ARLG
Antibacterial Resistance Leadership Group

Pneumonia Direct Pilot
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Pneumonia Direct Pilot (PDP)

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SPONSOR:

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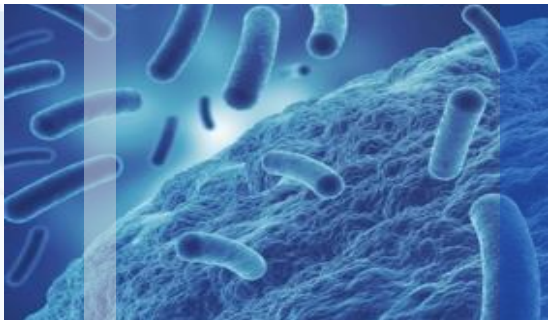


Pneumonia Direct Pilot Protocol Overview

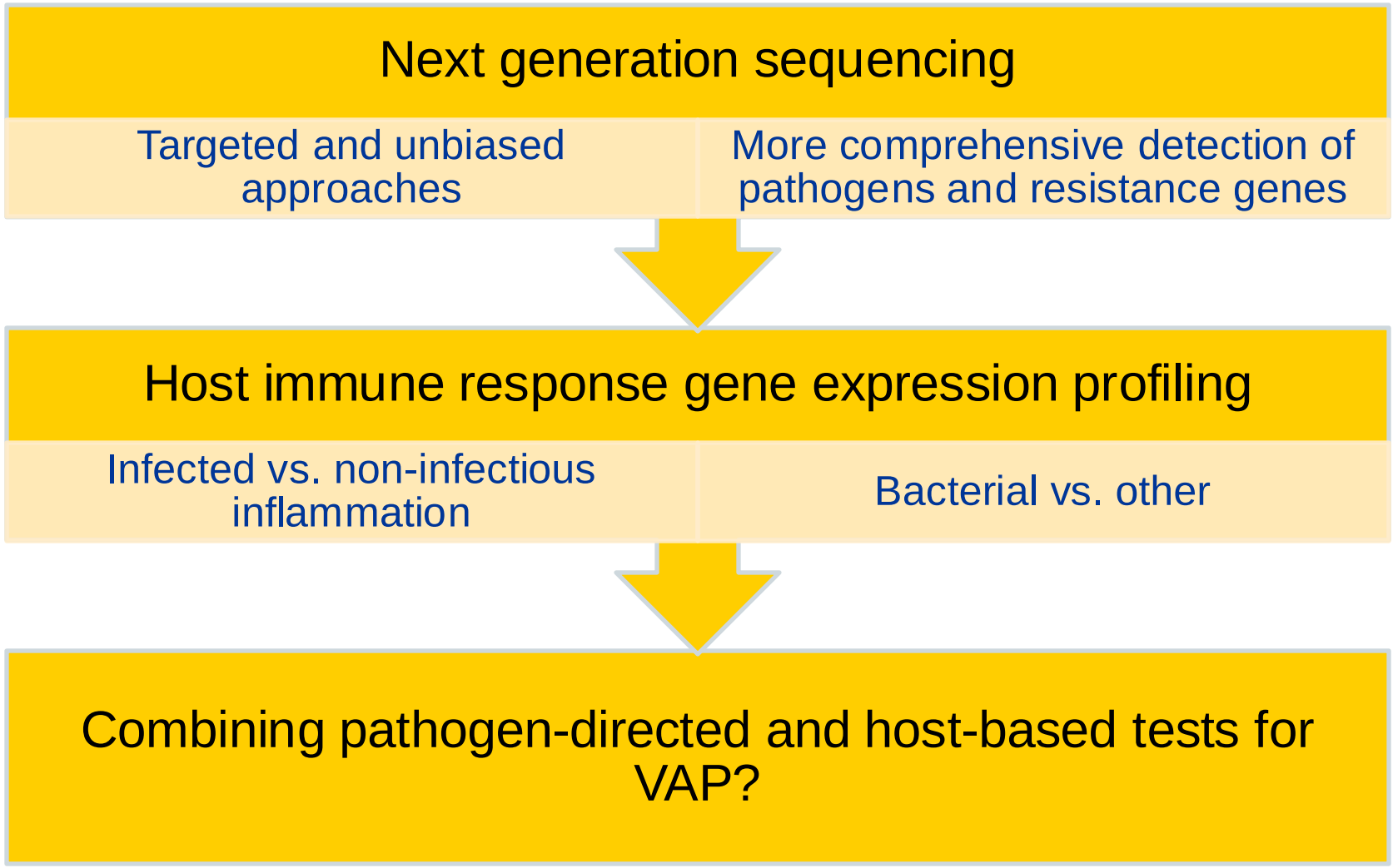
Study Description:	Prospective, observational, diagnostic, feasibility study to determine the accuracy of pathogen- and host-directed testing for the clinical diagnosis of ventilator-associated pneumonia (VAP)
Population:	Approximately **250 adult** patients admitted to the i**ntensive care unit and intubated** for at least 48 hours for reasons other than bacterial pneumonia
Number of Clinical Sites:	**15 sites** (within United States)
Duration of Participation:	Participants will be in the study for up to 15 days (14 days + 1 day of follow up). Study enrollment will occur over **approximately 12 months.**

Ventilator Associated Pneumonia

- Most common nosocomial infection in mechanically ventilated patients
  - 5-40 % of patients intubated for more than 2 days
  - Delayed treatment associated with poor outcome
  - Antimicrobial resistance (AMR) a growing concern
- Clinical signs and symptoms are non-specific
- Limitations of traditional culture-based diagnostics
  - Do not separate commensals from invasive pathogens
  - Median (IQR) time to ID 37.0 h (21.8 - 51.7 h) and AST 60.5 h (46.6 - 72.4 h)
  - Over diagnosis common

