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Adapting Real-World Data (RWD) into CDISC Submission Standards: Challenges and Potential Solutions

Presented by Lauren Green, Senior Manager, Biostatistical Programming, Amgen

Meet the Speaker

Lauren Green

Title: Biostatistical Programming Senior Manager

Organization: Amgen

Lauren Green is a senior manager of biostatistical programming within the Center for Observational Research at Amgen where she provides leadership to the US-based oncology programming team supporting the execution of real-world evidence observational studies. In her career, Lauren has led efforts in the evaluation of real-world data (RWD) aimed at improving the quality, safety, and value of healthcare. Her main interests include dissecting the challenges of RWD and the unprecedented opportunity it provides in preventative medicine and population health.

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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

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Agenda

Background

FDA Guidance – Value in RWD

RWD

SDTM

ADaM

- "**FDA recognizes** the potential utility of **using RWD** in interventional studies…**to serve as a comparator arm** in an externally controlled trial"
  - U.S. Food and Drug Administration, December 2021. *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products.* Accessed: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

- "**Sponsors submitting clinical** and nonclinical **study data** (including those derived from RWD sources) in submissions…**are required to use** the formats described in the Study Data Guidance and **the supported study data standards** listed in the Catalog"
  - U.S. Food and Drug Administration, October 2021. *Data Standards for Drug and Biological Product Submissions Containing Real-World Data.* Accessed: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data

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Supported Study Data Standards

- CDISC : "**Develop and advance data standards** of the highest quality to transform incompatible formats, inconsistent methodologies, and diverse perspectives into a powerful framework **for generating *clinical research data*** that is as accessible as it is illuminating."

## Study Data Tabulation Model (SDTM)

- Organizing and formatting data to streamline processes in collection, management, analysis and reporting clinical trial data

Analysis Data Model (ADaM)

- Efficient generation, replication, and traceability among analysis results, analysis data, and data represented in SDTM

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Study Design

- Objectives
  - Compare overall complete response (CR) rate estimates between:
    - Clinical Trial Arm
      - Clinical trial data
    - Observational Study Control Arm
      - Real-world data

Clinical Trial Arm

Observational Study Control Arm

Compare CR Outcomes
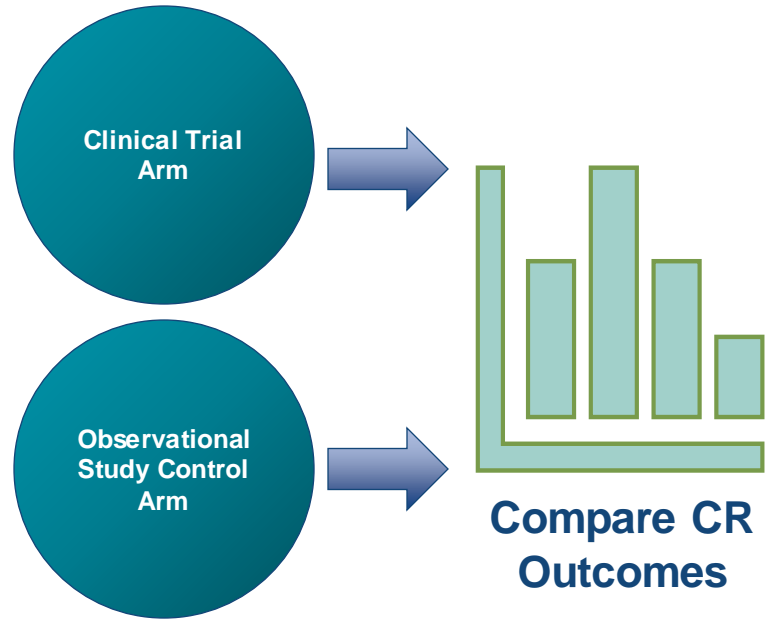
- Research Registry
- Tumor Registry
- Chart Abstraction
- Billing Documents

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Recognized Challenges and Proposed Solutions

Recognized Challenges

- Diverse RWD Sources
- Preceding Patient De-identification
- Poor Validation Scores
- Missing Data Elements
- Incorporating Algorithms
- Inconsistent Record-level Data
- Unique Source-to-Target Mapping
- Limited RWD Accessibility
- Constructing Visits
- Fitting Complex RWD Structures

