Sentinel

Monitoring Medication Use During the COVID-19 Pandemic in the Sentinel System

The Case of Anticoagulation for Thrombosis

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15 September 2021

Disclosures

- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

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- The Sentinel projects described herein are public health surveillance activities conducted under the authority of the FDA and, accordingly, are not subject to Institutional Review Board oversight.

Agenda

1. The Sentinel System
2. Surveillance in Public Health Emergencies
3. Case Study: Thrombotic Events in COVID-19

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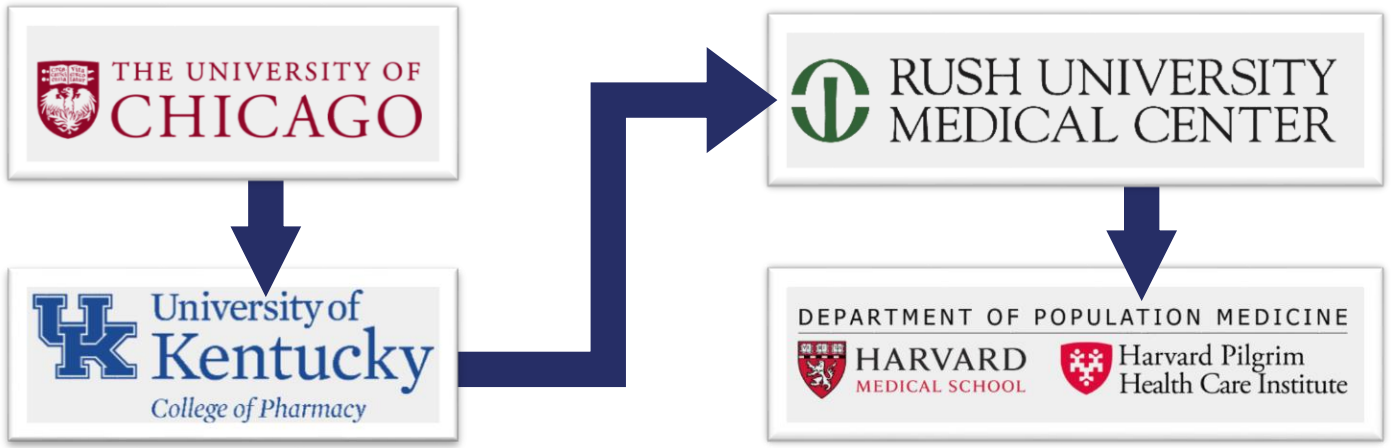
Pronouns: she/her

Experience



Research

Current portfolio contains routine and COVID-19 specific Sentinel queries, as well as federally funded grant work

Doctoral dissertation investigated impact of potentially inappropriate medication use on cognitive outcomes among older adults

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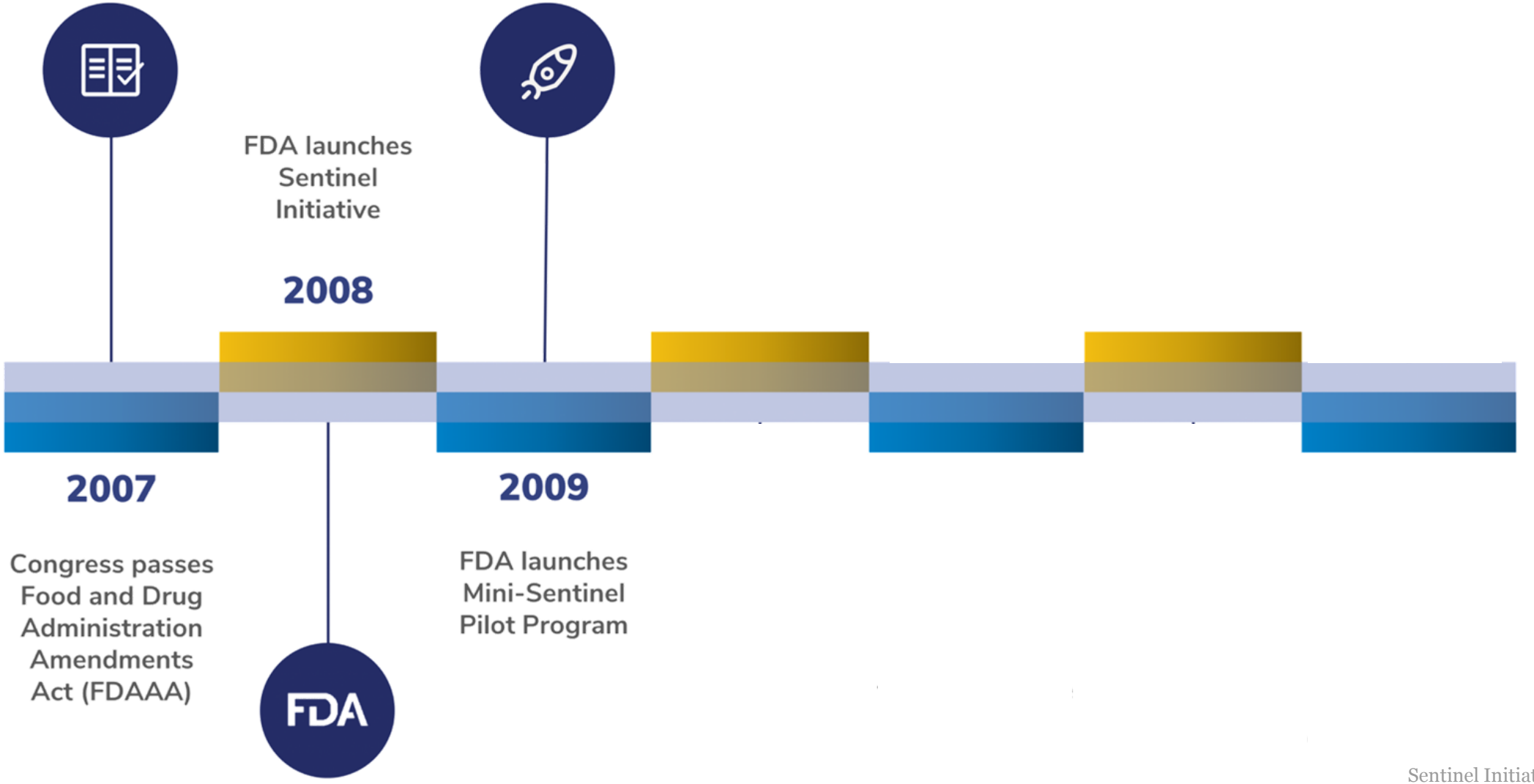
The Sentinel System

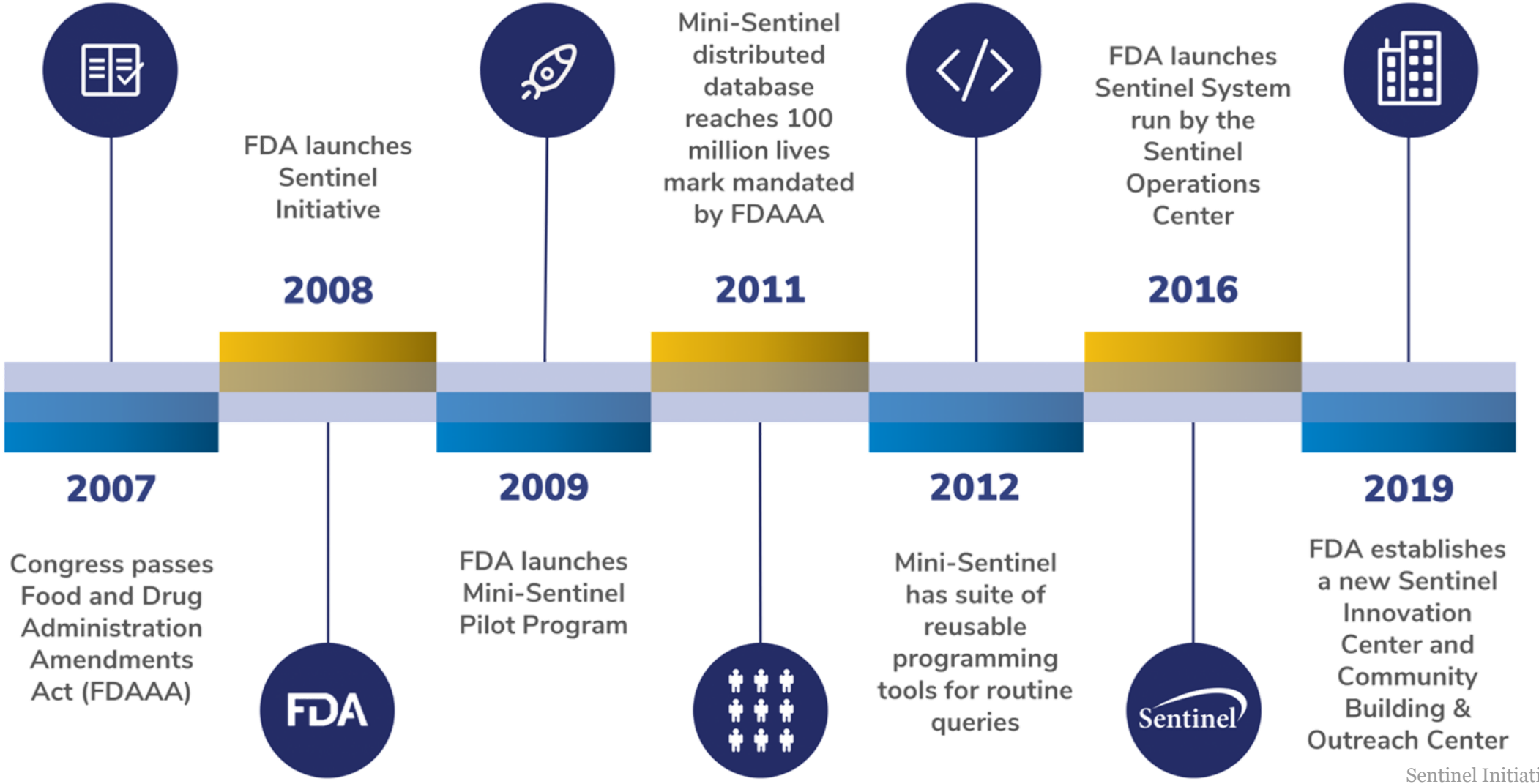
What is Sentinel?

