Beyond The Last Mile: MCM Monitoring and Assessment during Public Health Emergencies What capabilities do we need?

PHEMCE Stakeholders Workshop

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TRACK 1 – END USER CONSIDERATIONS

Challenges with Monitoring and Assessment of Public Health Emergency (PHE) MCM's Session

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How do we conduct MCM data collection, post market studies, and run clinical trials during a response?

Q&A

TRACK 2 – FEDERAL INITIATIVES AND PROGRESS

Ready…Go: Science during Crisis Response Session

Coordinator: Diane DiEuliis, PhD (NDU)

Lt Marcienne Wright, PhD (USPHS) (ASPR) Hurricane Sandy Science Preparedness Grants

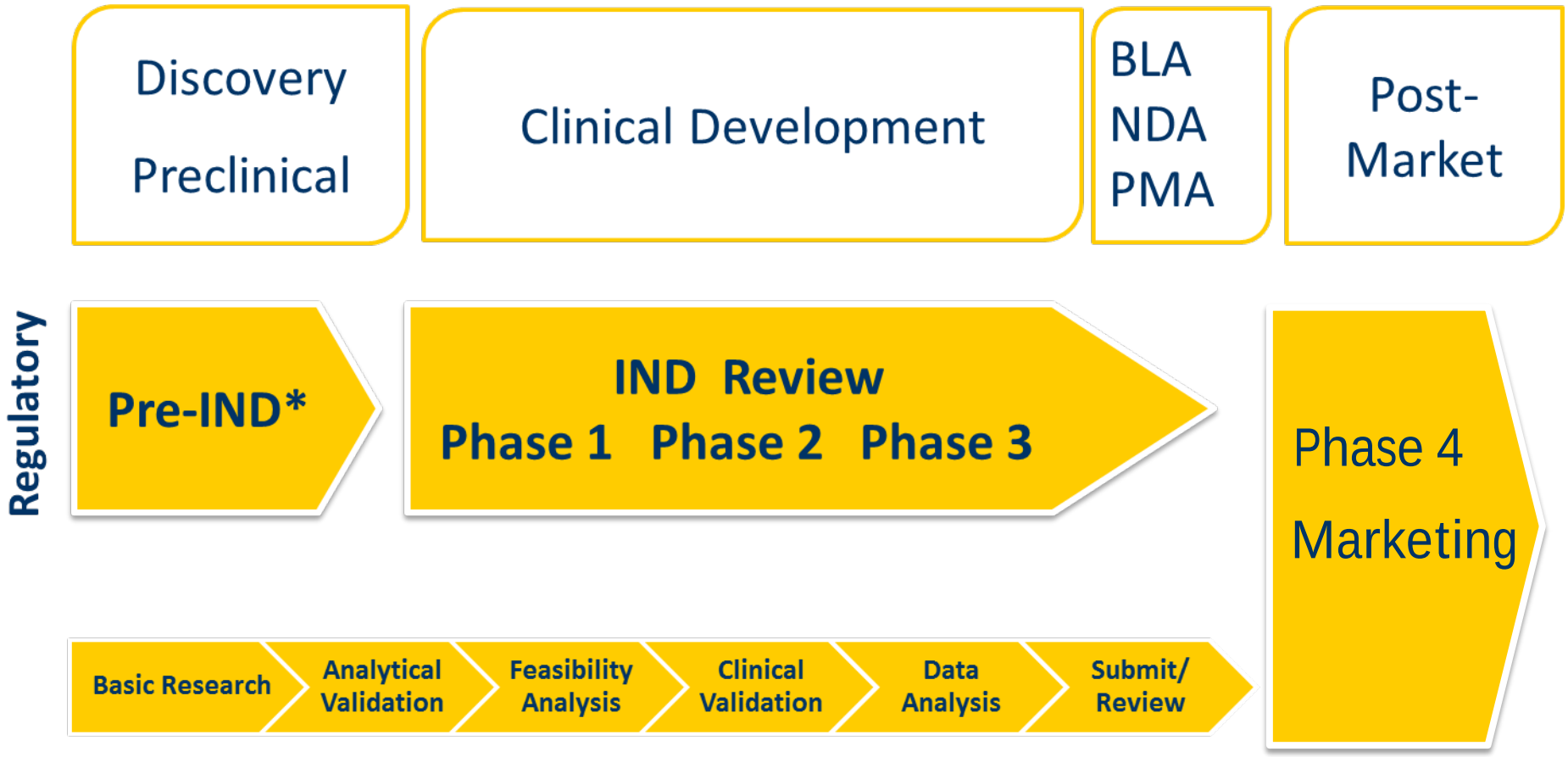
Robert Fisher, PhD (FDA) Monitoring and Assessment

