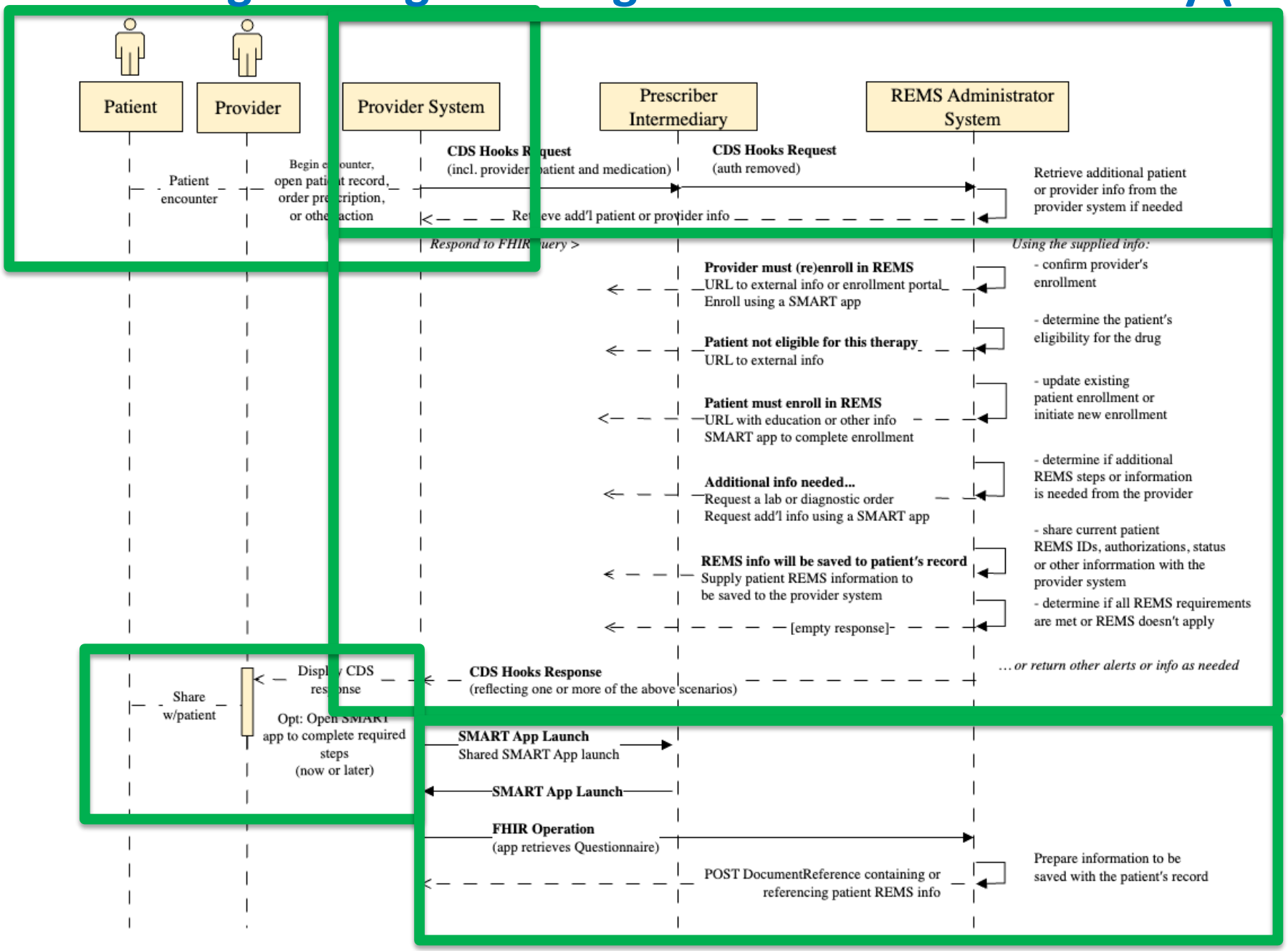
REMS Steps and Terminology - US Medication Risk Evaluation and Mitigation Strategies (REMS) FHIR IG v2.0.0 available at: https://build.fhir.org/ig/HL7/fhir-medication-rems-ig/process.html

Interaction initiated by the Provider System during the provider's workflow



Formal Specification - US Medication Risk Evaluation and Mitigation Strategies (REMS) FHIR IG v2.0.0 available at: https://build.fhir.org/ig/HL7/fhir-medication-rems-ig/specification.html

Support for forwarding messages through Prescriber Intermediary (NEW!)