- FDA's medical product **active safety surveillance system**
  - To assess the use, safety, and effectiveness of regulated medical products
  - To develop data, informatics, and methodologic capabilities to support these activities
- Key components:
  - Distributed data network of Data Partners
  - Electronic healthcare data
  - Common data model
  - Sophisticated quality assurance process

Timeline


2007
Congress passes Food and Drug Administration Amendments Act (FDAAA)
2008
FDA launches Sentinel Initiative
FDA
2009
FDA launches Mini-Sentinel Pilot Program

Timeline


2007
Congress passes Food and Drug Administration Amendments Act (FDAA)
2008
FDA launches Sentinel Initiative
FDA
2009
FDA launches Mini-Sentinel Pilot Program
2011
Mini-Sentinel distributed database reaches 100 million lives mark mandated by FDAAA
2012
Mini-Sentinel has suite of reusable programming tools for routine queries
2016
FDA launches Sentinel System run by the Sentinel Operations Center
Sentinel
2019
FDA establishes a new Sentinel Innovation Center and Community Building & Outreach Center

Sentinel Ecosystem

Lead

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

Data & Scientific Partners

HealthCore

HUMANA

Anthem

health care systems research network

VANDERBILT SCHOOL OF MEDICINE

DukeMedicine

OPTUM

HCA

Hospital Corporation of America

KAISER PERMANENTE

aetna

Scientific Partners

IQVIA

UAB

Penn Medicine

DEPARTMENT OF MEDICINE
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

RUTGERS

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

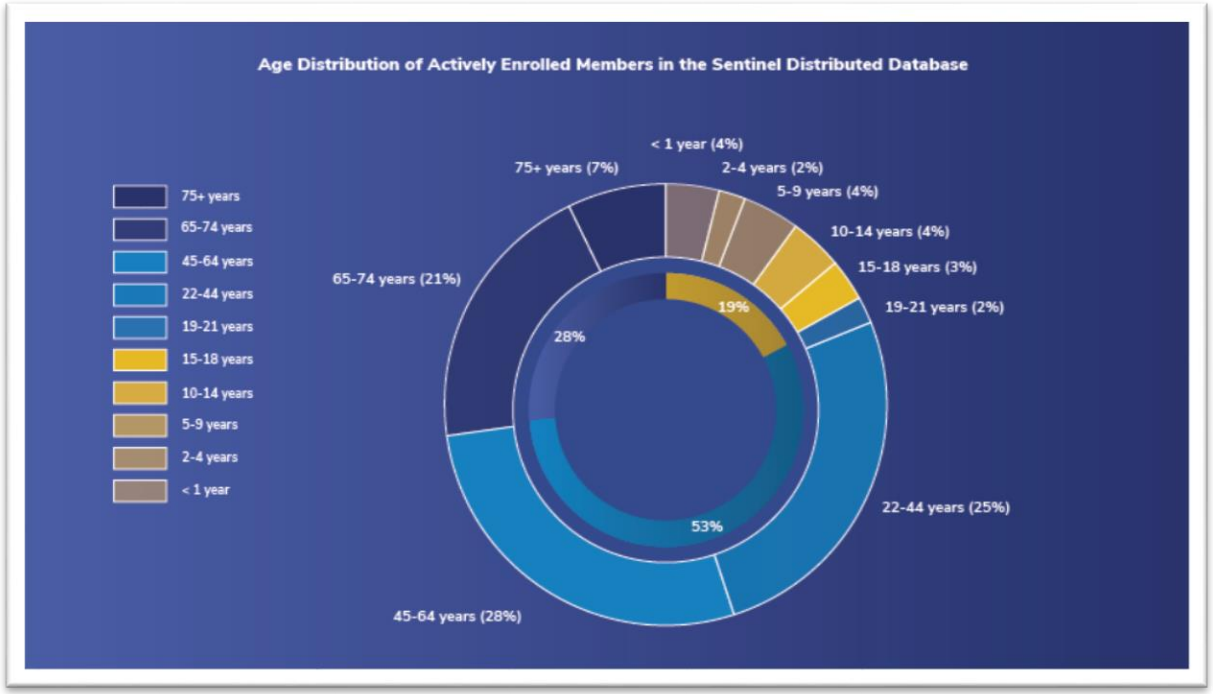
UF College of Pharmacy UNIVERSITY of FLORIDA

AHIP

THE UNIVERSITY OF IOWA College of Public Health

UIC

Sentinel Distributed Database



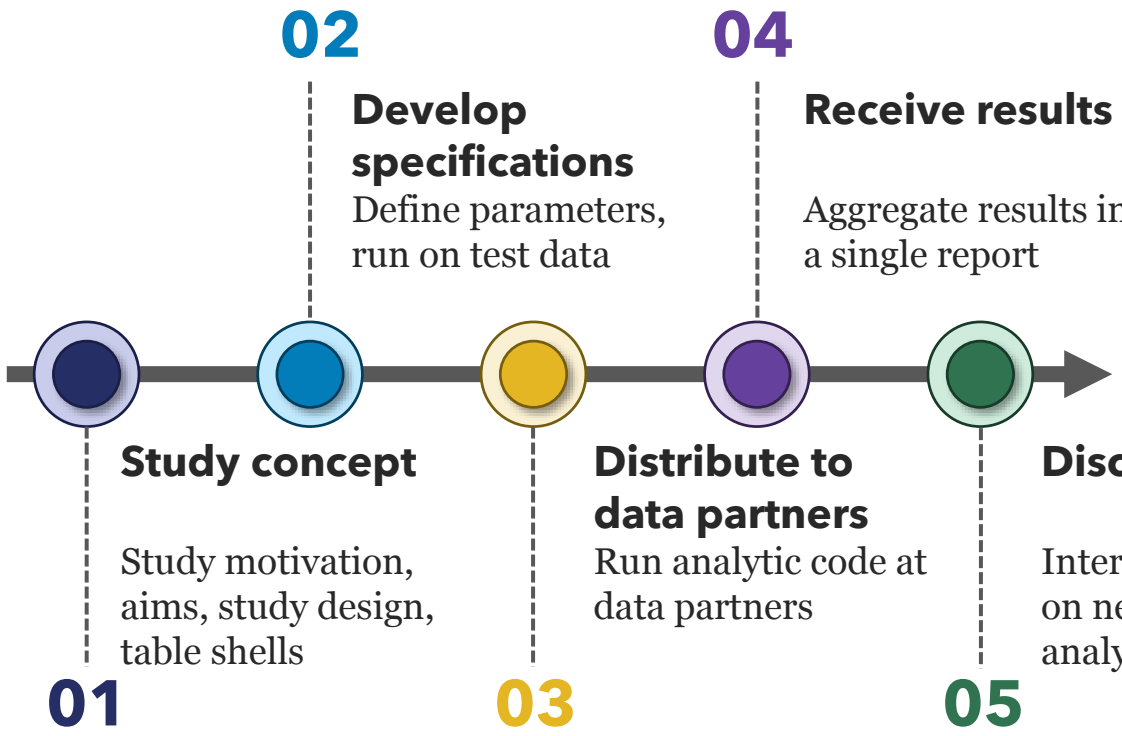
- >70 million patients actively accruing new data
- Privacy preserving distributed system where data partners retain full operational control of their data
- Data lag of 6-9 months from the date of health care
- Data refreshed quarterly and quality checked to be “analysis ready”

Active Risk Identification and Analysis

- Sentinel's routine query/analysis framework

- How is ARIA used?
  - **Pre-market**: ARIA sufficiency assessed during PMR process
  - **Post-market**: Newly Identified Safety Signals (NISS), real-world use questions, evaluate medication errors, generic drug equivalence, evaluate REMs, etc.