Q&A

Overview

- **Objective:**
  - Discuss challenges for Public Health Emergency (PHE) Medical Countermeasures (MCM) Monitoring and Assessment (MA)
  - Provide an overview of the PHEMCE Monitoring and Assessment Integrated Program Team (IPT) mission and activities for addressing these challenges
  - Discuss potential options for PHE MCM data collection and analysis
  - Discuss the potential infrastructure needed to conduct clinical trials during an evolving PHE
  - Seek input and thoughts from participants

Traditional Medical Product Lifecycle



* Pre-submission for medical devices

PHE MCM Lifecycle Challenges

- Many potential public health emergencies involving chemical, biological, radiological, nuclear and emerging infectious disease threats do not have MCMs available.

- MCMs in the pipeline are still under development and following the traditional R&D pathways may be infeasible or unethical
  - Inability to conduct efficacy studies in humans
  - Limited safety data in humans

- Desire to use less mature MCMs for PHE responses
  - H1N1, Ebola, MERS
  - Based on preclinical data and/or little or no human data

- Affected population is only available during the PHE

Traditional R&D vs. PHE

TRADITIONAL RESEARCH AND DEVELOPMENT	PUBLIC HEALTH EMERGENCY

• Intent – Generalizable Knowledge
• Planned/Deliberate
• Well controlled clinical trials
• Smaller numbers of individuals
• Stepwise progression/single product
• Careful decision making/time
• Strict oversight and monitoring
  • Informed Consent/Process
  • IRB Review and Approval
  • Adverse event reporting
	• Intent – respond and mitigate
	• Unplanned/Unexpected
	• Chaos or controlled chaos
	• Large numbers of individuals
	• Simultaneous administration/multiple products
	• Rapid decision making/response
	• Little or no tracking/monitoring
	  • Lack of primary provider oversight/interaction
	• Limited reporting or information dissemination

PHE MCM Assessment Challenges

- **H1N1**
  - Use of IV Peramivir under EUA
    - **Inability to assess product use**
      - Goal was access
      - Not to collect data for efficacy or effectiveness
    - Lack of appropriate MCM monitoring capabilities designed for PHEs
  - Many products, many regulatory mechanisms (IND, EUA, approved/licensed)
  - H1N1 Vaccine safety plan developed during response

- **Ebola, MERS, other Emerging Infectious Diseases (EIDs)**
  - Products in early development
  - Many with no human data yet
  - Need to expedite product development during an unfolding PHE

- **Product Sponsor and Government concerns over the ability to meet post marketing requirements and commitments when product is deployed during emergency responses**

Why do we need to improve monitoring and assessment capability?

- **What We Know**
  - **Expectation that the USG know everything possible about MCMs that are used for public health emergencies**
  - Need to collect and analyze MCM data but there is a gap in MCM data collection plans and infrastructure for PHEs
  - Assess off-label use of marketed/approved PHE MCM

- **What We Don't Know**
  - **PHE MCMs may have limited safety data and little or no effectiveness data in healthy individuals and in those with the indicated illness or conditions**
  - There is uncertainty surrounding what potential data collection model will work best during a response
  - Is it possible to leverage existing data collection models for use in monitoring and assessment of MCMs during a PHE?