Crit Care Med. Oct 2005;33(10):2184-93; *Journal of critical care*. Mar 2008;23(1):91-100; *Infection Control & Hospital Epidemiology*. 2014;35(3):278-284; *J Clin Microbiol* 2020. 58(11):e01468-20

Novel diagnostic approaches



Index Tests

Index Test Method	Manufacturer	Test Name	Sample
Pathogen-directed			
Multiplex PCR	BioFire	FilmArray Pneumonia Panel (**FDA-cleared**)	ETS/BAL
NGS Target Enrichment	Illumina + IDbyDNA	Respiratory Pathogen ID/AMR Panel (**Commercial RUO**)	ETS/BAL
Metagenomic NGS	Illumina	Laboratory developed test (**LDT**)	ETS/BAL
Microbial DNA	Univ. of California San Francisco	mcf DNA (**LDT**)	Plasma
	T2 Biosystems	T2Bacteria Panel (**FDA-cleared**)	Whole blood
	T2 Biosystems	T2Resistance Panel (**Commercial RUO**)	Whole blood
Host-biomarker			
Procalcitonin	Architect BRAHMS (Abbott)	PCT (**FDA-cleared**)	Plasma
Host gene expression	Inflammatix	TriVerity (**Commercial RUO**)	Whole blood
	Univ. of California San Francisco	Metagenomic (**LDT**)	Plasma
	Univ. of California San Francisco	Metagenomic (**LDT**)	ETS

Study Objectives

Primary objective	Primary outcome measures
• Evaluate the accuracy of novel pathogen-directed and host-directed diagnostic tests (collectively referred to as index tests) when the reference standard is a clinical diagnosis of VAP in participants who experience a clinical change suggestive of new-onset pneumonia	• The results of each **index test** at the time of clinical change compared to **clinical diagnosis of VAP**
Secondary objective	**Secondary outcome measure**
• Evaluate the accuracy of index tests using clinical criteria and adjudicated microbiological criteria for the diagnosis of VAP in participants who experience a clinical change	• The **adjudicated diagnosis** of proven, probable, possible, or no **VAP** at the time of clinical change utilizing **clinical and microbiological information**

Exploratory Objectives

Exploratory endpoints	Exploratory outcome measures
• **Compare each index test's** results at baseline against its results at clinical change • Evaluate the **agreement** between individual index tests at baseline • Evaluate the **agreement** between individual index tests at clinical change • Evaluate the **predictive value** of index tests in combination for the diagnosis of VAP as defined by the clinically and microbiologically adjudicated reference standards	• The results of each index test at baseline in participants who have a clinical change
• Assess whether **semi-quantitation** of the pathogen-directed index tests improves predictive value versus the clinically and microbiologically **adjudicated** reference standards	• The semi-quantitation of the pathogen-directed index tests
• Compare the relative abundance and diversity of **organisms** detected by metagenomic next generation sequencing **(NGS)** at baseline and clinical change	• Organisms detected by metagenomic next generation sequencing at clinical change and baseline
• Evaluate the agreement between antimicrobial resistance markers of index tests and standard of care microbiology	• Antimicrobial resistance markers detected by index tests and standard of care microbiology