Developing a Sentinel Study



02 Most labor-intensive; requires code list review and fitting tools to study question

03 Analytic package contains all SAS code and parameters; posted online

05 All results are posted online, with any data partner-specific results masked

Surveillance in Public Health Emergencies

What happens in an emergency?

- Traditional medical product lifecycle usually follows structured (and iterative) process
  - FDA reviews all available evidence to decide whether to approve, license, or clear a product

- During a public health threat, medical countermeasures (MCMs) are often made available earlier in the development stage

EUA: Emergency Use Authorization

Assessment in a Public Health Emergency

	Public Health Emergency	Traditional Research and Development
Intent	Respond and mitigate	Generalizable knowledge
Planning	Unplanned or unexpected	Planned or deliberate
Data collection	Uncontrolled or none	Well-controlled clinical trials
Environment	• Undefined number of individuals • Simultaneous administration and potential use of multiple products • Requires rapid decision-making	• Defined number of individuals • Stepwise progression and single product administration • Allows more time for decision-making
Oversight	• Little or no tracking or monitoring • Lack of or limited clinical provider interaction	• Strict oversight and monitoring • Principal investigator and clinical study staff interaction • Informed consent and institutional review board
Reporting	Limited reporting and information sharing	Clearly defined reporting requirements and information sharing

Table from Measer GT et al. *Am J Public Health*. 2018;108(Suppl 3):S224-S226. doi:10.2105/AJPH.2018.304526

First Effective Use of the EUA

- Peramivir granted EUA on 23 October 2009
- Lessons learned:
  - Drug delivered to >1,100 patients within 24 hours
    - Difficult to determine the number of patients actually treated (ranges from 1,185-1,490)
  - Unable to determine if any reported adverse events other than rash could be attributed to peramivir
  - Limited data on who was treated, their response, possible ADEs, little data collected in real-time

"A crisis is a terrible thing to waste."
--Paul Rohmer

Pavia AT. *Clinical Infectious Diseases*. 2012;55(1):16-18. doi:10.1093/cid/cis365

MCMs in Sentinel Pre-COVID-19

- In 2018, Sentinel System began work with FDA Office of Counterterrorism and Emerging Threats (OCET)

- Activity 1: assess and/or build capacity to monitor treatments and outcomes during a public health crisis without burdening the medical system
    - Used influenza as a use-case to test readiness and novel methods for active safety surveillance

https://www.sentinelinitiative.org/methods-data-tools/methods/assessing-sentinel-system-capability-collect-and-analyze-medical

Who Gets Treated for Influenza?

Table 1. Numbers and Characteristics of Those With an Influenza Diagnosis by Outpatient Influenza Antiviral Treatment Dispensing Timing

		Baseline Characteristics in the 183 Days Prior to and Through the Day of Influenza Diagnosis							Other Characteristics	
Outpatient Dispensing Timing Relative to Diagnosis Date	Diagnoses, No. (%)	Asthma, %	COPD, %	Diabetes, %	Obesity, %	Influenza Vaccine, %	Ambulatory Encounters, Mean (SD)	Any Filled Prescriptions, Mean (SD)	Influenza Testing, %[a]	Pneumococcal Vaccine, %[b]
July 1, 2014–June 30, 2015 (N=70,084,635 eligible members[c] with 1,090,333 total diagnoses[d])										
Same day dispensing (day 0)	527,725 (48.4)	9.1	4.6	11.8	6.3	35.1	7.4 (8.5)	12.3 (13.5)	71.2	24.7
Dispensed days 1–5	76,549 (7.0)	15.4	20.8	28.9	12.9	43.3	12 (14.5)	22.3 (21.2)	56.4	34.1
No dispensing within 5 d	486,059 (44.6)	11.7	13.2	19.3	9.3	33.5	9.5 (12.3)	15.4 (18.1)	46.9	25.8
July 1, 2015–June 30, 2016 (N=72,189,819 eligible members[c] with 578,548 total diagnoses[d])										
Same day dispensing (day 0)	250,087 (43.2)	8.8	3.6	9.7	7.6	21.8	6.9 (8.3)	10.8 (12.2)	69.4	24.8
Dispensed days 1–5	35,762 (6.2)	16.3	19.3	26.1	16.2	27.9	11.5 (14.5)	19.6 (19.7)	57.7	38.0
No dispensing within 5 d	292,699 (50.6)	11.1	11.6	17.8	10.9	24.4	9.1 (12.2)	13.9 (17)	46.1	28.8
July 1, 2016–June 30, 2017 (N=74,985,917 eligible members[c] with 1,005,240 total diagnoses[d])										
Same day dispensing (day 0)	483,346 (48.1)	8.9	4.4	11.4	9.3	28.6	7.3 (8.5)	11.8 (13.5)	75.3	29.8
Dispensed days 1–5	74,307 (7.4)	16.0	22.7	30.0	17.2	38.7	12.3 (14.5)	21.8 (21.2)	58.6	48.1
No dispensing within 5 d	447,587 (44.5)	10.8	12.1	18.2	12.5	29.5	9.2 (12.1)	14 (17.7)	54.2	34.6

Note. COPD, chronic obstructive pulmonary disease; SD, standard deviation.
[a]Influenza testing assessed in days −7 through +7 relative to influenza diagnosis date.
[b]Pneumococcal vaccination assessed in all available claims data history per individual.
[c]Eligible members are those individuals who met all cohort entry criteria on at least 1 day during the query period.
[d]Individuals can contribute more than one diagnosis. The totals do not include people who were censored within 5 days of diagnosis and did not have an end point in that window.

Cocoros NM, et al. *Infection Control & Hospital Epidemiology*. Published online undefined/ed:1-7. doi:10.1017/ice.2021.311

Can We Adjust for Confounding?

- Objective: determine **whether there is evidence of residual confounding** in the association between influenza antiviral(s) and influenza complications in observational studies
  - Compare study results to estimates derived from randomized controlled clinical trials, with the goal of replicating the known association shown in clinical trials
  - Conduct analyses using a negative control period & negative control endpoint to evaluate analysis model

https://www.sentinelinitiative.org/methods-data-tools/methods/examining-ability-conduct-influenza-antiviral-effectiveness-studies

Enter COVID-19!

- Several key Sentinel initiatives completed before the pandemic laid the groundwork for COVID-19 activities
  - Including expansion of inpatient EHR data from HCA Healthcare and TriNetX

- 3rd activity in the OCET work was a descriptive analysis similar to Activity 1, but set solely in the inpatient setting using electronic health record (EHR) data.
  - Assess baseline characteristics, treatment, and endpoints among patients hospitalized with ILI

- In March 2020, FDA requested that COVID-19 cohorts be added to the activity.

Describing Patients and Treatments

Proportion of COVID-19 hospitalizations with administration of select medications, by week, February 20, 2020-January 10, 2021, HCA Healthcare Sentinel System data