Proposed Solutions

FDA

- Documentation
  - Define XML
  - Study Data Reviewer's Guide
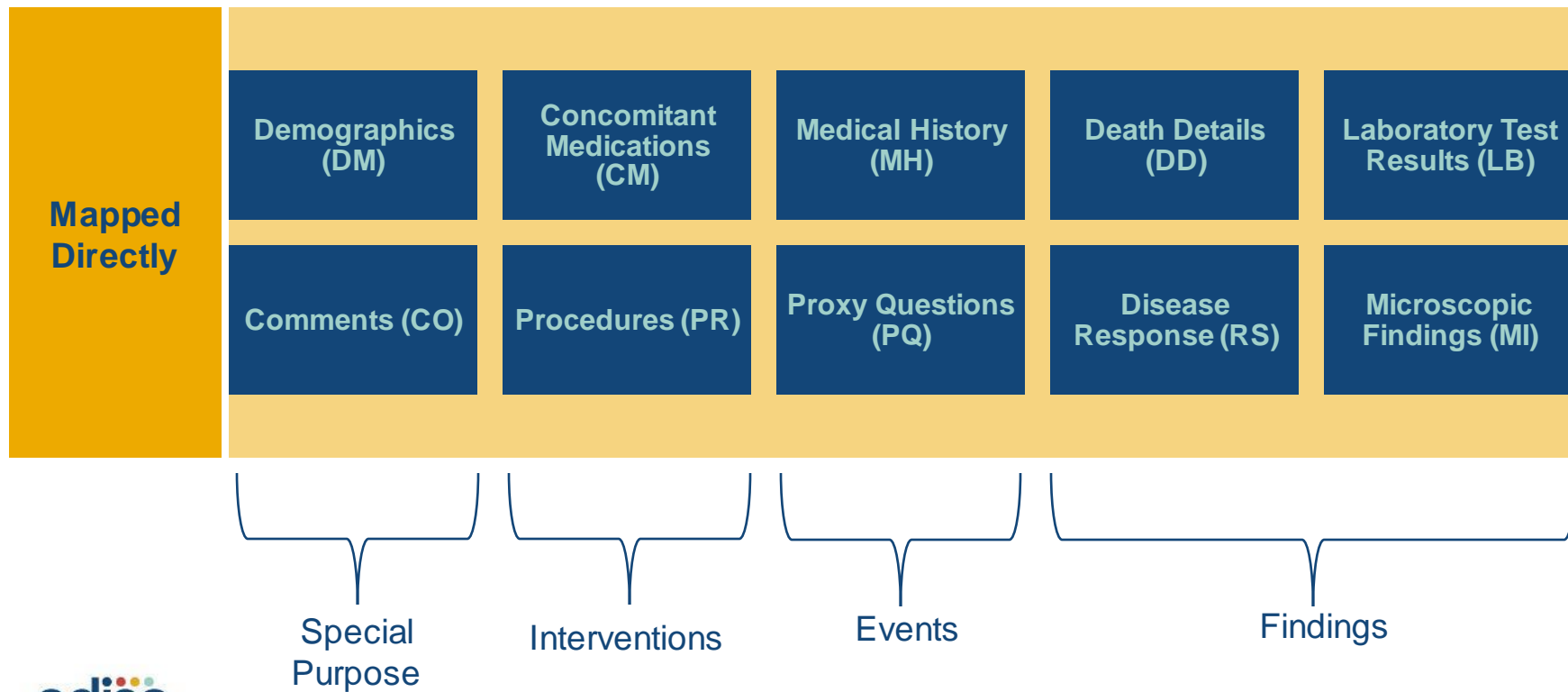 - Analysis Data Reviewer's Guide