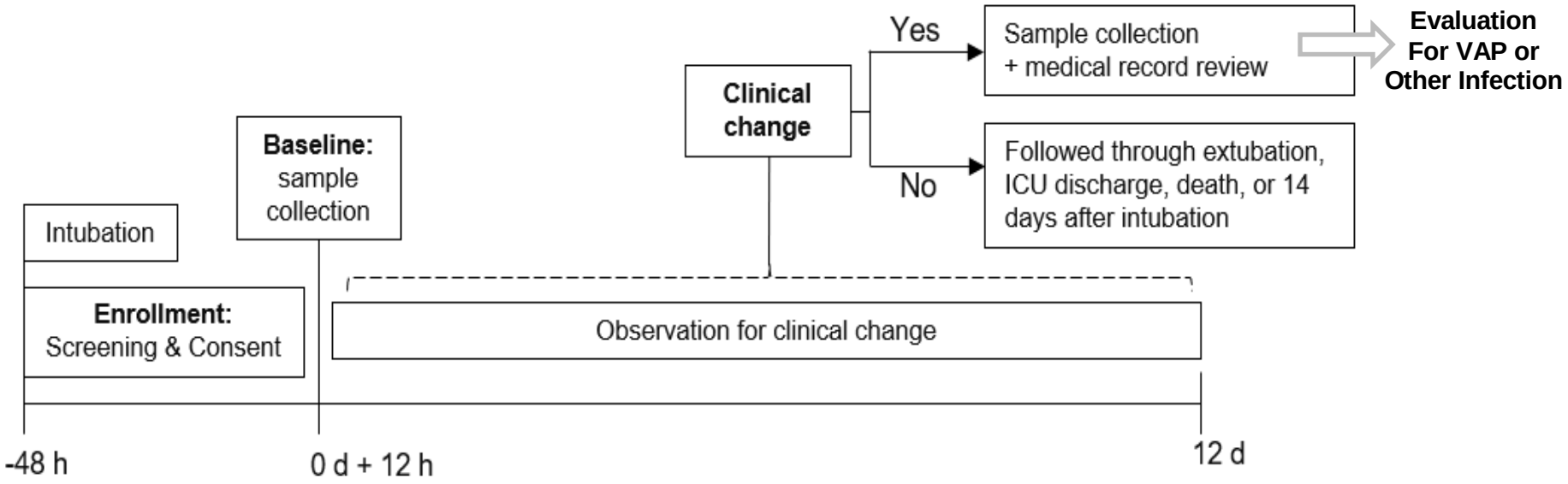
Inclusion Criteria

1. Are ≥18 years old
2. Are newly intubated for less than 48 hours and for reasons other than suspected bacterial pneumonia or microbiologically proven acute/active bacterial infection. The following antibiotic therapy is acceptable:
   - Prophylactic antibiotic for infection prevention,
   - Suppressive antibiotics for well-controlled chronic infection, as assessed by the provider, and
   - Empiric antibiotics for suspected infections other than pneumonia.
3. Are expected to require intubation for at least 48 hours, at the discretion of the treating clinician
4. Are able to provide protocol-accepted consent (legally authorized representative [LAR] is acceptable)
5. Are expected to live long enough to receive a VAP diagnosis, at the discretion of the treating clinician
6. Are able to provide study-required biological samples

Exclusion Criteria

1. Have a witnessed aspiration event prompting the need for current, new intubation
2. Have known active lung cancer or metastatic disease to a lung
3. Received a lung transplant
4. Have cystic fibrosis
5. Are receiving comfort care
6. Have a current or within-the-last-30-days diagnosis of active bacterial pneumonia
7. Were previously enrolled in this trial
8. Have a tracheostomy tube in place
9. Are currently participating in an interventional drug or device study

Schematic of Study Design

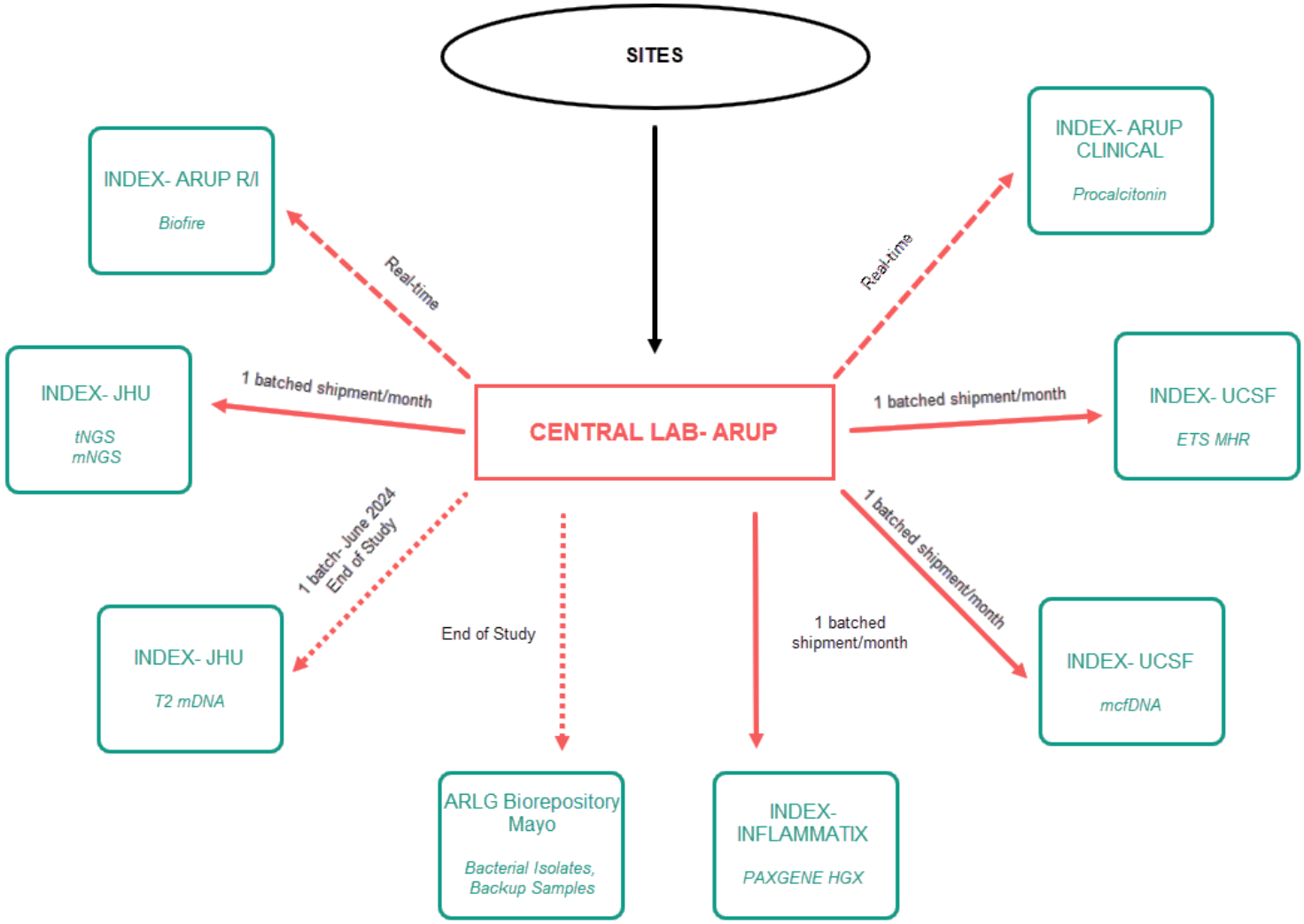


Clinical Change = **clinical suspicion of new-onset VAP** that prompts the collection of lower respiratory tract secretions for routine microbiologic testing and initiation, continuation, or modification of antibiotic therapy for a pneumonia indication.