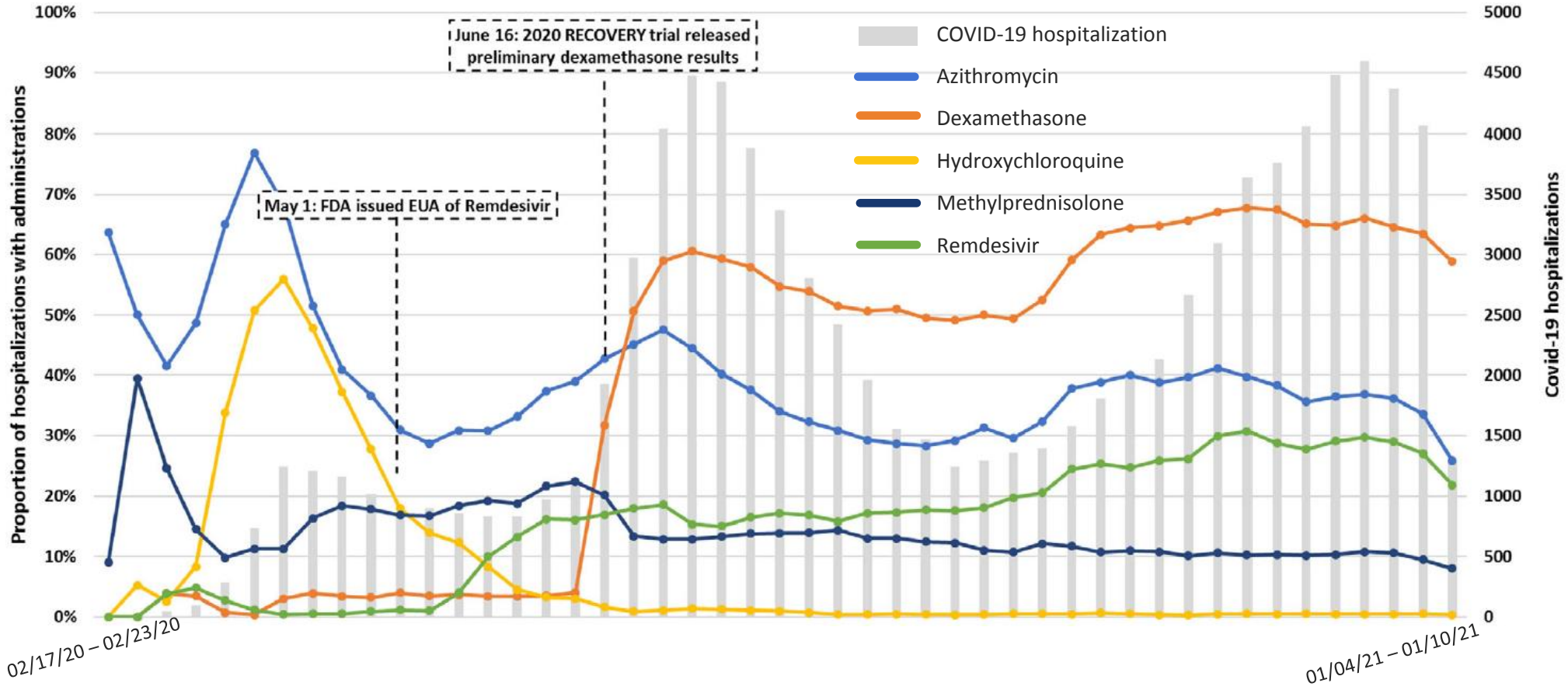
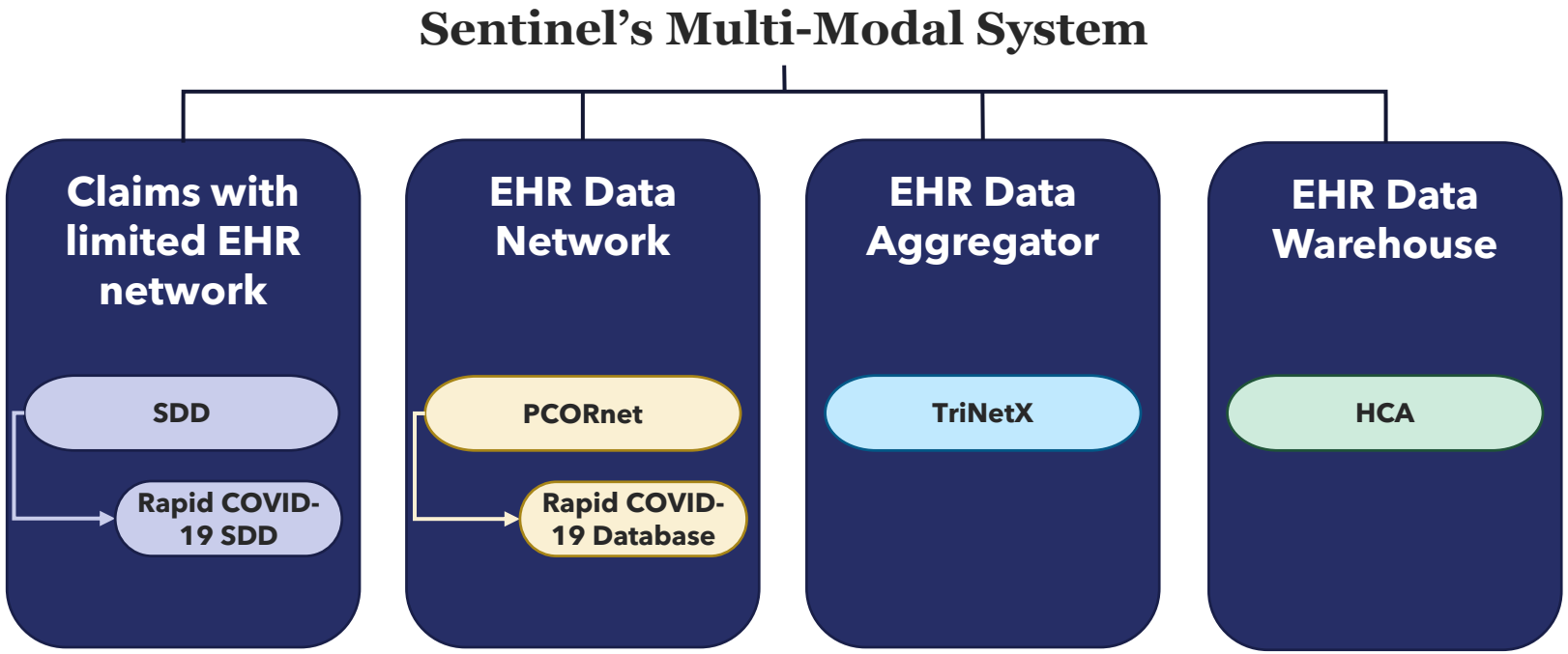


Figure from Cocoros NM et al. *Pharmacoepidemiology and Drug Safety*. 2021;n/a(n/a). doi: 10.1002/pds.5240

Expanding “Near Real-Time” Data Sources



SDD: Sentinel Distributed Database

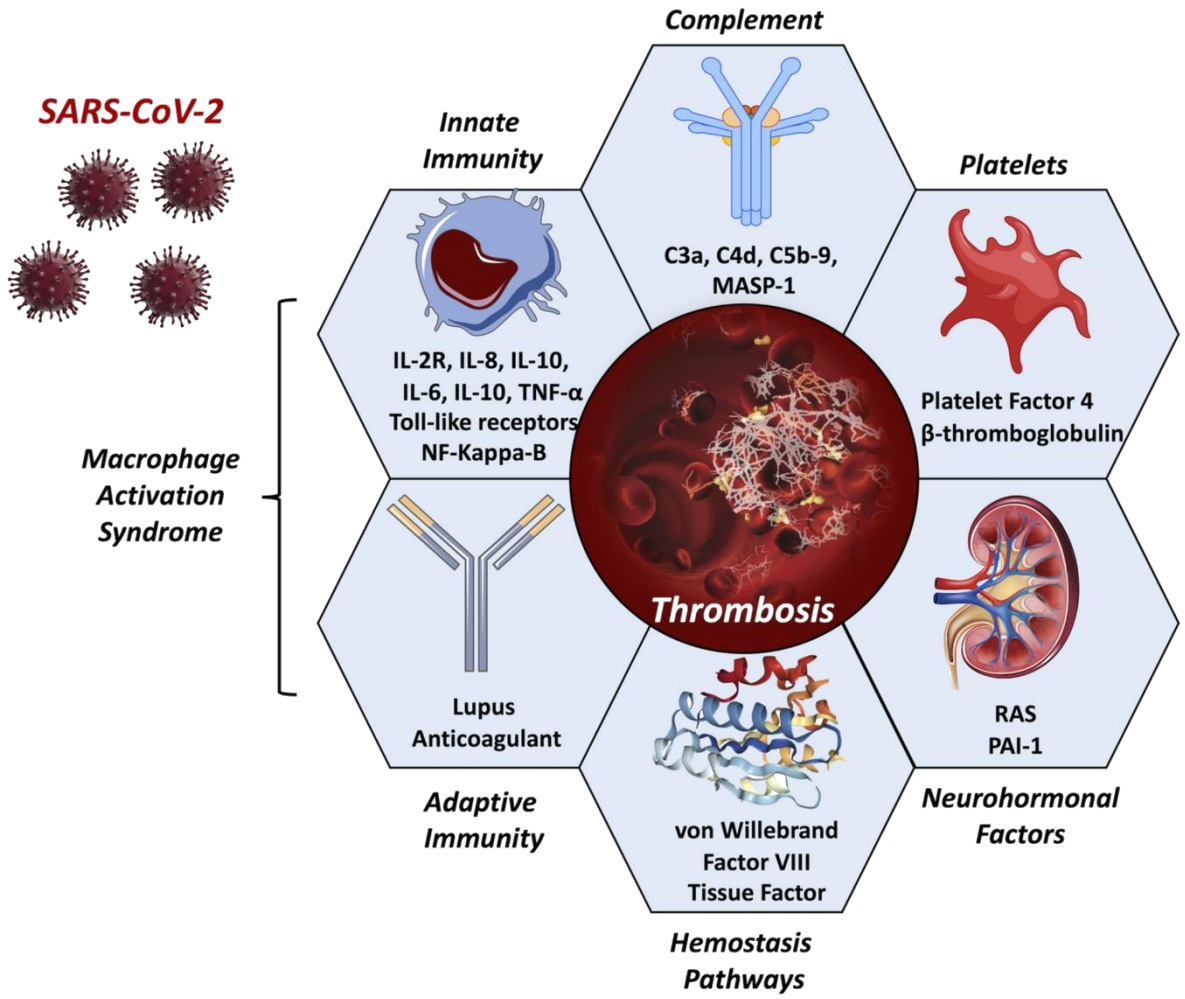
Thrombotic events in patients with outpatient COVID-19

