Sentinel COVID-19 Portfolio

Near-Real Time Drug Monitoring

COVID MyStudies eConsent App

Diagnostics Utilization Discovery Project

Engaging the Community via RUF

COVID-19 Algorithm Validation

Interactive Querying on Therapies

Natural History Master Protocol

Coagulopathy Protocol Synopsis

Available Data Sources

- Claims-based sources
  - National and Regional Insurers
- Linked EHR-claims sources
  - Integrated Delivery System partners
- Patient-level EHR data
  - PCORnet, TriNetX, HCA Healthcare, IBM Explorys, Veradigm

https://www.sentinelinitiative.org/drugs/fda-sentinel-system-coronavirus-covid-19-activities

Risk of Thromboembolic Events with COVID-19: A Sentinel System Investigation – Update on Methods

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Sentinel Coagulopathy Workgroup: Specific Aims

- **Aim 1**: Determine 90-day incidence of arterial and venous thromboembolic events (evaluated separately) with COVID-19 and its consequences.

  – <u>Hypothesis</u>: Events will occur within 90 days and may result in death.

Sentinel Coagulopathy Workgroup: Specific Aims

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- **Aim 2**: Evaluate patient characteristics present at COVID-19 diagnosis as risk factors for arterial and venous thromboembolic events (evaluated separately).

  - <u>Hypothesis</u>: Characteristics that promote endothelial injury, stasis of circulation, and hypercoagulability will be risk factors for thromboembolism.

Potential Risk Factors for Thromboembolic Events in COVID-19

Hypothesized Risk Factors at Covid-19 Diagnosis

Stasis
- Obesity
- Heart failure
- Polycythemia
- Older age
- Alcohol abuse
- History of atrial fibrillation

Endothelial Injury
- Diabetes
- Hypertension
- Vascular disease
- Current tobacco use

Hypercoagulability
- Cancer
- Pregnancy
- Medications
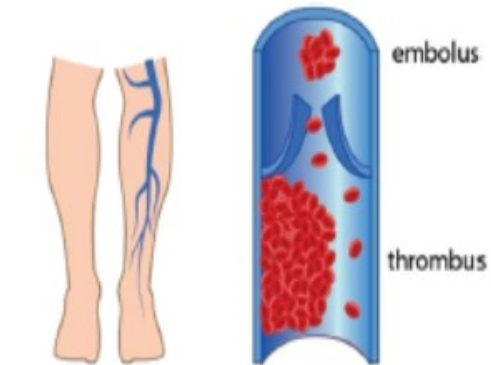- History of stroke or venous thromboembolism

SARS-CoV-2 Infection

Vascular Endothelial Injury

Inflammation

Platelet Aggregation

Arterial or Venous Thromboembolic Event (Evaluated Separately)

embolus

thrombus

Kovačič A. *Eur J Clin Pharmacol* 2019;75:751-67; Thachil J. *J Thromb Haemost* 2020;18:1023-6; Moores LK. *Chest* 2020. In Press.

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- **Aim 3**: Compare 90-day risk of arterial and venous thromboembolic events (evaluated separately) between health plan members with COVID-19 and those with influenza.

  - Hypothesis: Risk of thromboembolic events will be higher with COVID-19 than influenza.

Methods: Study Design / Data Source

- **Design**: Retrospective cohort studies (Aims 1-3)

- **Data Source**: **Sentinel System**
  - Priority Data Sources: Integrated health systems (EHR + claims)
    - Lab data available: COVID-19, influenza, coagulation labs
    - Can identify thromboembolic events via outpatient/hospital diagnoses
    - Can determine pre-existing comorbidities, medication exposures at diagnosis
    - Integrated systems minimize missed events
    - Will work with Data Partners to determine interest, lag times for data
  - Will consider added value of EHR-only and claims-only sources

Study Patients (Aims 1 and 2)

	Criteria
Inclusion Criteria	1) Positive COVID-19 diagnostic test between Jan. 20, 2020 (first lab-confirmed COVID-19 case in US) and 90 days before date of closure* 2) ≥180 days of continuous enrollment at time of diagnosis
Exclusion criteria	Initial COVID-19 test result pending or inconclusive at dataset creation
Selection	All eligible health plan members will be selected

* Date of closure to be determined by logistical considerations.

Study Patients (Aims 1 and 2)

Prior thromboembolism increases risk for subsequent event, so will <u>not</u> be exclusion criterion.