- **What We Need**
  - **"Everything in place the day before we need it"**
  - Establish a "network of networks" for PHE MCM data collection
  - Establish a "middle lane" to bridge the gap between limited or no data collection during a PHE (e.g., EUA) and traditional Randomized Controlled Trial (RCT) data collection

Lessons Learned & Lessons Applied

- 2009 H1N1 Improvement Plan
- 2012 PHEMCE Implementation Plan
- Portfolio review: Influenza
- Portfolio review: CBRN
- **Monitoring and Assessment IPT**

MCM Monitoring and Assessment Integrated Program Team (MA IPT)

MA IPT Mission Statement:

To establish a **comprehensive**, **PHEMCE-wide coordinated** capability to monitor and assess MCM use (safety, compliance, clinical benefit) through **data collection and analysis** during and after an emergency event to **enable assessment and decision-making during** both present and future public health responses

"Everything in place the day before we need it!"

Five Core Capabilities

1. Collect Data on MCMs
   - Coordinated approach to data capture
2. Manage, Analyze & Interpret Data
   - Establish data management policies and procedures
   - Establish plan for reviewing and interpreting data
3. Build recommendations for MCM use based on key evidence
   - Establish procedure for submission of summary data to key public health decision makers and advisers
4. Communicate evidence-based recommendations
   - Establish multidirectional communication flow plan
5. Establish administrative & budget preparedness across agencies to enable the first 4 capabilities

MCM MA IPT Objectives

- “Real-time” MCM data collection, analysis and feedback to inform decision makers regarding the use or continued use of PHE MCMs
- Understand, coordinate, and integrate monitoring and surveillance activities being done across all internal and external stakeholders
- Assess assumptions, identify and resolve gaps in data capture and analysis to enable rapid decision making
- Build and /or Augment Infrastructure – Healthcare Systems, Clinical Trials Networks, CROs, etc.
- Address MCM Sponsor and USG concerns over the ability to meet post marketing requirements and commitments when product is deployed during emergency responses

Where is the MCM MA IPT in the process?

- Established relevant workgroups to evaluate MCM MA plans for specific scenarios/case studies to focus/scope the issue
- **Through regular workgroup meetings, assess past and current monitoring and surveillance plans and activities**
- Work through the feasibility of the IPT's Five Core Capabilities
- Compile information into a draft outline plan/strategy for monitoring and assessment of MCMs
- Execute the plan/strategy

Action Plan

- **Product-specific**
  - Influenza Antivirals
    - Approved and/or investigational MCMs
  - Pandemic Vaccine
    - Effectiveness and safety data

- **Scenario-specific**
  - Anthrax Response
    - Vaccine
    - Therapeutics

- **Cross cutting issues-specific**
  - Electronic Health Records
  - Big Data

Antiviral Workgroup: Activities

- **Charge**:
  - **Need to be highly operational "the day before we need it"**
  - Develop a readiness capability for responding at the start of a PHE for real-time MCM data collection, analysis and feedback to inform decision-makers at all levels (government and clinical) regarding the use or continued use of the PHE MCM (safety and effectiveness)
  - Develop a method for conducting PHE studies to assess the performance of MCMs

- **Activities to Date:**
  - Developed the concept of a "network-of-networks" for data collection during a PHE
  - Received consensus for a CRO hub coordination role and overarching data collection for the "network-of-networks"
  - Received initial buy in from existing networks as potential participants in the "network-of-networks"
  - Developed a framework for the initial (adaptive) study design to use in PHE (based on Ebola exp.)

Antiviral Workgroup: Next Steps

- With PHEMCE agencies, conduct a workshop to discuss the implementation of the “network-of-networks” approach
- Engage BARDA clinical studies network to determine their role in the “network-of-networks” concept
- Utilize best practices from PREPARE (Platform for EUR Preparedness Against (Re-)emerging Epidemics) to help inform the “network-of networks” approach
- Integrate the centralized USG IRB, the Public Health Emergency Research and Review Board (PHERRB), into the “network-of-networks” approach.