Evaluation within the Sentinel System

Results posted publicly at: https://www.sentinelinitiative.org/assessments/drugs/individual-drug-queries/thrombotic-events-covid-19-patients-not-requiring

COVID-19 Associated Coagulopathy

- Likely multi-factorial and potentially distinct from other commonly-seen consequences of critical illness, including DIC
- Linked with poor clinical outcomes



DIC: disseminated intravascular coagulation; Figure from American Journal of Hematology, DOI: (10.1002/ajh.25982)

Open Questions

Clinical Research

- Do outpatients with COVID-19 have higher rates of thrombotic events than similar patients without COVID-19?
- Should outpatients with COVID-19 be monitored for pro-thrombotic laboratory values?
- Should outpatients with COVID-19 be treated with therapeutic dose anticoagulation?

Public Health Surveillance

- What are the rates of thrombotic events among outpatients with COVID-19?
- Are outpatients with COVID-19 being monitored for pro-thrombotic laboratory values?
- Are outpatients with COVID-19 being treated with therapeutic dose anticoagulation?

Studying Coagulopathy in Sentinel

- Sentinel developed a protocol to estimate the incidence of arterial and venous thrombotic events among patients with COVID-19 and compare risk of these events to patients with seasonal influenza using propensity score-based adjustment
  - Will also identify risk factors, particularly patient characteristics that promote stasis of circulation (e.g., obesity, atrial fibrillation), endothelial injury (e.g., diabetes, hypertension), and hypercoagulability (e.g., cancer, history of prior venous thromboembolism)

https://www.sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19

Ongoing Clinical Trial

- NIH-funded RCT investigating whether **anticoagulation** reduces life-threatening cardiovascular or pulmonary complications in newly diagnosed COVID-19 patients who do not require hospital admission
  - ACTIV-4: *"A Multicenter Adaptive Randomized Double-Blind Placebo Controlled Platform Trial of the Efficacy and Safety of Antithrombotic Strategies in COVID-19 Adults not Requiring Hospitalization at Time of Diagnosis"*

https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4

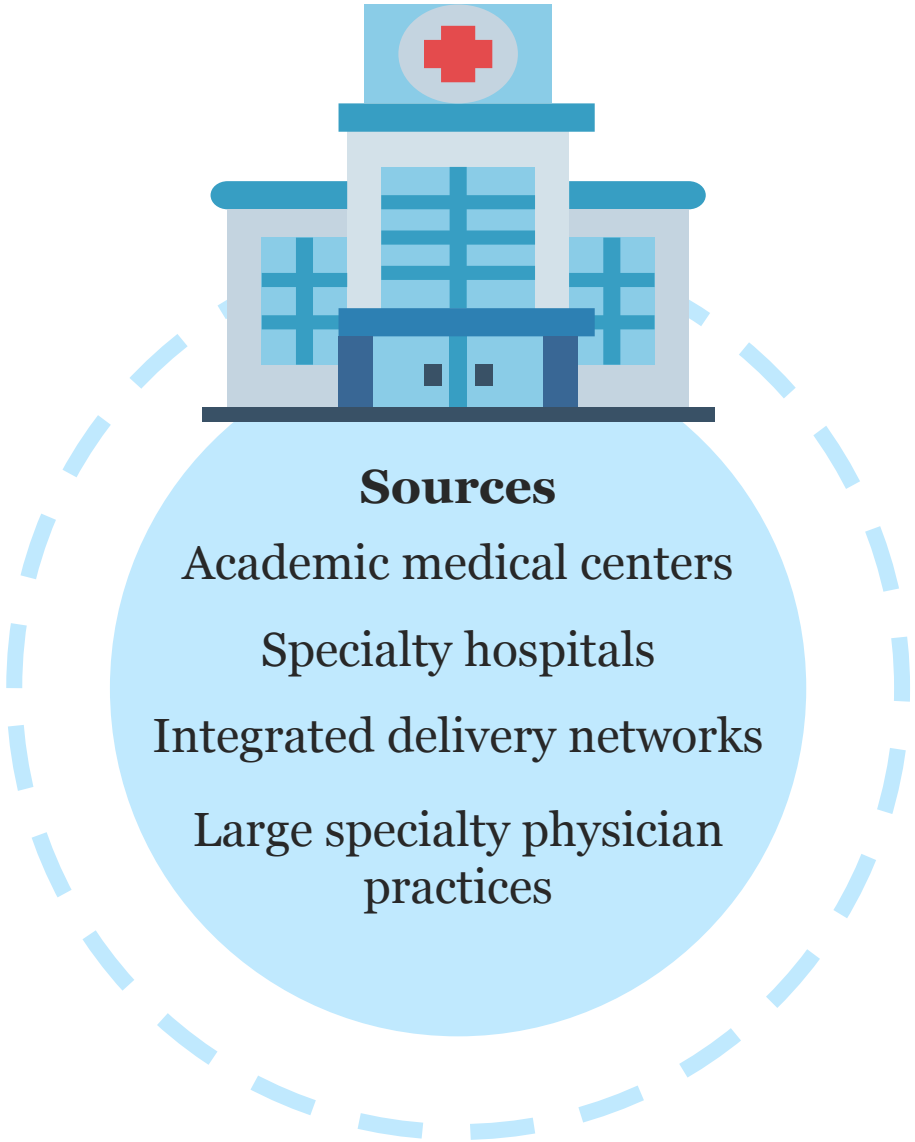
Outpatients with COVID-19 in Sentinel

- We describe **baseline characteristics** of outpatients with COVID-19 and further describe **occurrence of thrombotic events and death** among patients aged 40-79 years not hospitalized at the time of COVID-19 identification

- Simulate enrollment into ACTIV-4b clinical trial to inform sample size calculations
  - Will present findings NIH Panel to aid recruitment efforts

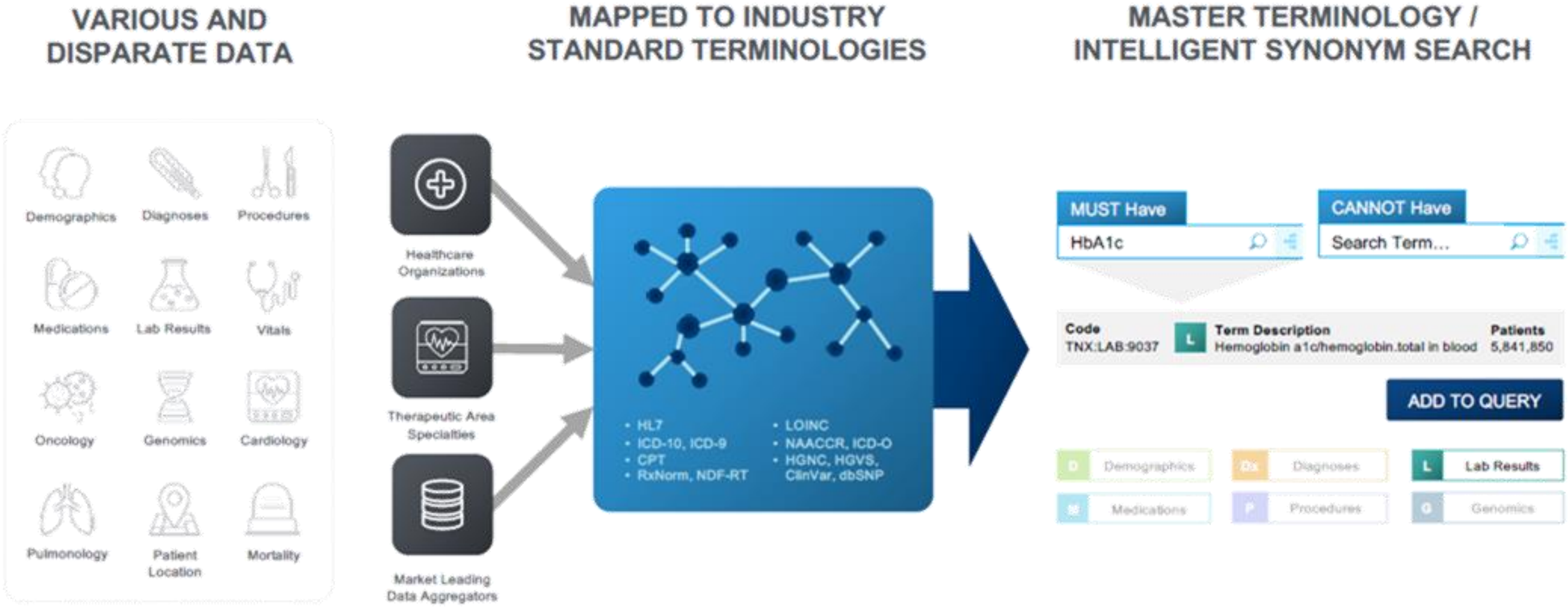
Data Source

- TriNetX is a "**global health research network**"
- USA Network includes electronic healthcare records (**EHR**) from 66 healthcare organizations (HCOs)
- Live® platform is a **cloud-based solution** allowing instant access to data and analytical tools