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Study Patients (Aim 3)

	COVID-19 Cohort	Influenza Cohort
Inclusion Criteria	1) COVID-19 lab test+ between Jan. 20, 2020 and 90 days before closure* 2) ≥180 days of continuous enrollment at time of diagnosis	1) Influenza lab test+ between Oct. 1, 2018 and Apr. 30, 2019 2) ≥180 days of continuous enrollment at time of diagnosis
Exclusion criteria	1) Initial COVID-19 test result pending or inconclusive at dataset creation 2) Coinfection with other respiratory virus	1) Initial influenza result pending or inconclusive at dataset creation 2) Coinfection with other respiratory virus
Selection	All eligible members will be selected	All eligible members will be selected

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Study Patients (Aim 3)

Ensure that influenza patients will not have COVID-19

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Primary Outcomes (Aims 1-3): Thromboembolic Events

Primary

Arterial Thromboses

Acute MI, angina

Acute ischemic or embolic stroke, TIA

Peripheral arterial disease

Limb ischemia, amputation

ICD-10 Diagnoses

Primary

Venous Thromboses

Deep venous thrombosis

Pulmonary embolism

Venous thrombosis with device, implant, graft

Planned Data Elements (Aims 1-3)

Demographic	Clinical	Laboratory*	Medication/Transfusions†
Enrollment status	Hospitalization	Hemoglobin	Anticoagulants
Age	ICU admission, ventilation	Platelet count	Anti-platelet drugs
Sex	Diabetes	PT/INR/PTT	Oral contraceptives
Race	Hypertension	D-dimer	Estrogen replacement
Body mass index	Vascular disease	Fibrinogen	Testosterone replacement
Location of care	COPD / asthma	Ferritin	Furosemide
Tobacco use	Liver disease	CRP / ESR	Morphine
Alcohol use	Chronic kidney disease	Procalcitonin	Thrombolytic agents
	Malignancy	Factor V Leiden	Blood transfusion
	Prior thromboembolism	Factor VIII	Immunoglobulin transfusion
	Severity of illness at diagnosis	Antiphospholipid Ab	
	Thrombophilia history	ABO blood type	

* On or within +/- 7 days around index date; if multiple results available, will collect closest to index date
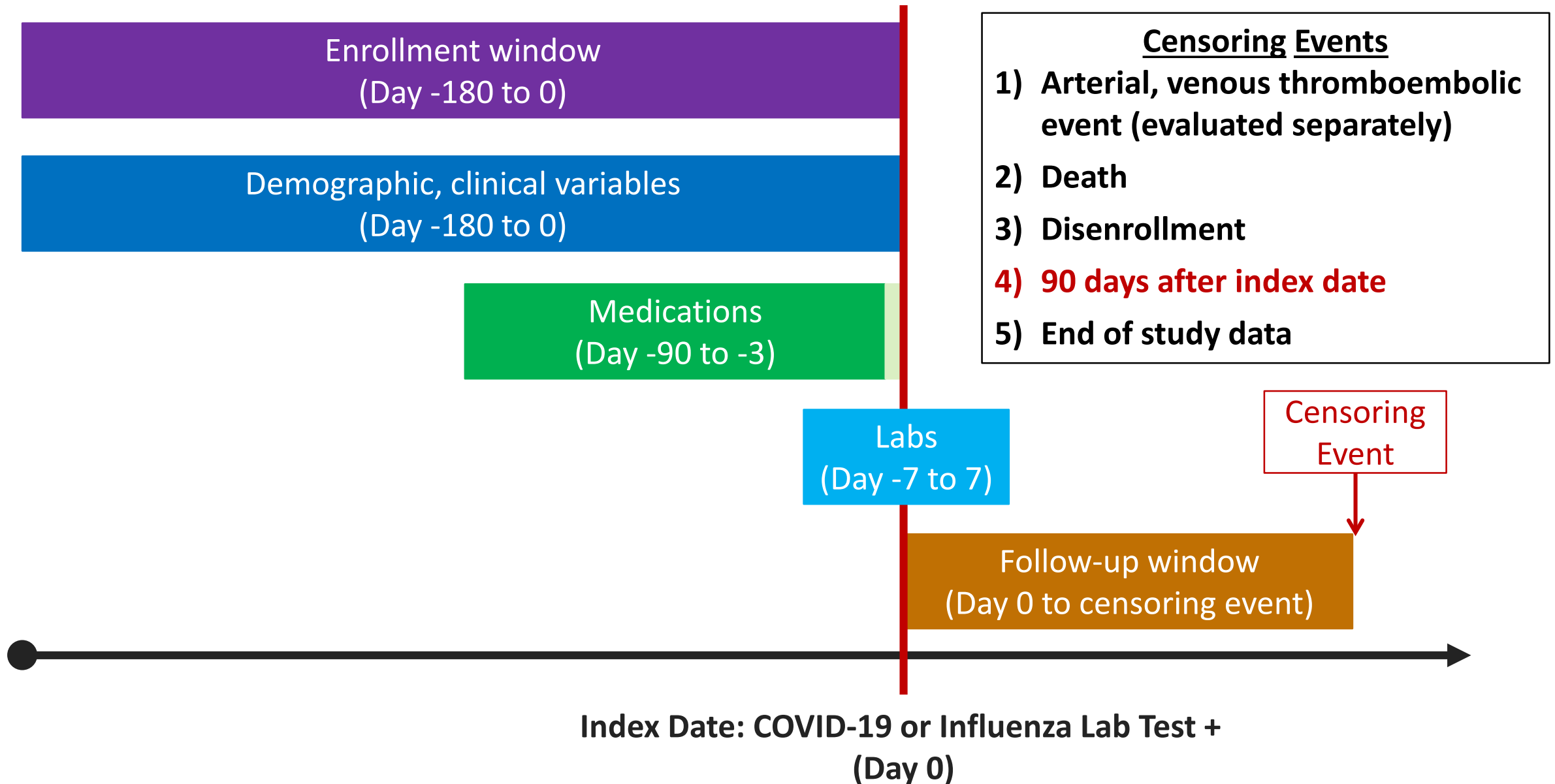† **Based on outpatient medication fills between 90 and 3 days prior to index date**