Sample Collection

Time Point	Collected by	Supply*	mL	Method of Collection
Baseline *(48-60 hrs post-intubation)* **AND** **Clinical Change** *(0-12 hrs)*	***Blood***	*** If a peripheral stick is not an option, use of a venous line is acceptable*		
	Study Team	**(2) PaxGene** *Red stopper*	4ml	Central, peripheral line or stick (venous)
	Study Team	**(5) EDTA** *Purple top*	4ml	Peripheral stick **
	Endotracheal Suctioning (ETS) Samples		*† min-max volume per protocol: 3ml-20ml*	
	Study Team	**(1) Specimen trap** in suction line	30ml †	SOC procedure dedicated aliquot
Clinical Change *(only)*	***Bacterial Isolates (optional, highly desired)***		***‡4 tubes provided, contact CRA for more***	
	Clinical Micro Lab	**(4‡) Microbank** *Blue lid*	2ml	Respiratory/Blood SOC AST purity plate(s) *Grown nearest to Clin Change*
Baseline *(48-60hrs post intubation)* **Clinical Change** *(0-24 hrs)*	***BAL/mini-BAL (optional)***		*reclaimed sample from SOC procedure/testing*	
	Clinical Micro Lab	**(1) Conical Tube** *Blue lid*	≤30ml	Reclaimed sample from SOC procedure

Central → Index Lab Shipments



VAP – Clinical Case Definition (Primary Outcome)

After at least 48 hours of intubation the VAP case definition requires new findings in each category of signs/symptoms and imaging

SIGNS & SYMPTOMS

- At least 1 of the following signs of inflammation:
  - Fever ≥38C or ≤35C
  - Leukocytosis (≥12K) or ≤ (4K)
  - Greater than 15% immature neutrophils (bands) noted on peripheral blood film

AND

- At least 1 of the following:
  - increased respiratory secretions or increased suctioning requirement
  - Increased ventilator support requirements
    - A worsening (decrease >10%) of the PaO2/FiO2 ratio
    - Increase in the amount of positive end-expiratory pressure

PLUS

IMAGING

- New or progressive changes suggestive of bacterial pneumonia
  - infiltrate
  - consolidation
  - cavitation

FDA definition (2016 IDSA/ATS guidelines)

Adjudication Classification (Secondary Outcome)

Expert adjudication blinded to index test results

- Proven VAP
  - **Meets clinical** case **definition** with **criteria 1** microbiologic evidence **of bacterial lung infection**
- Probable VAP
  - **Meets clinical** case definitions with microbiologic **criteria 2 or 3** and no alternative diagnosis
- Possible VAP
  - **Meets clinical case definition**s, but **without compatible microbiology** and/or possible alternative diagnosis
- Not a nosocomial lung infection
  - Alternative diagnosis and/or not treated and improved

Adjudication – Microbiologic Criteria#

MICROBIOLOGY

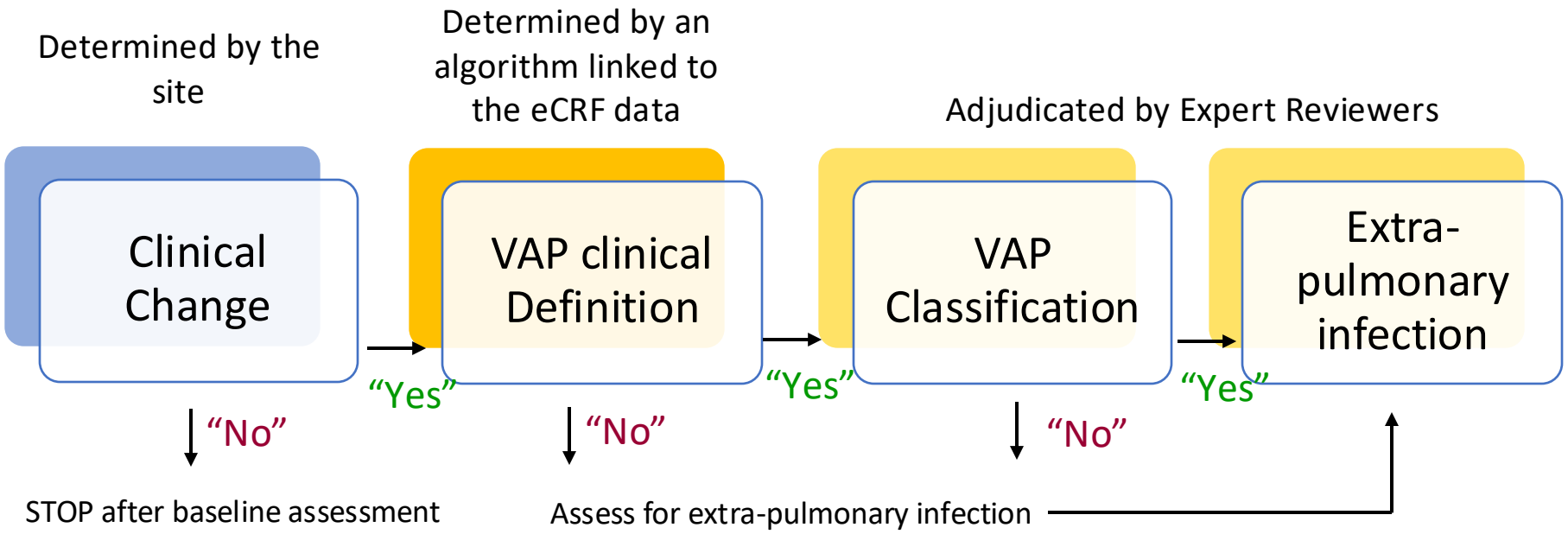
- *Criteria 1* - One of the following **positive tests**
  - Positive blood culture with a compatible organism* and no other source identified
  - Pleural fluid culture
  - Lung histopathology
  - Positive test for *Legionella*