Current as of February 2021

Data Intake and Harmonization



Special Considerations

- Refresh schedule
  - TriNetX allows **HCOs to determine timing of data upload**; no central resource for users to reference
  - Query results may vary substantially if data updated between runs

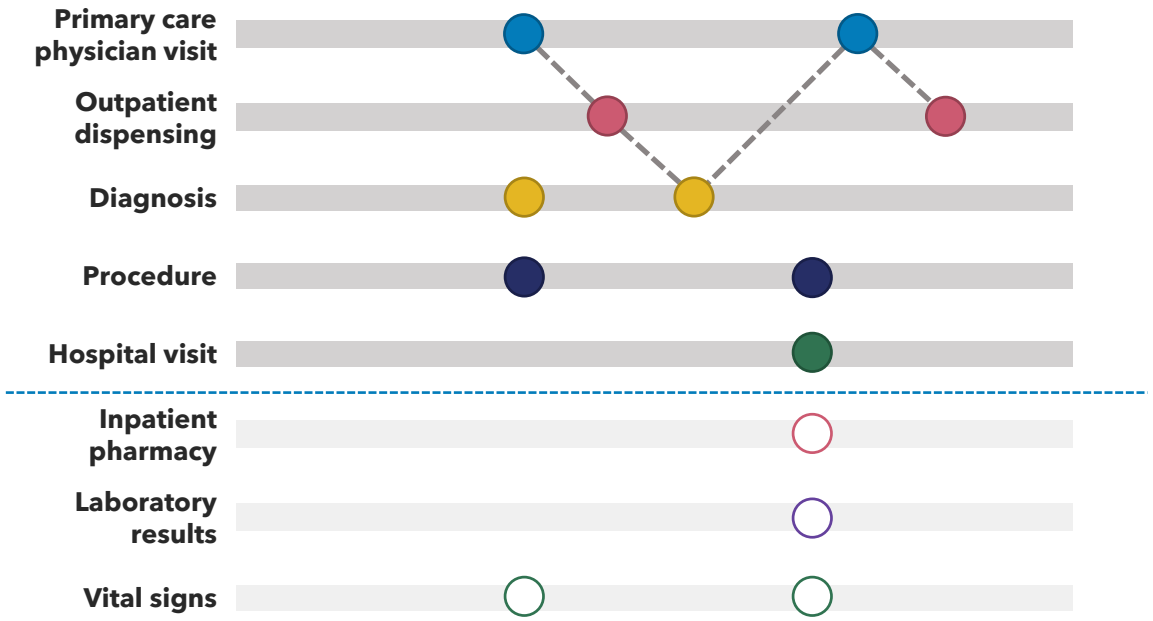
- Relationship with HCOs
  - Sentinel does not have access to HCOs
  - Some data characterization and quality questions cannot be answered

Current as of March 2021; HCO: health care organization

Capturing Patient Experience

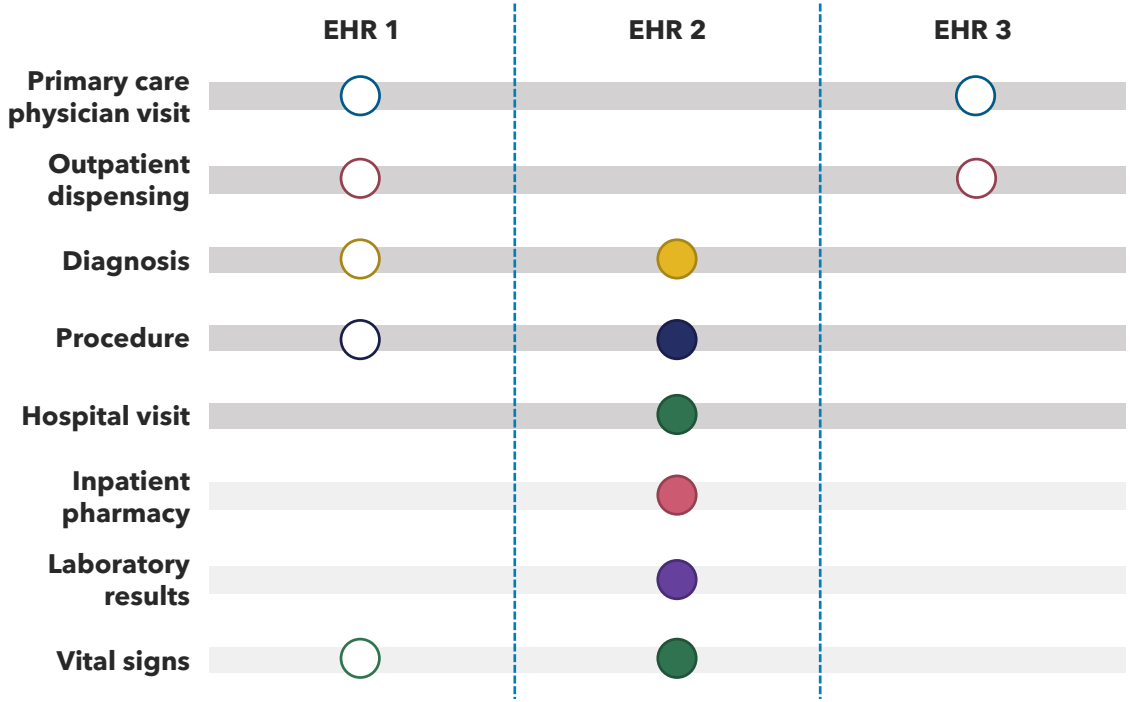
Claims Data

- Comprehensive data across all encounters & settings
- Misses some clinical detail



Electronic Healthcare Data

- Detailed data within a single encounter
- Misses other encounters



Filled circles indicate captured data; Open circles indicate missing data; Figures adapted from Sentinel Operations Center and FDA collaborations

Study Population: Inclusion

Criteria	ACTIV-4 outpatient trial	Presented analyses
Age	40-79 years	40-79 years
COVID-19 identification	Polymerase chain reaction (PCR)-positive symptomatic COVID infection	• COVID-19 ICD-10 diagnosis (B97.29, U07.1, B34.2, B97.2, J12.81) • COVID-19-positive lab: PCR or antigen
Hospitalization	No hospitalization at time of diagnosis	No hospitalization [-2, 0 days] from COVID-19 record
COVID-19 identification care setting	Diagnosed in emergency department or other appropriate outpatient urgent care setting with on-site physician and blood draw capability	Not factored into these analyses
Pregnancy	Not pregnant or lactating	No evidence of pregnancy [-84, 0 days]
Inflammatory labs	• D-dimer > than the upper limit of normal (ULN) • High-sensitivity C-reactive protein (hs-CRP) > 10mg/L	• Included patients regardless of laboratory values • Subgroup analysis restricted to individuals with d-dimer > ULN and hs-CRP or CRP > 10 mg/L

Study Population: Exclusion

Criteria	ACTIV-4 outpatient trial	Presented analyses
Anticoagulation	Indication for therapeutic anticoagulation or indication for single or dual antiplatelet therapy	Anticoagulant, antiplatelet or thrombolytic use [-183, -2 days] from COVID-19 record
Concomitant medications	Concomitant need for p-gp or CYP3A4 strong inducers/inhibitors	Record of p-gp or CYP3A4 strong inducers/inhibitors [0, 45 days] from COVID-19 record
Bleeding risk	Bronchiectasis/pulmonary cavitation, gastroduodenal ulcer, recent major surgery, recent ischemic stroke, recent intracranial hemorrhage	Bronchiectasis, ischemic stroke, intracranial hemorrhage [-30, 0 days] from COVID-19 record
Cancer	Active cancer	Evidence of cancer [-30, 0 days] from COVID-19 record
Platelets	Platelet count < 100,000 per microliter	N/A
Kidney function	Calculated creatine clearance < 30 ml/min	N/A