EHR Workgroup: Activities

- **Charge**:
  - Assess the current and future EHR landscape, as it pertains to MCM surveillance
  - Determine how EHRs can be leveraged during a PHE to monitor and assess MCMs
- **Activities and Plans:**
  - Evaluated DoD and VHA systems' current capabilities to monitor the safety/effectiveness of MCMs during a PHE
  - Utilize a proof of concept scenario and minimum data set to assess the feasibility of capturing meaningful data from the DoD and VHA EHR systems.

Anthrax Vaccine and Antibiotic Workgroup: Activities

- **Charge:**
  - Assess traditional & non-traditional processes to determine how they impact MCM monitoring and assessment
  - Evaluate current tracking systems & determine if/how they could be utilized to monitor MCMs during a PHE
- **Activities and Plans:**
  - Evaluated systems' current capabilities to monitor the safety/effectiveness of MCMs during a PHE
  - Collaborate with current and potential FDA Sentinel projects, and other ongoing surveillance projects, to assess data collection during the administration or dispensing of anthrax MCMs.
  - Engage OEM to develop a table top exercise focused on the post administration of MCMs to assess the assumptions and strategies and identify gaps.

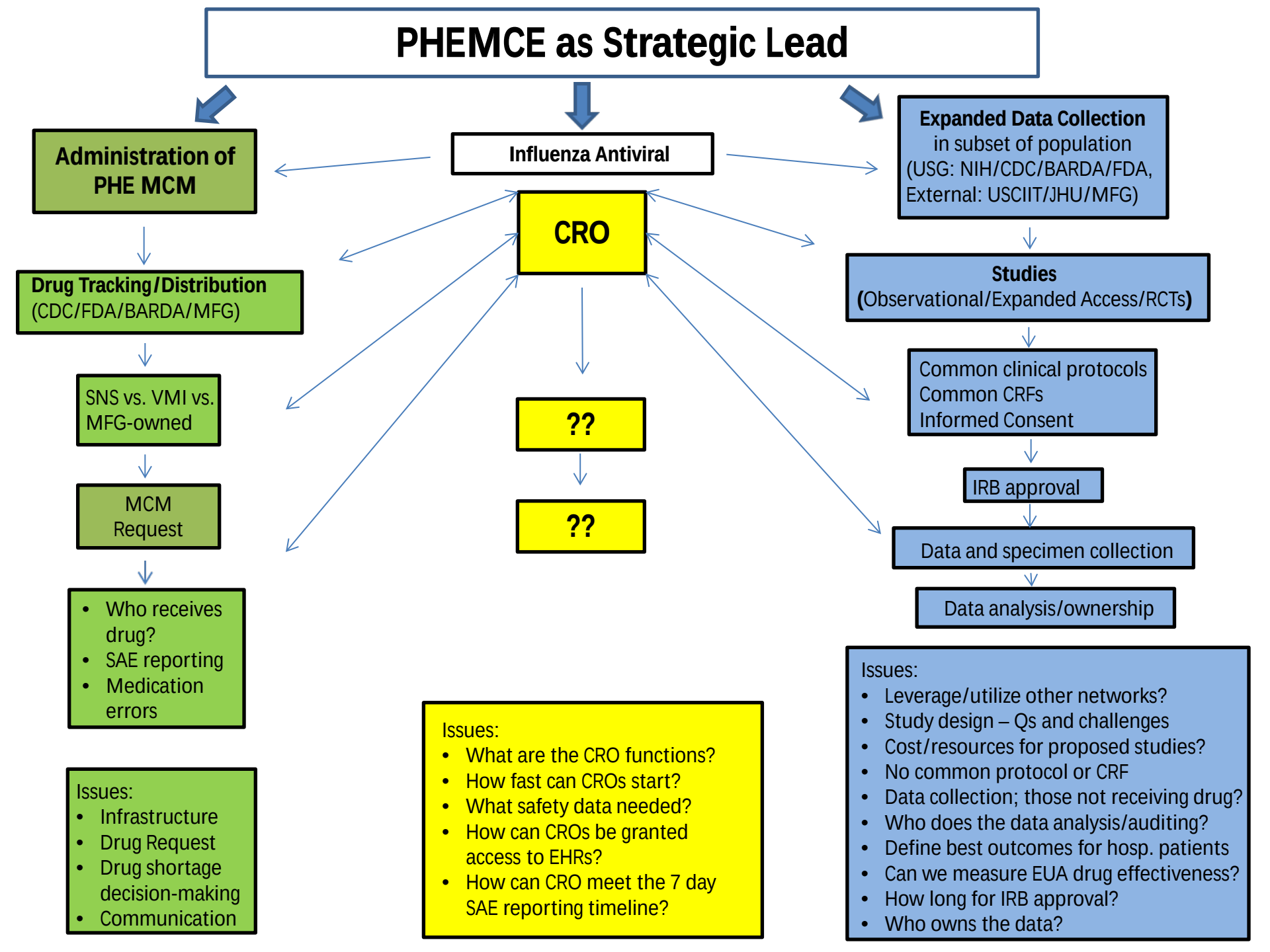
Big Data Workgroup: Activities

- **This is a relatively new workgroup that has been focusing and scoping potential activities.**

- **Charge:**
  - Assess the big data landscape and determine if big data can be leveraged to:
    - monitor and assess a MCM during a PHE
    - signal adverse effects (or that a product works)
    - identify upticks in acute illness related to the PHE and MCM use
    - gauge the scope of emergency to inform MCM deployment and assessment during that emergency
  - Identify and explain how different types of “Big Data” streams (social media, Google, medical claims based data, etc.) could be useful for MCM monitoring and assessment, determine big data collection points, and determine the roles/responsibilities for Big Data analysis.

Potential infrastructure needed to conduct clinical trials during an evolving PHE

Influenza Antivirals as a case study


PHEMCE as Strategic Lead
Administration of PHE MCM
Influenza Antiviral
Expanded Data Collection in subset of population (USG: NIH/CDC/BARDA/FDA, External: USCIIT/JHU/MFG)
CRO
Drug Tracking/Distribution (CDC/FDA/BARDA/MFG)