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- Expanding data standards
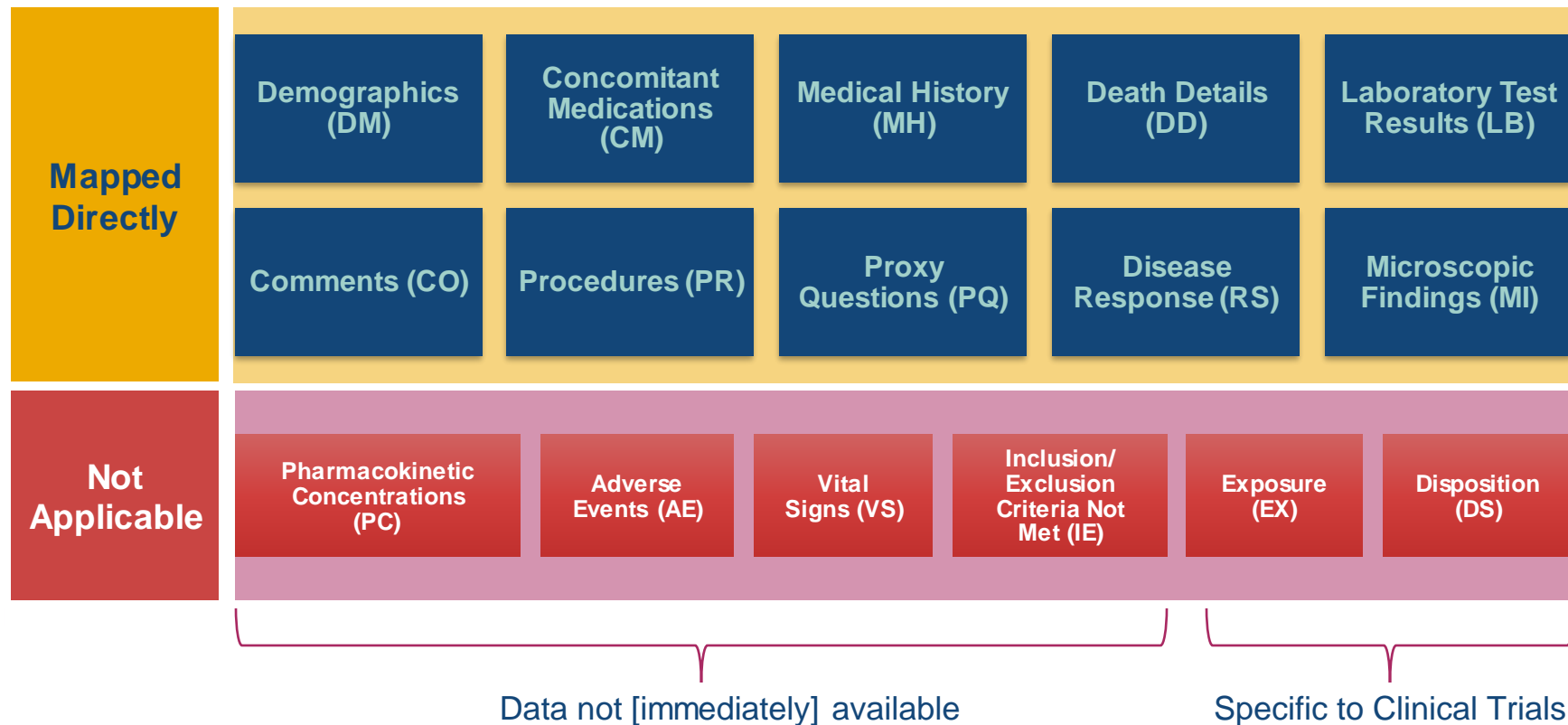- Repurposing and/or relabeling existing domains/variables

Missing Data Elements

Missing Data Elements for SDTM Domains

Missing Data Elements for SDTM Domains

Mapped Directly	Demographics (DM)	Concomitant Medications (CM)	Medical History (MH)	Death Details (DD)	Laboratory Test Results (LB)
	Comments (CO)	Procedures (PR)	Proxy Questions (PQ)	Disease Response (RS)	Microscopic Findings (MI)

Not Applicable	Pharmacokinetic Concentrations (PC)	Adverse Events (AE)	Vital Signs (VS)	Inclusion/ Exclusion Criteria Not Met (IE)	Exposure (EX)	Disposition (DS)

Data not [immediately] available • Specific to Clinical Trials

Missing Data Elements for SDTM Domains

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Not Applicable	Pharmacokinetic Concentrations (PC)	Adverse Events (AE)	Vital Signs (VS)	Inclusion/ Exclusion Criteria Not Met (IE)	Exposure (EX)	Disposition (DS)