Study Outcomes

- Composite of **thrombotic events** (DVT, PE, MI, ischemic stroke), ascertained in the "hospital" and in "any setting," and **all-cause mortality** at 45 days
  - Defined using ICD-10 algorithms validated in previous Sentinel analyses

- Safety outcome: **Major bleeding** (including gastrointestinal bleeding, hemoptysis, hemarthrosis, and intracranial hemorrhage) at 75 days using a modified/simplified case-definition[1]

[1] Cunningham A et al. Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):560-6.; DVT: deep venous thrombosis; MI: myocardial infarction; PE: pulmonary embolism

Subgroup Analyses

- **CRP/hs-CRP**
  - Elevated (> 10 mg/L)
  - Normal (≤ 10 mg/L)
- **D-dimer[1]**
  - Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)
  - Normal (≤ 500ng/mL for FEU; ≤ 250ng/mL for DDU)
- **D-dimer & CRP/hs-CRP**
  - Elevated d-dimer (>500 ng/mL [FEU] or >250 ng/mL [DDU]) and elevated CRP/hs-CRP (>10mg/L)

[1] Bilaloglu S, et al. *JAMA*. 2020;324(8):799; DDU: d-dimer units; FEU: fibrinogen equivalent units

Study Design

Cohort Identification Criteria

COVID-19 Diagnosis (ICD-10 or PCR or antigen +ve test)

Exclusions

Exclusion 1: No hospitalization [-2,0]
Exclusion 2: Prior conditions (IH, bronchiectasis, IS, and cancer) [-30,0]
Exclusion 3: Pregnancy indicators [-84,0]
Exclusion 4: Anticoagulants/anti-platelet/thrombolytic agents [-183,-2]
Exclusion 5: inhibitors or inducers of p-gp and CYP3A4 [0,45]

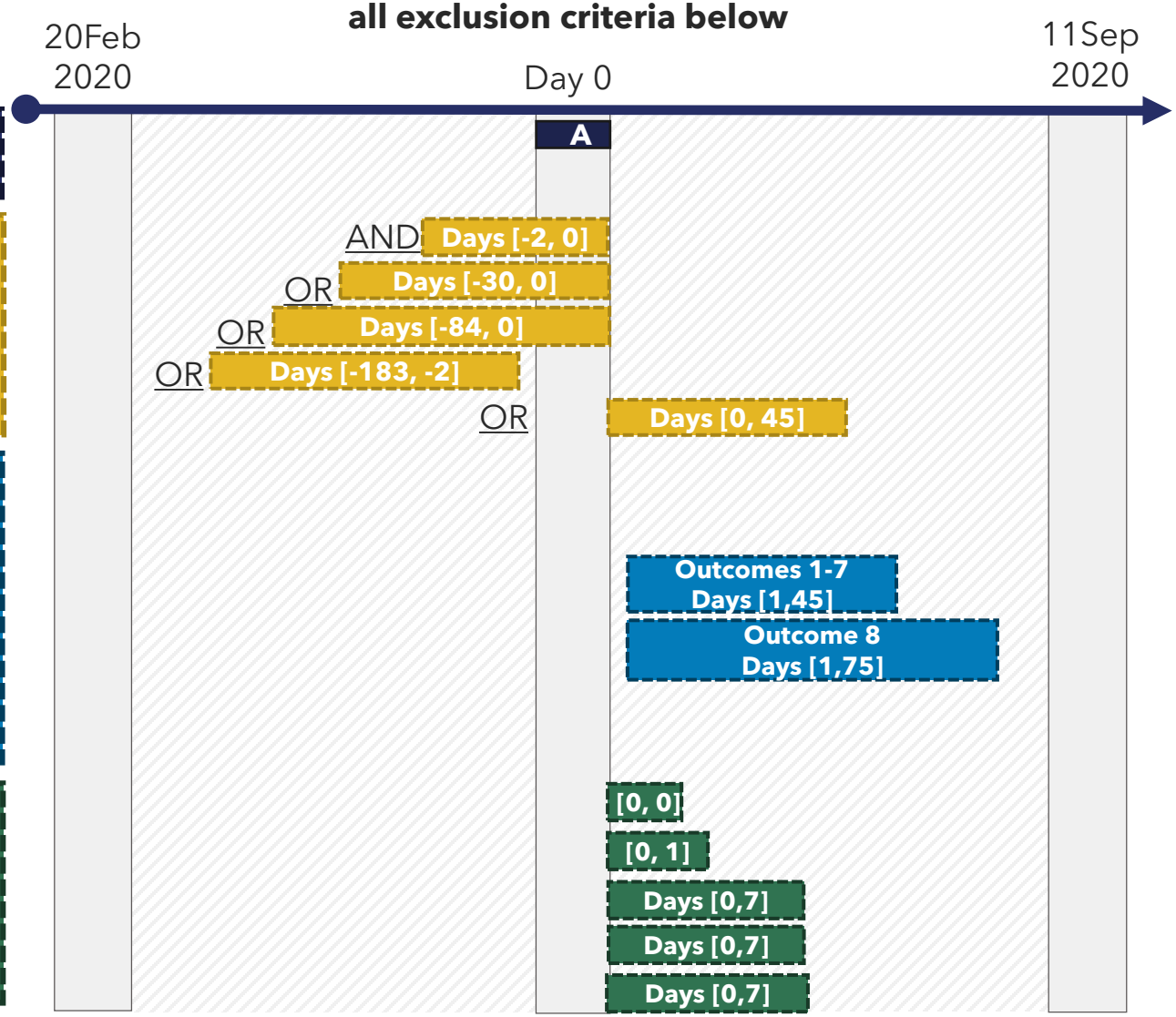
Outcomes

Outcome 1: Hospitalized [1,45] + DVT/PE [1,45]
Outcome 2: Hospitalized [1,45] + MI/IS [1,45]
Outcome 3: Hospitalized [1,45] + DVT/PE/MI/IS [1,45]
Outcome 4: Hospitalized [1,45] + Death [1,45]
Outcome 5: Death [1,45]
Outcome 6: Hospitalized [1,45] + DVT/PE/MI/IS/Death [1,45]
Outcome 7: DVT/PE/MI/IS/Death
Outcome 8: Hospitalized [1,75] + Major bleeding [1,75]

Cohort Characterization (CC) and Stratification (S)

CC1. Method of COVID diagnosis
CC2. S1. Treatment with anticoagulants/antiplatelets/thrombolytics
CC3. S2. D-dimer lab test: Missing, ≥ULN, <ILN
CC4. S3. CRP test: Missing, ≥10mg/L, <10mg/L
CC5. S4. D-dimer ≥ULN & CRP ≥10mg/L

Index Date
First COVID diagnosis/PCR +ve/antigen test and all exclusion criteria below



CRP: C-reactive protein; DVT: deep vein thrombosis; IH: intracerebral hemorrhage; IS: ischemic stroke; MI: myocardial infarction; PCR: polymerase chain reaction; PE: pulmonary embolism

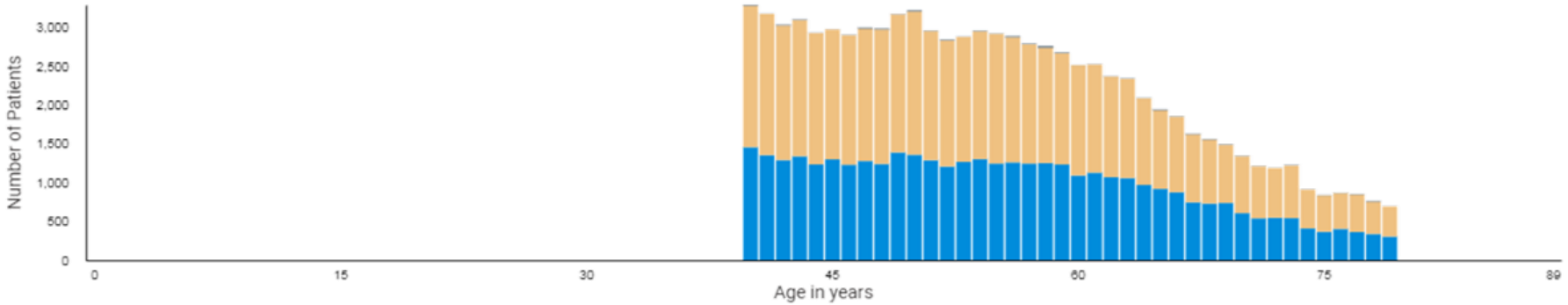
Attrition

	Patients		HCOs
Network	92,513,780		64
Base Population	262,900	(-100%)	61
Population 40 - 79 years, Any sex	135,240	(-49%)	60
Event 1A: Hospitalization [-2,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94308-4 Sars coronavirus 2 n gene [presence] in unspecified ···	106,910	(-20%)	60
Event 3A: Blood thinners [-183,-2] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ···	93,500	(-13%)	60
Event 2A: Comorbidities [-30,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94308-4 Sars coronavirus 2 n gene [presence] in unspecified ···	90,620	(-3%)	59
Event 4A: Enzyme inhibitors/enhancers [0... The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in ···	89,920	(-1%)	59
Event 5A: Pregnancy [-84,0] The terms in this event occurred between Feb 20, 2020 and Sep 11, 2020 **Must Have:** 94307-6 Sars coronavirus 2 n gene [presence] in unspecified ···	89,640	(0%)	59
	89,640 Patients		**59** HCOs