Studies (Observational/Expanded Access/RCTs)
SNS vs. VMI vs. MFG-owned
Common clinical protocols
Common CRFs
Informed Consent
??
MCM Request
IRB approval
??
Data and specimen collection
Data analysis/ownership
• Who receives drug?
• SAE reporting
• Medication errors
Issues:
• Infrastructure
• Drug Request
• Drug shortage decision-making
• Communication
Issues:
• What are the CRO functions?
• How fast can CROs start?
• What safety data needed?
• How can CROs be granted access to EHRs?
• How can CRO meet the 7 day SAE reporting timeline?
Issues:
• Leverage/utilize other networks?
• Study design – Qs and challenges
• Cost/resources for proposed studies?
• No common protocol or CRF
• Data collection; those not receiving drug?
• Who does the data analysis/auditing?
• Define best outcomes for hosp. patients
• Can we measure EUA drug effectiveness?
• How long for IRB approval?
• Who owns the data?

Expanded Data Collection, Analysis and Feedback

- PHE studies designed to assess the performance of MCMs. Includes, but not limited to:
  - Randomized controlled trials (RCT) in affected populations
  - Controlled cohort trials in affected populations accessing the PHE MCMs (including under EUA)
  - Public Health response or observational studies looking at clinical outcomes or epidemiological data

- Largest gap is in the hospitalized population (ED à ICU)
  - Sickest population (most resource intensive)
  - Where more lives are at stake
  - Where we need the fastest response
  - Pre-planning, pre-positioned protocols and infrastructure are critical

- Prioritize “connecting” identified clinical trial networks to establish a PHE “network of networks” that can scale up or transition to conduct pre-positioned PHE studies (“warm base” concept)

PHE Network of Networks Concept

- This requires a *fundamental* shift in our response paradigm
  - The H1N1 pandemic provided limited information largely due to insufficient pre-planning and lack of ready infrastructure
    - Networks
    - Pre-positioned protocols
    - MOUs/MOAs
    - Processes in place
      - Data collection, sharing, and analysis
      - Communications
      - Strategic Guidance and Oversight
    - Resources/Sustained Funding
  - New, engine running approach: **We need to be highly operational "the day before we need it,"** and the networks need to be "linked", "exercised" and "tested at least every year"

What do we need?