- *Criteria 2* - **microbiologic thresholds** with a compatible microorganism* regardless of respiratory secretions:
  - ETS ≥ 10^5 CFU/mL or corresponding semi-quant value
  - BAL ≥ 10^4 CFU/mL or corresponding semi-quant value
  - Protected brush ≥ 10^3 CFU/mL or corresponding semi-quant value

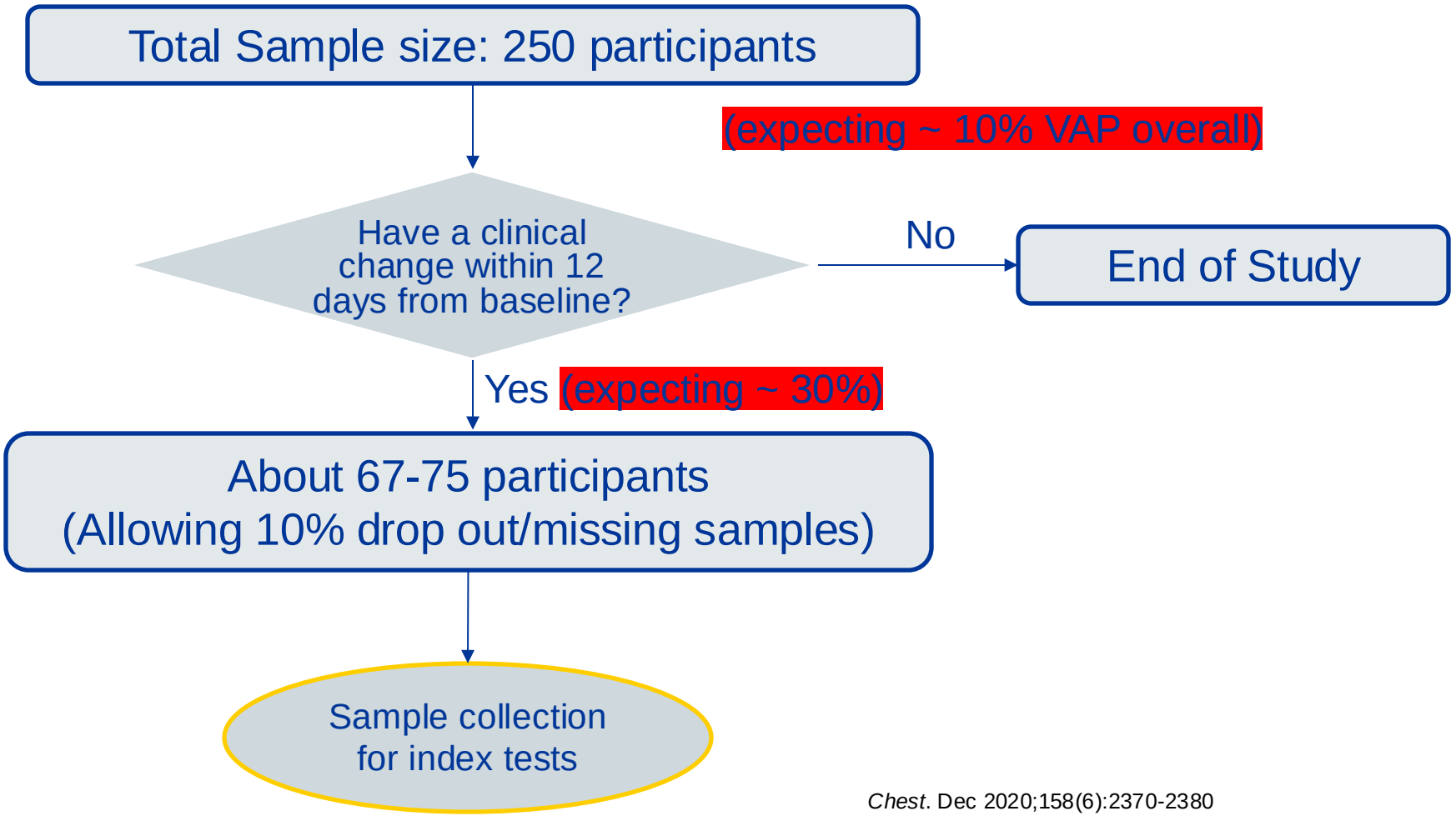
- *Criteria 3*- **increased secretions** with compatible organism* identified from any of the following:
  - ETS
  - BAL
  - Protected brush
  - Lung tissue

*Compatible microorganism assessment = putative pathogen associated with VAP. #Criteria derived from NHSN Ventilator-Associated Event Algorithm

Participant Evaluation Process



Statistical Analysis Plan Overview
Sample Size



Chest. Dec 2020;158(6):2370-2380

Analysis of Outcome Measures

Analysis of outcome measures:

- Positive percent agreement (PPA) and Negative percent agreement (NPA) with 95% score CIs.
- Positive predictive value (PPV) and Negative predictive value (NPV) as a function of true prevalence, with confidence bands.
- Intention-to-diagnose (ITD) scenarios