Definitions of Risk Factors for Thromboembolic Events (Aim 2)

Category	Risk Factor	Definition
Stasis of Circulation	Obesity	Body mass index >30 kg/m^2
	Heart failure	ICD-10-CM diagnosis codes
	Polycythemia	Hemoglobin >16 gm/dL
	Older age	Will explore different age thresholds
	Alcohol abuse	ICD-10-CM diagnosis codes
Endothelial Injury	Diabetes	ICD-10-CM diagnosis codes or registry
	Hypertension	ICD-10-CM diagnosis codes
	Vascular disease	ICD-10-CM diagnosis codes
	Current tobacco use	Health factors data
Hypercoagulability	Cancer	ICD-10-CM diagnosis codes
	Pregnancy	ICD-10-CM diagnosis codes

Data Analysis: Health Plan Member Follow-up for Aims 1-3

**Enrollment window
(Day -180 to 0)**

**Demographic, clinical variables
(Day -180 to 0)**

**Medications
(Day -90 to -3)**

**Labs
(Day -7 to 7)**

**Follow-up window
(Day 0 to censoring event)**

Censoring Events
1) **Arterial, venous thromboembolic event (evaluated separately)**
2) **Death**
3) **Disenrollment**
4) **90 days after index date**
5) **End of study data**

Censoring Event

**Index Date: COVID-19 or Influenza Lab Test +
(Day 0)**

Data Analysis: Aims 1-3

Aim	Planned Statistical Analyses
Aim 1	Characteristics of COVID-19 cohort

	Calculate incidence rates (events/1000 persons-years) of thromboembolic events:
	   Overall, by arterial and venous events
	   Stratify by age, sex, race, setting of diagnosis (ambulatory, hospital, nursing home)
	   Stratify by disease severity at diagnosis, prior thromboembolism history
	   Stratify by baseline anticoagulant use, anti-platelet use

	Calculate incidence rate of death within 90 days of thromboembolism event
Aim 2	Poisson regression: adjusted RRs (95% CIs) of events for risk factors
Aim 3	Compare characteristics between COVID-19 and influenza cohorts
	Poisson regression: adjusted RRs (95% CIs) of events in persons with COVID-19 vs. influenza
	Stratify by disease severity, setting of diagnosis, prior thromboembolism history

Approaches to Address Potential Study Limitations

Limitation	Reasons Limitation May Occur	Methods to Address
Selection Bias	Variations in COVID-19 testing by: • Geography • Calendar time • Disease severity	Sensitivity analyses: • Condition on geography • Restrict to time when testing more available • Stratify on severity, setting at diagnosis (e.g., hospital)
Misclassification	Lack of validation of ICD-10 diagnoses for thromboembolic events	Sensitivity analyses: • Evaluate validated events
Uncontrolled Confounding	Incomplete data on race, tobacco, alcohol in some data sources	Sensitivity analyses: • Assess effects of unmeasured confounders on results

Acknowledgements