- **Monitoring and Assessing System Implementation Issues**
  - Surge capacity and capabilities need to be identified and addressed
  - Need resources to assist with identifying and setting up a CRO prior to a PHE
  - The roles and responsibilities of a CRO need to be determined
  - Need a method for capturing the population that does not receive the MCM either because they refused it, opted out, or are unable to receive the MCM.

- **IRB approval**
  - Identifying what the role of a centralized US IRB will play in a PHE (e.g., Public Health Emergency Research and Review Board)
  - States/local partners may need separate IRB approval impacting their ability to collect data during a PHE

Existing USG Supported Networks

Networks to Leverage:

- NIH Clinical Trials Networks (La Red, IRC)
- CDC's Influenza Research Platforms and Pandemic Research Expansion Sites
- Critical Illness and Injury Trial Group (USCIITG) (FDA/BARDA Contract, SPRINT SARI, ISARIC)
- Johns Hopkins University ED Network (BARDA Cooperative Agreement)
- BARDA's Clinical Studies Network (CSN)
- FDA's Sentinel Network
- Others?

- Public Health Emergency Research and Review Board (PHERRB) as the centralized USG IRB

Randomized Cohort and/or Observational Studies

- To assess clinical outcomes data associated with MCM use
- Observational studies in a subset of PHE MCM recipients who could be offered the option to participate in such studies
- Opting out of participation in these studies would not affect ability to receive an approved or EUA PHE MCM

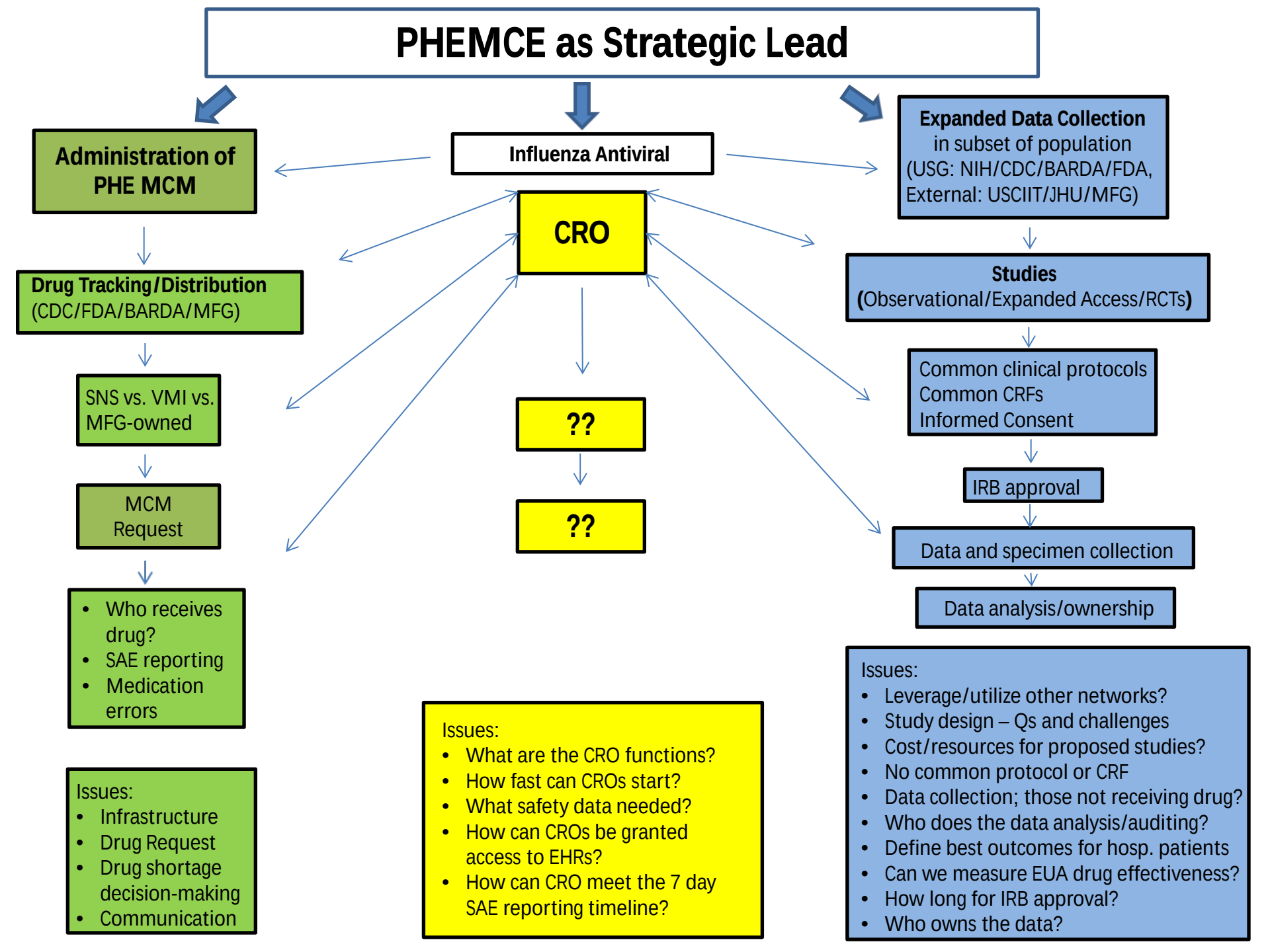
RCT (Adaptive) Trial

- Definition
  - A study that includes a **prospectively planned** opportunity for **modification** of one or more specified aspects of the study design and hypotheses, **based on analysis of data** (usually interim data) from subjects in the study*****

- Currently under development to guide national trials for Ebola virus disease (EVD) and MERS-CoV

- Proposed as second stage of the “network of network” approach using seasonal influenza to “test/exercise” the “network of networks”

*** FDA Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, April 6, 2010**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2015 – Progress Snapshot
Improvements since 2009 H1N1

- BARDA Cooperative Agreement with JHU – awarded 2012
- NIH PHERRB – formed 2012
- CDC Pandemic Preparedness Contract – awarded 2013
- BARDA's Clinical Studies Network (CSN) – awarded 2014
- USCIIT contract funded by FDA and BARDA – awarded 2014
- Acceptance of adaptive study design for use in EVD and MERS-CoV – 2015
- Advanced Development Pipeline (Phase 2 or later)
  - 2009; two approved NAIs and one IV NAI/Phase 2
  - 2015; three approved NAIs, one IV NAI/Phase 3, ~six mAbs/Phase 2, ~two with different MOAs/Phase 2
- PREPARE – Platform for EUR Preparedness Against (Re-)emerging Epidemics (EUR-wide CRN "of unprecedented size and scope") – initiated 2014

Next Steps

- Establish regular communication and coordination with other groups and stakeholders
  - Avoid duplication of efforts
  - Identify best practices to establish prospective cross-threat and MCM independent data capture and analysis approaches
  - Connect the dots
- "Everything in place the day before we need it"
  - surveillance systems, pre-positioned protocols, data analysis agreements, policies, etc.
- Establish a "network of networks" for data collection of public health emergency MCMs.
- Create a "middle lane" to bridge the gap between limited or no data collection under widespread use during a PHE (i.e., approval and EUA) and traditional RCT data collection under ideal conditions.

USG is expected to figure this out and execute it!!

Questions?

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