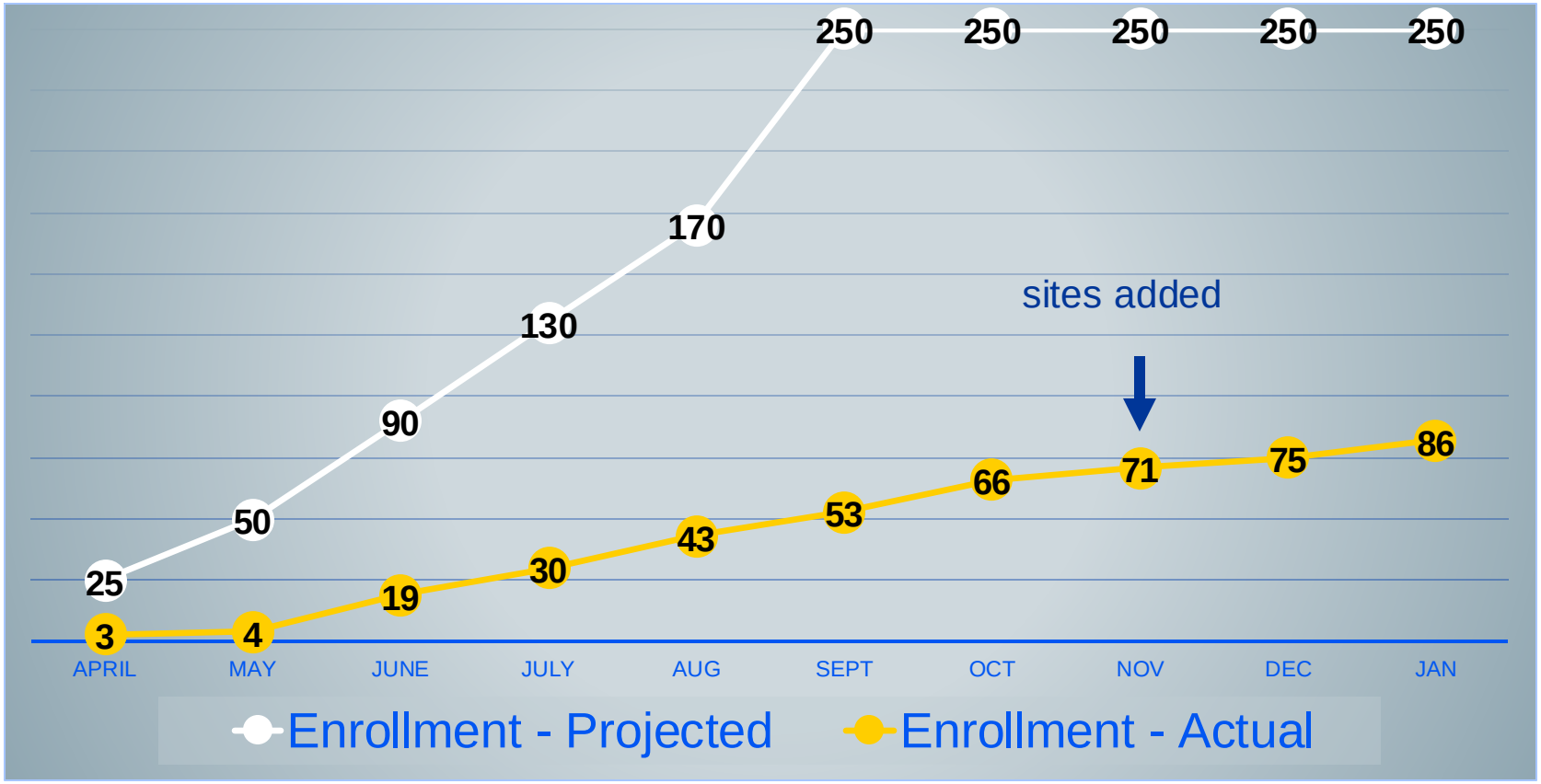
Separate analyses for each index test

- Analyses repeated the adjudicated VAP definition.