All values are rounded up to the highest 10 to protect patient privacy

Baseline Demographics

Base Cohort: Adults (aged 40-79) not hospitalized at the time of their COVID-19 diagnosis



Patients 90 and Older: 0

Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
89,640	40	79	55	10

Sex

Female	56%
Male	44%
Unknown	0%

Ethnicity

Not Hispanic or Latino	54%
Unknown Ethnicity	30%
Hispanic or Latino	16%

Race

White	52%
Black or African American	23%
Unknown Race	22%
Asian	3%
American Indian or Alask...	0%
Native Hawaiian or Other ...	0%

All values are rounded up to the highest 10 to protect patient privacy

Selected Baseline Characteristics

	Base Cohort (non-hospitalized COVID-19 at diagnosis)	
	n	%
Total Patients	**89,640**	
Method of COVID-19 Diagnosis (not mutually exclusive)		
PCR	43,290	48.3%
Antigen Test	90	0.1%
ICD-10 code	54,210	60.5%
Medications initiated on the same day or the day after index date [0, 1 days]¥		
Any blood thinner	3,310	3.7%
Anticoagulants*	2,780	3.1%
Heparin (excluding heparin flushes)	570	0.6%
LMWH (enoxaparin, dalteparin)	2,140	2.4%
Anti-platelets	1,270	1.4%
Thrombolytics	10	0.0%
Inflammatory/coagulation lab results on the same day or after index date [0, 7 days]		
CRP/hs-CRP		
Elevated (>10 mg/L)	3,120	3.5%
Normal (≤ 10 mg/L)	1,370	1.5%
Not measured	85,150	95.0%
D-dimer		
Elevated (> 500 ng/mL for FEU; > 250 ng/mL for DDU)	770	0.9%
Normal (≤ 500ng/mL for FEU; ≤ 250ng/mL for DDU)	2,420	2.7%
Unknown§	1,070	1.2%
Not measured	85,380	95.2%
D-dimer and CRP/hs-CRP elevated	590	0.7%

¥ Some of these medications may have been initiated in the inpatient setting and/or following a thrombotic event diagnosed within 1 days post-COVID diagnosis;
* Dabigatran, rivaroxaban, warfarin, desirudin, defibrotide, apixaban, argatroban, edoxaban, betrixaban, lepirudin, fondaparinux, heparin, bivalrudin, enoxaparin, dalteparin, tirofiban, and eptifibatide; § There is evidence that there was a lab obtained but no result provided

Outcomes

Total patients	N=89,640	
Outcomes	**n**	**%**
Hospitalized*	2,440	2.7%
Hospitalized DVT or PE	60	0.1%
Hospitalized MI or ischemic stroke	60	0.1%
Hospitalized and death (in-hospital death)	100	0.1%
All-cause death (any setting)	420	0.5%
Hospitalized DVT, PE, MI, or ischemic stroke*	110	0.1%
Hospitalized DVT, PE, MI, ischemic stroke or death*	520	0.6%
Hospitalized or non-hospitalized (any setting) DVT, PE, MI, ischemic stroke, or death*	890	1.0%
Hospitalized major bleeding*	130	0.1%

* Outcomes presented in subsequent slides
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by d-dimer

5.0% of patients with normal d-dimer and 7.8% of patients with elevated d-dimer had DVT, PE, MI, ischemic stroke, or death in any setting

	D-dimer					
	≤ ULN		> ULN		Unknown	
Total patients	n=2420	100.0%	n=770	100.0%	n=1070	100.0%
Outcomes						
Hospitalized	350	14.5%	120	15.6%	90	8.4%
Hospitalized DVT, PE, MI, or ischemic stroke	20	0.8%	10	1.3%	10	0.9%
Hospitalized DVT, PE, MI, ischemic stroke or death	90	3.7%	20	2.6%	90	8.4%
Any setting DVT, PE, MI, ischemic stroke, or death	120	5.0%	60	7.8%	90	8.4%
Hospitalized major bleeding	20	0.8%	10	1.3%	10	0.9%

D-dimer values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by CRP/hs-CRP

2.9% of patients with normal CRP and 6.7% with an elevated CRP had DVT, PE, MI, ischemic stroke, or death in any setting

	CRP/hs-CRP			
	≤ 10mg/L		> 10mg/L	
Total patients	n=1370	100.0%	n=3120	100.0%
Outcomes				
Hospitalized	190	13.9%	380	12.2%
Hospitalized DVT, PE, MI, or ischemic stroke	10	0.7%	10	0.3%
Hospitalized DVT, PE, MI, ischemic stroke or death	30	2.2%	140	4.5%
Any setting DVT, PE, MI, ischemic stroke, or death	40	2.9%	210	6.7%
Hospitalized major bleeding	10	0.7%	20	0.6%

CRP values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Outcomes stratified by d-dimer and CRP/hs-CRP

Trial inclusion criteria

6.8% of patients with an elevated D-dimer and CRP/hs-CRP had had DVT, PE, MI, ischemic stroke, or death in any setting

	D-dimer > ULN and CRP/hs-CRP > 10mg/L	
Total patients	n=590	100.0%
Outcomes		
Hospitalized	100	16.9%
Hospitalized DVT, PE, MI, or ischemic stroke	10	1.7%
Hospitalized DVT, PE, MI, ischemic stroke or death	20	3.4%
Any setting DVT, PE, MI, ischemic stroke, or death	40	6.8%
Hospitalized major bleeding	10	1.7%

CRP values resulted [0, 7] days from COVID-19 identification
All values are rounded up to the highest 10 to protect patient privacy

Conclusions, Part 1

- >95% of patients had **no data available** for D-dimer or CRP/hs-CRP
  - *Among those who had data,* ~70% had elevated CRP/hs-CRP
  - *Among those who had data,* ~18% had elevated d-dimer
  - *Among those who had data,* ~25% had a d-dimer value without units
  - We identified *~0.7% of COVID-19 patients with both elevated d-dimer and CRP/hs-CRP levels*
- Approximately **3.7%** of patients had record of an **anticoagulant, antiplatelet, or thrombolytic medication** on [0, 1 days] **after COVID-19** identification

CRP/hs-CRP > 10mg/L is elevated; d-dimer > 500 ng/mL FEU or > 250 ng/mL is elevated

Conclusions, Part 2

- Among COVID-19 patients with both elevated D-dimer and CRP/hs-CRP levels:
  - **3.4%** developed DVT, PE, MI, ischemic stroke or death in the **inpatient setting**
  - **6.8%** developed DVT, PE, MI, ischemic stroke or death in **any care setting**
- Comparable to the 4-12% estimation used to inform sample size calculations in the ACTIV-4 outpatient clinical trial
  - *The trial will include additional arterial thromboembolic events and non-thrombotic pulmonary events*
- Also similar to published estimates of ~3-5% for VTE and 2.8% in arterial thrombotic events in a non-ICU setting[1, 2]

[1] Goyal P at al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med*. 2020 Jun 11;382(24):2372-2374.; [2] Al-Samkari et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020 Jul 23;136(4):489-500.
Primary outcome: Composite endpoint of deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, & mortality ≤ 45 days post-COVID-19

Limitations, Part 1

- Unable to capture events occurring outside of the HCOs providing data → underestimation?
- Sample was relatively young and more female → affects counts and limits generalizability
- Tested asymptomatic patients may have been included in this analysis → underestimation?
- Arterial thromboembolic events (other than MI and stroke) and hospitalization for non-thrombotic pulmonary events (i.e. hypoxemia, hypoxemic respiratory failure, ARDS) were not evaluated in this analysis
- Date-stamps for data within a single healthcare encounter not visible in application, limiting the ability to assess temporality of events
- Confounding by indication?
    - Patients at higher risk for thrombotic events (esp. those with elevated D-dimer and/or CRP/hs-CRP) may have been treated with anticoagulant therapy shortly after COVID-diagnosis

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