Mapped Contextually	Trial Summary (TS)	Trial Arms (TA)	Trial Elements (TE)	Trial Inclusion (TI)	Subject Status (SS)

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Challenge 2: Source-to-Target Mapping

Unique Source-to-Target Mapping

Source to Target Mapping – ADaM Chronology

**General Pathway for Clinical Trials**

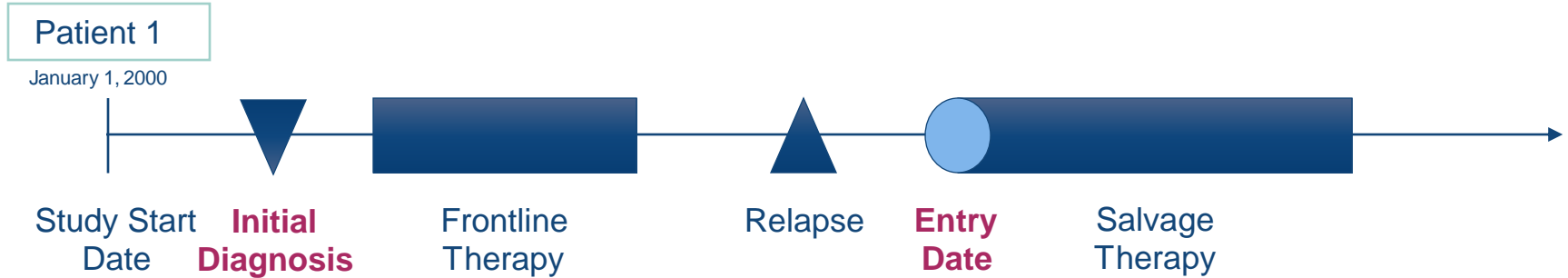| SDTM | ➤ | Subject-level Analysis Dataset (ADSL) | ➤ | All other ADaM Domains |

- Data in clinical trials is collected prospectively
  - Variables can be constructed based on patient visits
  - Data can be collected for all the information that is needed at each visit
    - Data can be easily recorded in SDTM domains without retrospective analysis
- Data in the observational study were already collected
  - Data was aggregated from medical encounters such as registries, medical charts, and billing documents
  - Variables and values that are not provided directly from the RWD must be derived via retrospective analyses

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Source to Target Mapping – ADaM Chronology

Patient 1

January 1, 2000

Study Start Date   Initial Diagnosis   Entry Date
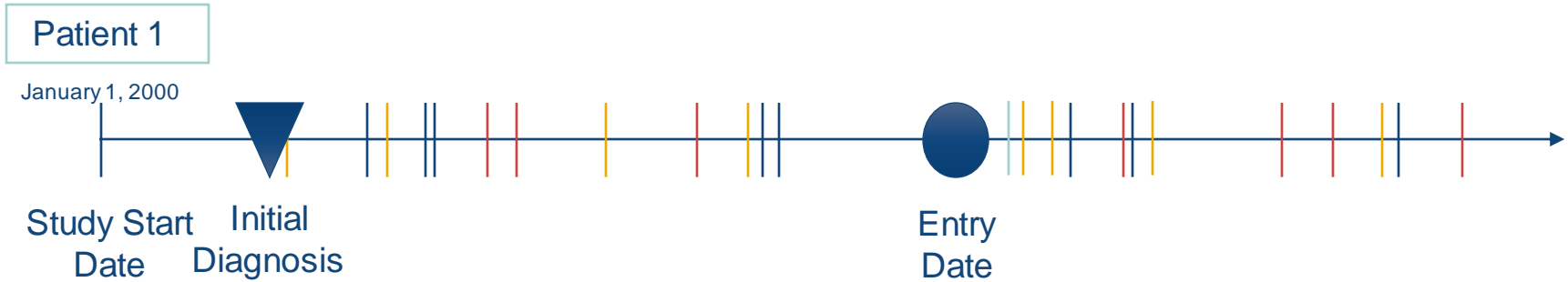
- **Subject-level Analysis Dataset (ADSL)**
    - Demographic information
    - Population flags
    - Treatment variables
    - Subgrouping and stratification variables
    - Important dates

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Proposed Transformation

Patient 1

January 1, 2000

Study Start Date | **Initial Diagnosis** | Frontline Therapy | Relapse | **Entry Date** | Salvage Therapy

- **<u>Subject-level Analysis Dataset (ADSL)</u>**
  - Demographic information
  - Population flags **| Needed to derive analysis set flags**
  - Subgrouping and stratification variables **| Most needed to be derived**
  - Treatment variables **| Actual treatment records were available but needed to derive lines of therapy**
  - Important dates **| Some were available, but others needed to be derived (e.g., relapse, remission, etc.)**

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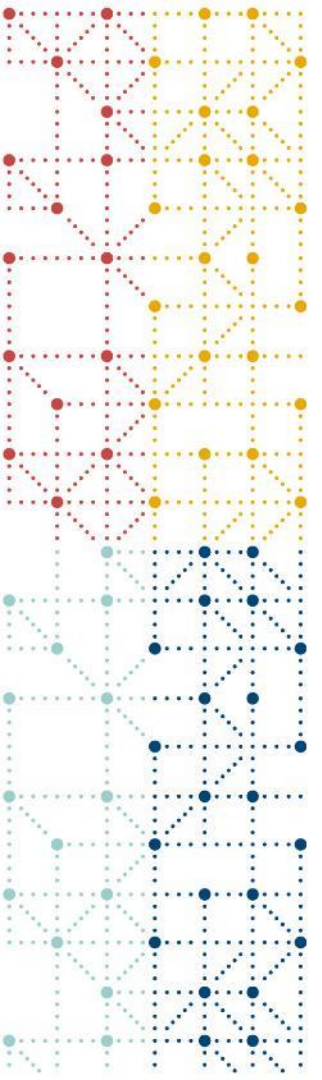
Proposed Solutions

Source to Target Mapping – ADaM Chronology

General Pathway for Clinical Trials

SDTM → ADSL → All other ADaM Domains

Pathway for Observational Study Control Arm

SDTM → ADPRE → ADCM → ADLOT → ADSL → All other ADaM Domains

ADPRE – Prior Response Analysis Dataset
ADCM – Concomitant Medications Analysis Dataset
ADLOT – Line of Therapy Analysis Dataset

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# Proposed Solution for Source to Target Mapping

- Prior Response Analysis Dataset (ADPRE)
  - Combined labs, procedures, and other information to assess dates of relapse and remission

- Concomitant Medications Analysis Dataset (ADCM)
  - Translated treatment information to controlled terminology

- Line of Therapy Analysis Dataset (ADLOT)
  - Applied line of therapy algorithm to assign treatment progression

SDTM → **ADPRE** → **ADCM** → **ADLOT** → ADSL → **All other ADaM Domains**

Documentation for **TRACEABILITY**

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Final Comments

- Clinical trials are designed with CDISC standards in mind, whereas RWD is collected for purposes other than primary research

- RWD does not always fit perfectly within existing standards but there are concepts, strategies, and components that can be utilized to support data transformation

- When challenges arise, researchers should seek out and test best practices for conforming RWD to data standards

- Identifying and sharing challenges and potential solutions will support the enhancement of data submission standards for RWD

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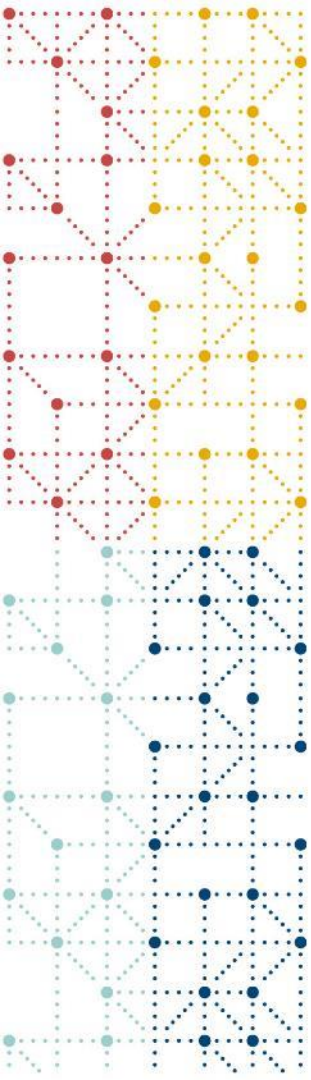
Thank You!

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