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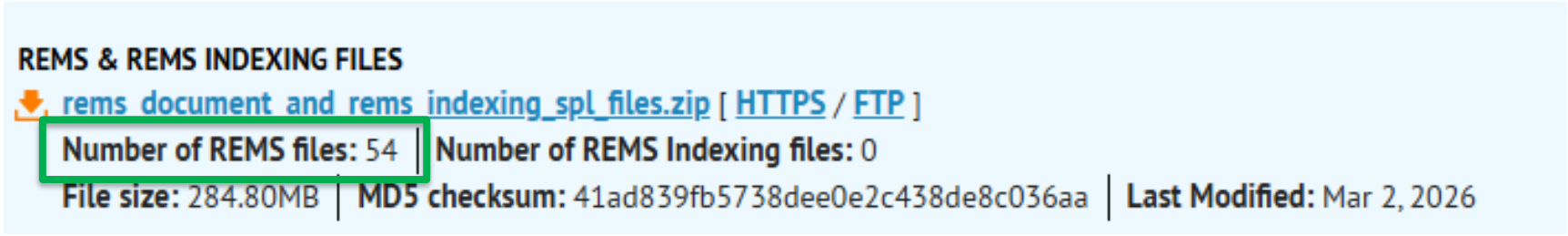
REMS SPL Submissions to FDA‡

- **WHEN:**
  - ***NOW!***
- **WHO:**
  - Applicants must submit 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 available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-content-risk-evaluation-and-mitigation-strategies

REMS SPL submissions as of March 2, 2026

- 54 **total** REMS SPLs
  - 12 **shared system** REMS SPLs
- National Library of Medicine (NLM) DailyMed website:
  - https://dailymed.nlm.nih.gov/dailymed/spl-resources-all-indexing-files.cfm
  - 

REMS SPL Lessons Learned

- Ensure the title, text, and **all formatted content** within the final REMS SPL submission are **verbatim** from the approved **REMS Document**
- Update the REMS SPL file **effectiveTime element** to match the **Most Recent REMS Update date**
- Complete a **REMS Requirement table entry for each requirement** (do not leave out REMS Requirements in the coded REMS requirements entries)
- Ensure **all application numbers** included in a Shared System REMS SPL are **approved** before submission of the final REMS SPL

REMS SPL Resources (spl@fda.hhs.gov)

- **REMS Document Technical Conformance Guide**
  - REMS Document Technical Conformance Guide at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-document-technical-conformance-guide
- **REMS SPL submission requirements began Dec 28, 2022**
  - Providing Regulatory Submissions in Electronic Format -- Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-content-risk-evaluation-and-mitigation-strategies
- **FDA REMS SPL coding pages**
  - REMS SPL Sample at https://www.fda.gov/media/104656/download
  - https://www.fda.gov/industry/structured-product-labeling-resources/rems-approval
  - https://www.fda.gov/industry/structured-product-labeling-resources/rems-protocol
  - https://www.fda.gov/industry/structured-product-labeling-resources/rems-requirements
  - https://www.fda.gov/industry/structured-product-labeling-resources/rems-stakeholder
- **DailyMed SPL Indexing files**
  - REMS and REMS indexing files
    - https://dailymed-data.nlm.nih.gov/public-release-files/rems_document_and_rems_indexing_spl_files.zip