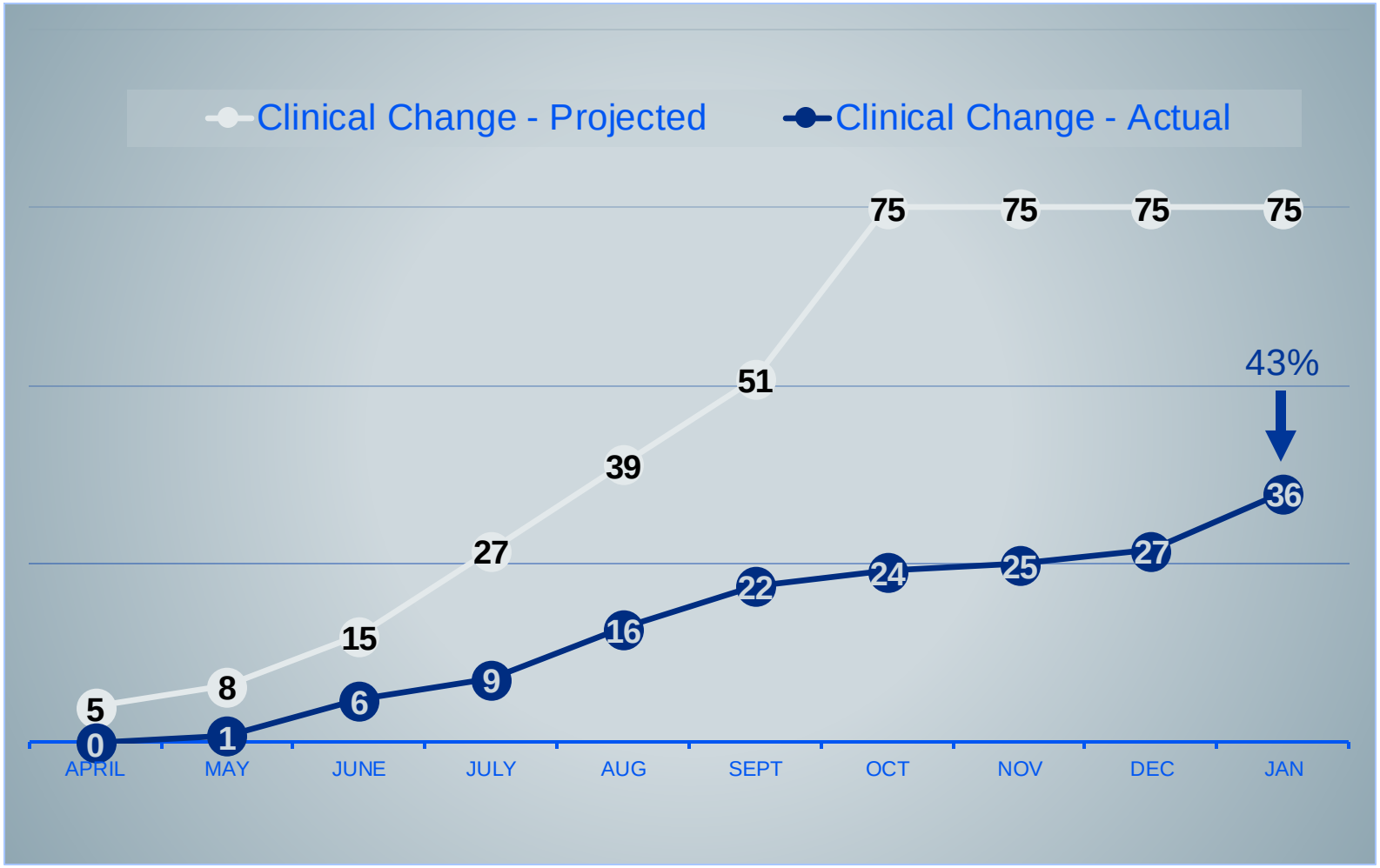
Study Sites

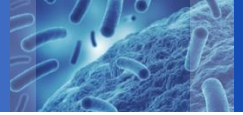
Activated Sites	PI	Activation Date
Washington University	Dr. Patrick Mazi	Q1 2024
University of Pittsburgh	Dr. Ryan Shields	
Henry Ford Health System	Dr. Geehan Suleyman	Q2 2024
Corewell Health (Beaumont)	Dr. Matthew Sims	
Ochsner Medical Center	Dr. Jonathan Hand	
University of Louisville	Dr. Rodrigo Cavallazzi	
Duke University	Dr. Christopher Cox	
University of South Florida	Dr. Kami Kim	
Weill Cornell Medical College	Dr. Markus Plate	
Johns Hopkins University	Dr. Bradford Winters	
New York Presbyterian Queens	Dr. William McCarthy	Q3 2024
Carilion Roanoke Memorial Hospital	Dr. Valerie Renard	Q4 2024
University of Kansas Medical Center	Dr. Samuel Windham	
Torrance Memorial Medical Center	Dr. James McKinnell	
Houston Methodist	Dr. Max Adelman	

Enrollment – As of 1-13-26



Clinical Change – As of 1/13-26

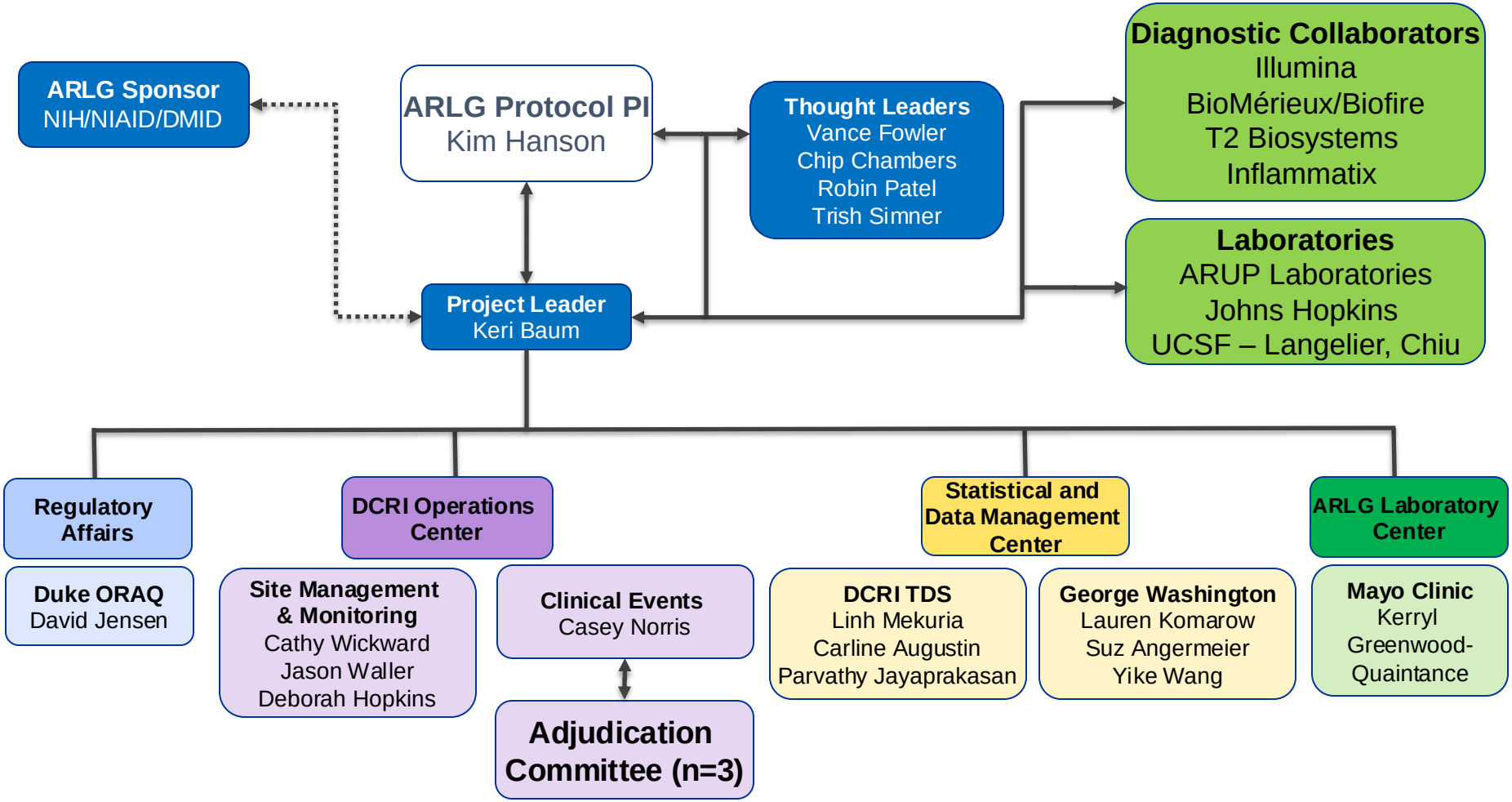




Lessons learned

- Sites generally over-estimated number of eligible participants
- Major barriers to enrollment
  - Intubated for <48 hrs
  - Surrogate decision maker declined participation
- Clinical change
  - Do not collect ETS (i.e. treat empirically)
  - Do not start antibiotics right away (i.e. wait for mPCR result in non-severe cases?)
- Specimen collection
  - Arterial blood and line draws
  - Reliance on residual BAL specimen / SOC suctioning suctioning

PDP Project Team- Thank you



Collaborators – Thank you

ARUP LABORATORIES

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University of California San Francisco

Charles Chiu
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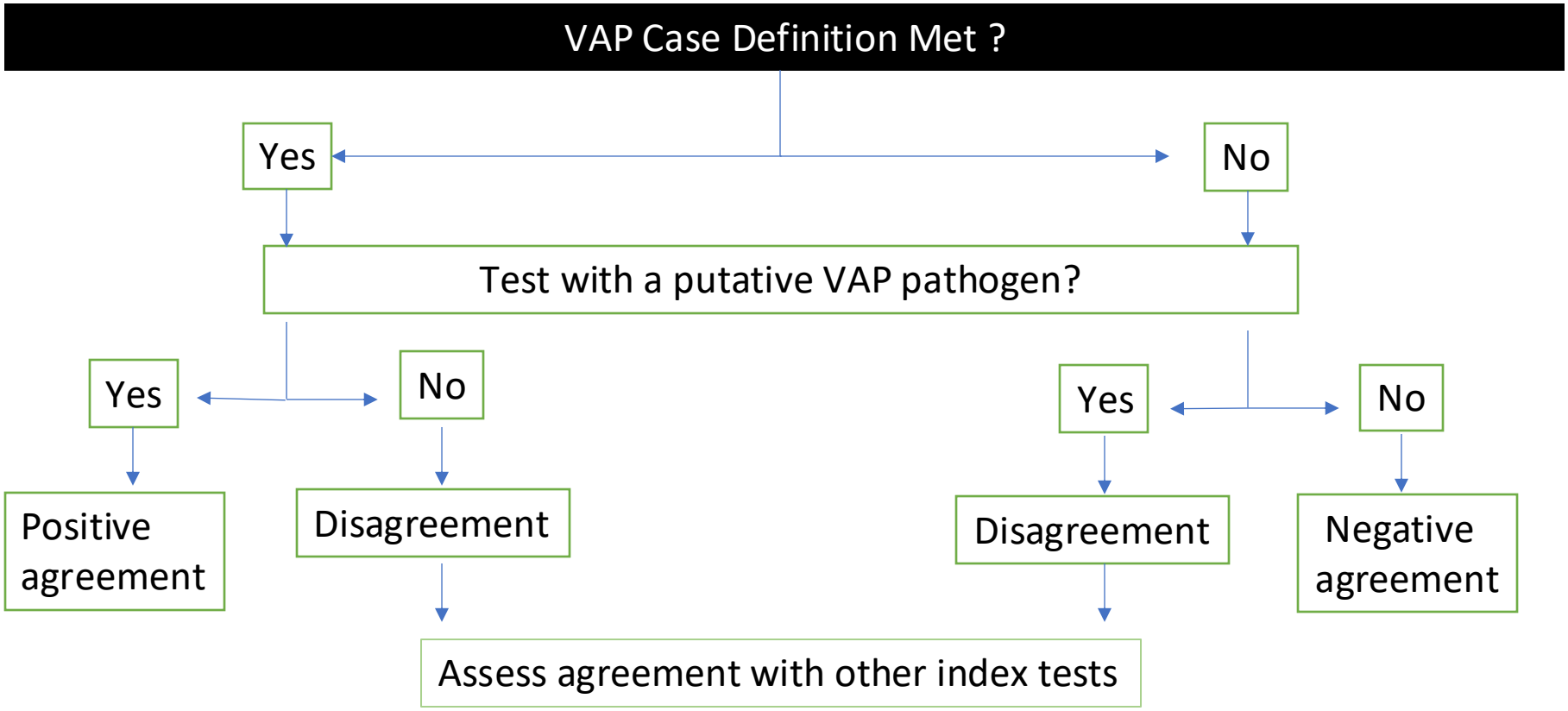
Pathogen –Directed Respiratory Tests

Primary outcome assessment



Host-Directed and Pathogen-Directed Blood Tests

Secondary outcome assessment