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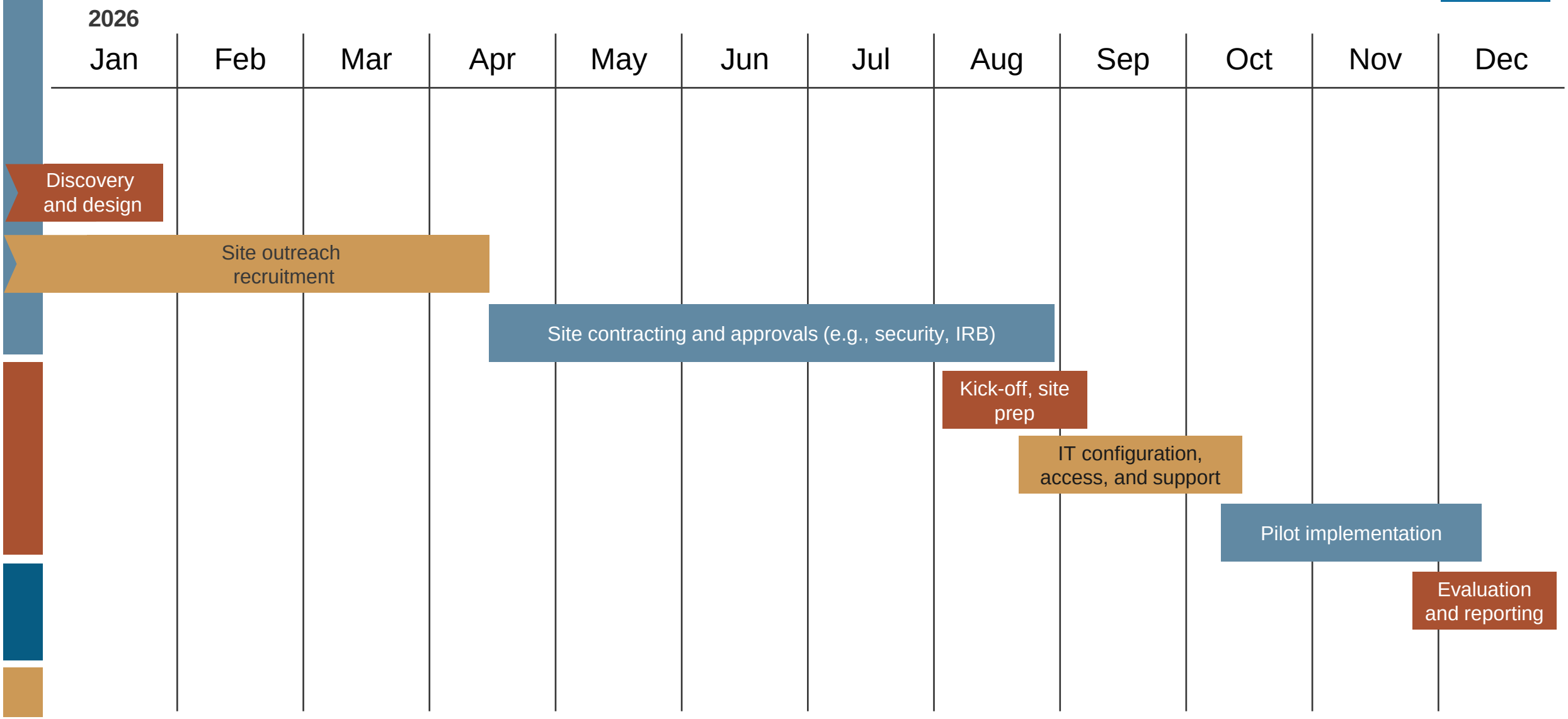
Notional Timeline for REMS Integration Real-world Pilot



Slide adapted from CodeX™ Pharmacovigilance and Risk Management Use Case Public Call on January 21, 2026.
See: https://confluence.hl7.org/spaces/COD/pages/413048123/01-20-2026+Pharmacovigilance+and+Risk+Management+Public+Call+Meeting+Minutes

Future State

- Leading to an automated, connected REMS ecosystem
- Consistent with advances in health data standards and technology
- Building towards an app- and API- (application programming interface) based healthcare ecosystem

What do we need now?

YOU

Get Involved

- **Mark your calendars and engage in future public calls for the CodeX Pharmacovigilance and Risk Management Use Case. Registration information is available on the REMS confluence page:**
  - https://confluence.hl7.org/spaces/COD/pages/358886982/GenomeX+-+Pharmacovigilance+and+Risk+Management
- **CodeX Pharmacovigilance and Risk Management Use Case Coordinator:**
  - Kelee Petzelt (kelee.petzelt@synerio.com)

- **CodeX Pharmacovigilance and Risk Management Use Case Contact Information:**
  - Lauren DiCristofaro laurend@mitre.org
  - Nicole Ng nng@mitre.org
  - Ammu Irivinti ammu@mitre.org

Slide adapted from CodeX™ REMS Integration Use Case Slide Deck titled, "CodeX Risk Evaluation and Mitigation Strategies (REMS) Integration Prototype: Release version REMS 1.5" available on the CodeX™ Confluence page. See https://confluence.hl7.org/download/attachments/81003813/REMS%201.5%20Slides.pptx?version=1&modificationDate=1759803276078&api=v2

U.S. FOOD & DRUG ADMINISTRATION

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION