Draft CISA Project clinical consult work plan document for vaccine safety planning

December 5, 2020

Clinical Immunization Safety Assessment (CISA) Project: COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (CISA COVIDvax): Draft Work Plan

Prepared by the CISA Project Team, Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC), with input from CISA sites

Disclaimer

This is a draft technical document to guide CDC's Clinical Immunization Safety Assessment (CISA) Project emergency response preparations for the COVID-19 response. This document may be updated in the future.

Summary

CDC's Immunization Safety Office (ISO) is expanding the role of the Clinical Immunization Safety Assessment (CISA) Project to implement the COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (**CISA COVIDvax**). This effort is a collaboration between CDC and partners in the CISA Project medical research centers. This document describes the organization, activities, and key roles for this service. **CISA COVIDvax** aims to provide a secondary level of support for complex clinical vaccine safety inquiries from U.S. healthcare providers and health department staff that are not readily addressed by CDC or Advisory Committee on Immunization Practices (ACIP) guidelines. The key activities include: providing expert consultation for approximately 10 complex COVID-19 vaccine safety case reviews or clinical inquiries per week from healthcare providers and health departments in the United States; providing CDC staff with ready access to medical experts in infectious diseases and other medical disciplines for adult and pediatric medicine; maintaining a 24/7 on-call service to address emergency clinical inquiries about COVID-19 vaccine safety; and, assisting CDC and partners in assessing emerging COVID-19 vaccine safety issues. In addition, **CISA COVIDvax** staff will operate secure tracking databases for COVID-19 vaccine safety clinical consults conducted through the service.

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Purpose

The purpose of this working document is to guide implementation of the CISA Project COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (**CISA COVIDvax)**. This document includes information relevant for staff at CDC and CISA sites. This effort is part of the CISA Project Emergency Response Plan (planning and initiation step), under the routine CISA Project clinical consultation activity.

Section 1: Background

1.1: Coronavirus Disease-19 (COVID-19) and CDC's Public Health Response

On January 31, 2020 the U.S. Department of Health and Human Services (HHS) Secretary declared a public health emergency to respond to the novel coronavirus (2019-nCoV [COVID-19]).[1] In the span of a few months COVID-19 spread throughout the United States and world. As of December 5, 2020 there were >14 million COVID-19 cases reported in the United States and >270,000 deaths associated with COVID-19.[2] CDC is responding to this pandemic by conducting surveillance, research, and public health education activities to support state, local, tribal and territorial governments and healthcare workers on the front lines of this pandemic.[3] CDC is also working closely with health departments and other partners to plan and operationalize a national COVID-19 vaccination program and monitor impacts of this program.[4]

1.2: Coronavirus Disease-19 Vaccine Development

As of December 5, 2020 no authorized or approved U.S. vaccines are available to prevent COVID-19, but it is anticipated that COVID-19 vaccines may be available in the near future under Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs).[5] In November, 2020 Pfizer and BioNTech[6] and Moderna Inc.[7] each submitted applications to the FDA for a COVID-19 vaccine EUA. Multiple COVID-19 vaccine candidates are in development or clinical trials worldwide. These include nucleic acid (RNA and DNA), viral vector, protein-based vaccines and virus (inactivated and live attenuated) vaccines.[8] On May 15, 2020 HHS announced the framework for Operation Warp Speed (OWS).[9] A goal of

OWS is to deliver 300 million doses of a safe and effective COVID-19 vaccines, with the initial doses anticipated to be available by December 2020. CDC is guiding the program implementation and has released an interim COVID-19 vaccination program playbook for jurisdictions .[4] As of December 5, 2020, four phase 3 trials of COVID-19 vaccines are being conducted in the United States: 1) Moderna mRNA vaccine in adults (ClinicalTrials.gov Identifier: NCT04470427) 2) Pfizer and BioNTech mRNA vaccine (BNT162b2) in children and adults aged ≥12 years (ClinicalTrials.gov Identifier: NCT04368728) 3) AstraZeneca non-replicating chimpanzee adenovirus vector vaccine (AZD1222) in adults (ClinicalTrials.gov Identifier: NCT04516746); and 4) Janssen non-replicating adenovirus vector vaccine (Ad26.COV2.S Vaccine) in adults (ClinicalTrials.gov Identifier: NCT04505722). [10] These studies exclude pregnant women. Preliminary results from phase 1/2 studies of these vaccine candidates have been reported.[11,12,13,14]

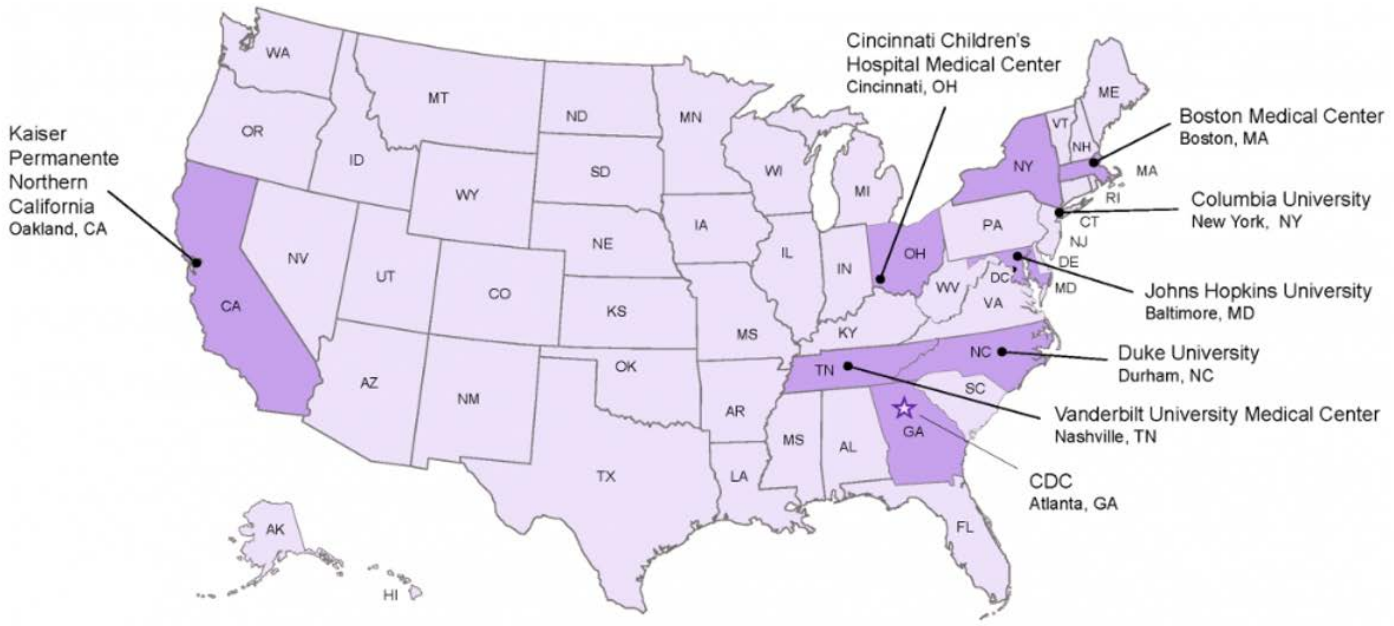
1.3: CDC Vaccine Safety Monitoring Plans for COVID-19 Vaccines

CDC's Immunization Safety Office (ISO) and its collaborators have developed plans to monitor the safety of COVID-19 vaccine(s) after vaccine(s) are authorized or approved by the FDA and recommended for use in the U.S. population. ISO is expanding and enhancing its current infrastructure to monitor COVID-19 vaccine safety. This approach is similar to how ISO responded to the 2009 H1N1 influenza emergency response for vaccine safety monitoring.[15] The Vaccine Adverse Event Reporting System (VAERS), operated jointly by CDC and FDA, is a spontaneous reporting system that will be used to rapidly detect COVID-19 vaccine safety signals.[16] The Vaccine Safety Datalink (VSD) is a collaboration between CDC and nine integrated healthcare systems.[17] VSD will conduct near real-time surveillance and epidemiological studies to assess risk of adverse events after COVID-19 vaccination. ISO also supports an inquiry response program about vaccine safety for the general public, healthcare providers, and other stakeholders through the VAERS Project and Response Team (VPRT).[18] The CISA Project provides additional clinical expertise and support for ISO vaccine safety activities.[19] In addition, CDC is implementing expanded monitoring systems for COVID-19 vaccine safety. These include a smartphone-based active surveillance program and the National Healthcare Safety Network (NHSN) surveillance system for long-term care facilities.[20] The remainder of this document describes the CISA Project goals, structure and proposed CISA COVID-19 clinical consultation work plan in more detail.

1.4: CISA Project Background

The CISA Project is a collaboration between CDC ISO and medical research centers that have specific expertise in vaccine clinical research and vaccine safety. CDC's CISA activity started in 2001 and since 2012 the CISA Project has been operated through 10-year contracts with 7 sites (Figure 1).

Figure 1: CISA Project Sites



The CISA Project mission is to improve understanding of adverse events following immunization (AEFI) at the individual patient level. The CISA Project has 3 main goals:

- Serve as a vaccine safety resource for U.S. healthcare providers with complex vaccine safety questions about a specific patient to assist with immunization decision-making (clinical consultation)
- Assist CDC and its partners in evaluating emerging vaccine safety issues (clinical consultation)
- Conduct clinical research studies to better understand vaccine safety and identify preventive strategies for AEFI

The CISA Project supports clinical vaccine safety consultation for U.S. healthcare providers or health departments with questions about individual patients or issues. Seven CISA sites are participating in this consultation service. The CISA Project sites are supported to conduct 24 clinical case consults about vaccine safety per year (for routine vaccines). Vanderbilt University serves as the lead site for CISA clinical consultation. Currently, U.S. healthcare providers with a complex vaccine safety question about a specific patient residing in the United States may contact CISA at CISAeval@cdc.gov to request a case consultation.[19] All requests are reviewed by CDC-CISA medical officer(s) and addressed by CDC-CISA staff. Selected requests are accepted for a CISA consultation and are usually those which involve a complex question for which there is little or no published guidance elsewhere. Advice from CDC and the CISA Project is meant to assist in decision-making, rather than provide direct patient management.

One example of a CISA case consult was an inquiry from a healthcare provider who wanted to know if it was safe to administer influenza vaccine to a child with a history of Stevens-Johnson Syndrome (SJS) after influenza B infection.[21] After close review of available safety information and discussion, CISA medical experts suggested administering the quadrivalent inactivated influenza vaccine (IIV4). Given the absence of data to support a causal relationship between influenza vaccine and SJS, the CISA experts assessed that the child would be at greater risk from influenza B than from influenza vaccine. The healthcare provider chose to administer IIV4 and the child experienced no AEFI.

CISA also conducts clinical research studies. CISA sites have medical experts in multiple areas of medicine, experience in conducting vaccine clinical trials, and ability to recruit and enroll patients in special populations. These attributes make CISA particularly well-suited to study vaccine safety in understudied populations, such as pregnant women.[22,23]

1.5: Clinical Vaccine Safety Importance

With the historic, rapid pace of COVID-19 vaccine development, preparing to address complex clinical vaccine safety inquiries from healthcare providers and assess vaccine safety issues efficiently and effectively is important. This role provides a service to U.S. healthcare providers and public health officials at state and local health departments. Additionally, the systematic review and tracking of complex clinical AEFI cases after COVID-19 vaccine can augment

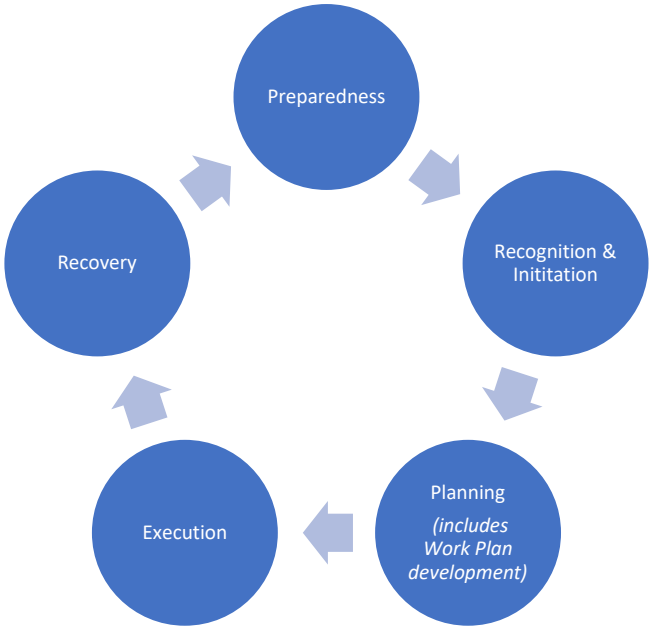
national vaccine safety surveillance data.[18] Clinical trials may be too small to detect rare AEFI that might be seen only after tens to hundreds of thousands of people are vaccinated.[16]

COVID-19 vaccine safety assessment presents clinical challenges. First, COVID-19 has a wide spectrum of clinical presentations and complications and it may be difficult to distinguish clinical features of COVID-19 disease from AEFI after COVID-19 vaccination in the setting of a COVID-19 pandemic. One clinical example is multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A).[24,25,26] It may also be challenging to assess AEFI after COVID-19 vaccination if it is administered simultaneously or closely spaced with influenza vaccine or other vaccines. Additionally, there is potential concern for vaccine-mediated enhanced disease (VMED) to occur after COVID-19 vaccination in humans.[27] This potential concern for disease enhancement is based on results of another coronavirus vaccine (SARS-CoV-1) in-vitro and in animal models, as well prior human RSV and MMR historical vaccine experience.

1.6: Activation of the CISA Emergency Response Plan and Planning Assumptions

The CISA Project maintains a general emergency response plan (ERP) as part of national preparedness. The phases of the emergency response plan are illustrated below (Figure 2). This work plan corresponds with the later stages of the **Planning** phase. The **Execution** phase will start after COVID-19 vaccines are authorized and distributed for use in the United States. In September 2020, CDC implemented COVID-19 vaccine safety clinical consultation and associated support activities in the CISA Project.

Figure 2: CISA Emergency Response Plan Framework



Part 2: Organization and Staffing Roles for the CISA COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (CISA COVIDvax)

2.1: Overview

CDC's Immunization Safety Office and the CISA sites, are leveraging current CISA Project infrastructure to implement the CISA COVID-19 On-Call Clinical Consultation Service for Vaccine Safety **(CISA COVIDvax)** in the United States. **CISA COVIDvax** covers the first two CISA Project objectives noted above (see section 1.4). **CISA COVIDvax** is a collaboration between CDC staff and staff at the seven CISA sites. Additional federal partners may also participate in CISA Project activities. **CISA COVIDvax** will also collaborate with the CDC COVID-19 Vaccine Task Force and other vaccine safety and clinical teams and units involved in the COVID-19 emergency response or vaccine inquiry response at CDC. **CISA COVIDvax** provides a secondary (escalation) level of support for vaccine safety clinical inquiries and is not a front-line

CDC inquiry response function. **CISA COVIDvax** will focus on clinical inquiries about COVID-19 vaccine safety. If an inquiry is about a COVID-19 vaccine and another vaccine (e.g., influenza vaccine) it will be considered a COVID-19 vaccine inquiry. Healthcare providers or health departments in the United States can request a consultation from **CISA COVIDvax** for a complex COVID-19 vaccine safety question that is (1) about an individual patient residing in the United States or vaccine safety issue that might affect multiple patients and (2) not readily addressed by CDC or Advisory Committee on Immunization Practices (ACIP) guidelines. **CISA COVIDvax** will assist U.S. healthcare providers and health departments involved in caring for patients with adverse events after COVID-19 vaccine or in making clinical decisions about administering a COVID-19 vaccine to a person who may be at increased risk for an adverse event after vaccination; the service will also contribute to COVID-19 vaccine safety education and monitoring efforts. **CISA COVIDvax** includes 24/7 on-call capacity for COVID-19 vaccine safety emergencies requiring clinical consultation that cannot wait until the next business day. **CISA COVIDvax** will also assist CDC and its partners in assessing emerging vaccine safety issues about COVID-19 vaccine. This function includes maintaining a roster of clinical experts in vaccine safety and infectious diseases (from 7 CISA sites) and multiple adult and pediatric medical specialists at the CISA Project research medical centers. The CDC CISA Project Team has also recruited experienced CDC medical officers, public health physicians, and other clinicians to contribute to operating the on-call service. The Vanderbilt lead site for clinical consultation will maintain a secure Research Electronic Data Capture (REDCap) database for tracking vaccine safety cases reviewed.[28] CDC also will house a separate REDCap tracking system for tracking clinical inquiries regarding COVID-19 vaccine safety, which will contain less clinical detail than the database residing at Vanderbilt. Vanderbilt and CDC will also analyze data and generate summary reports form these databases. CISA Project clinical case reviews are conducted under a CDC Assurance of Confidentiality for the CISA Project.[29]

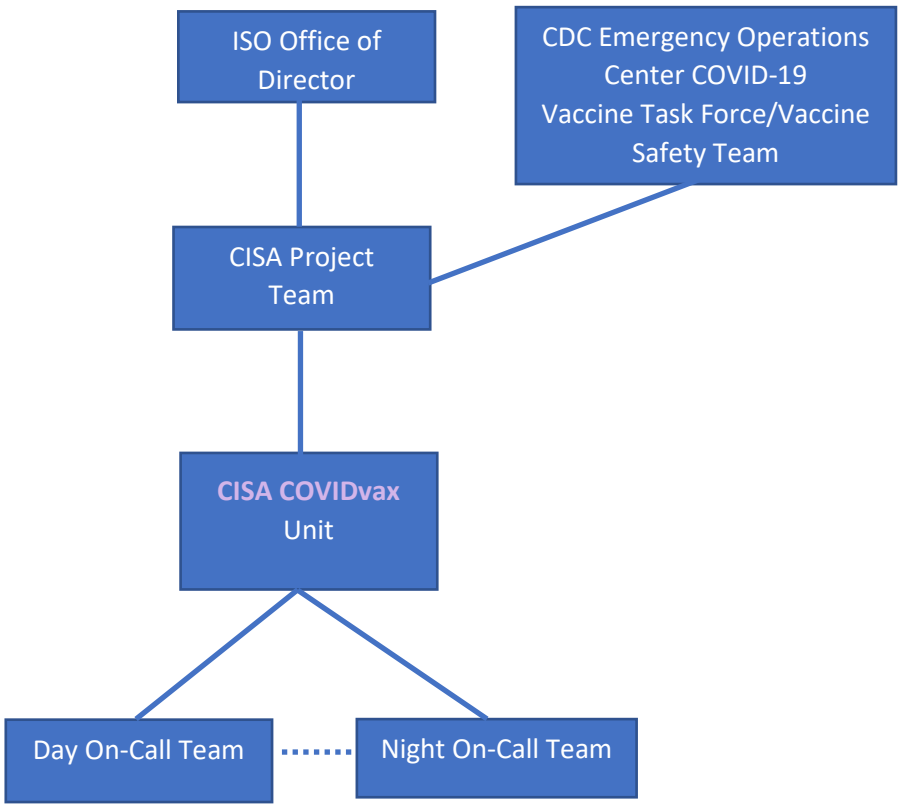
2.2: CDC Organization and Staffing

The CISA Project is a team in the Immunization Safety Office (ISO), Division of Healthcare Quality Promotion, Center for Emerging and Zoonotic Infectious Diseases (NCEZID), CDC. ISO and CISA Project staff are also engaged with the CDC

COVID-19 emergency response through the CDC Emergency Operations Center Incident Management Structure (IMS).[30]

The CISA Project team's COVID-19 proposed staffing structure for **CISA COVIDvax** is shown in Figure 3.

Figure 3: CDC COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (CISA COVIDvax) Staff Organization



2.3: CISA Site Staff Organization

2.3.1: Principal Investigators

All seven CISA Project sites are participating in **CISA COVIDvax**. Table 1 lists the CISA site physician roles. (see Part 3 for details).

Table 1: Participating CISA Project Sites

CISA Site	CISA Sites Physician Roles
Vanderbilt University Medical Center, TN (Lead site)	**Primary**[A, B] **Secondary**[A, B]
Boston Medical Center, MA	**Primary**[A, B] **Secondary**[A, B]
Cincinnati Children's Hospital Medical Center, OH	**Primary**[A, B] **Secondary**[A, B]
Columbia University, NY	**Primary**[A] **Secondary**[A]
Duke University, NC	**Primary**[A, B] **Secondary**[A, B]
Johns Hopkins University, MD	**Primary**[A, B] Secondary[C]
Kaiser Permanente Northern California, CA	Primary[C]

A. **Participating in day on-call functions**
B. **Participating in night on-call functions**
C. Participating as vaccine safety expert; not serving as on-call site physician

2.3.2: Medical Specialist Subject Matter Experts

Adverse events following immunization may present through different body systems and COVID-19 natural infection has a complex clinical picture.[27] To respond readily to clinical questions about COVID-19 vaccine safety, CISA sites will maintain a list of medical specialists in diverse areas of adult and pediatric medicine. Table 2 shows the categories of experts that will be available to provide consultation for **CISA COVIDvax**. All sites will provide expertise in vaccine safety or infectious diseases through the main CISA site physicians (Table 1). Vanderbilt will maintain a list of additional medical experts in all categories on the roster. Five other sites will provide medical experts in some or most of these categories: Boston, Cincinnati, Duke, Columbia, and Johns Hopkins. Some medical experts participating in **CISA COVIDvax** will have experience through work on the routine CISA Project clinical consultation activity.

Table 2: CISA COVID-19 Medical Subject Matter Expert Roster

	Medical Expert Specialty		
Tier Level		**Adult**	**Pediatric**
Tier 1: several experts across 6-7 CISA sites	Infectious Diseases		
	Vaccine Safety		
Tier 2: 2-3 experts; provided by Vanderbilt and some other CISA sites	Geriatrics	Yes	N/A
	Obstetrics and gynecology	Yes	N/A
	Allergy/Immunology	Yes	Yes
	Neurology	Yes	Yes
	Pulmonary/Critical Care Medicine OR Pediatric Critical Care Medicine	Yes	Yes
	Hematology	Yes	See Tier 3
	Cardiology	See Tier 3	Yes
	Rheumatology	See Tier 3	Yes
Tier 3: At least 1 expert provided by Vanderbilt and possibly some other sites			
	Dermatology	Yes	Yes
	Cardiology	Yes	See Tier 2
	Rheumatology	Yes	See Tier 2
	Nephrology	Yes	See Tier 4
	Hematology	See Tier 2	Yes
	Pulmonology	See Tier 2	Yes
	Gastroenterology	See Tier 4	Yes
Tier 4: Vanderbilt or another site should be able to arrange for ad hoc consultation for disciplines not listed if needed		Examples: ophthalmology, ENT, genetics, nephrology	

2.3.3: Licensure and Board Certification

CISA site physicians participating in a clinical on-call capacity in **CISA COVIDvax** are required to have a valid U.S. medical license. For CISA site physicians, board certification in infectious diseases or substantive vaccine safety expertise is required for participation as a primary on-call physician on the service. Clinical specialists on the CISA site subject matter expert rosters are all expected to be board certified; exceptions may be considered on a case-by-case basis. Persons without a medical license may assist the responsible CISA site physician(s) with clinical consultation activities.

The CDC **CISA COVIDvax** medical supervisors for the CDC CISA on-call service activities are required to have a valid U.S. medical license. CDC staff with relevant experience in medical, nursing, pharmacy or other clinical fields may serve as on-call clinicians for the CDC CISA on-call service functions. CDC medical supervisors will be available to provide consultation as needed.

2.3.4. Coordination and Data Management Roles

The staffing model plans for each site participating in **CISA COVIDvax** includes at least one coordinator on their site team. The coordinator will assist the on-call site physician with clinical consultation functions (outlined in part 3) specific to their site, including data entry. Vanderbilt has additional staffing responsibilities related to coordination for the entire **CISA COVIDvax** operation in conjunction with CDC. Vanderbilt and CDC teams also include staff to manage the consult and inquiry tracking databases (see part 3).

Part 3: Specific Functions to Operate the COVID-19 On-Call Clinical Consultation Service for Vaccine Safety (CISA COVIDvax)

3.1: Overview of Specific CISA COVIDvax Functions

The planned functions of **CISA COVIDvax** include:

- Provide expert consultation for approximately 40 complex COVID-19 vaccine safety case reviews or clinical inquiries per month (increased from 2 per month for routine vaccines) from healthcare providers and health departments in the United States (six CISA sites in day on-call pool). The weekly volume is expected to fluctuate during the response
- Maintain a 24/7 on-call roster (CDC clinical officers and CISA Project site physicians with infectious diseases expertise), with rapid response capacity for calls about clinical COVID-19 vaccine safety emergencies (five CISA sites in night/after hours on-call pool)
- Roster clinical experts in infectious diseases and multiple adult and pediatric specialties at U.S. medical research centers (six CISA sites; site-specific rosters are in development)
- Assist ISO/CDC to assess 1–2 emerging COVID-19 vaccine safety issues per week and conduct adjunct scientific functions (seven CISA sites)
- Educate and train ISO, CDC, and partners about clinical aspects of COVID-19 vaccine safety (seven CISA sites)
- Manage secure REDCap databases housed at Vanderbilt and CDC for tracking COVID-19 vaccine safety clinical inquiries and cases reviewed in **CISA COVIDvax**; produce summary reports of data (Vanderbilt and five contributing CISA sites participating in on-call services to enter data into Vanderbilt database; CDC staff to enter inquiry tracking data into the CDC database)

3.2: Basic CISA Functions

All CISA sites have current CISA Project contracts to conduct regular clinical consultation work for the CISA Project, but some activities are site-specific for the COVID-19 vaccine safety consultation activities. The general CISA Project clinical consultation functions for COVID-19 vaccines are similar to those described in part 2 above. One key difference is that in addition to Vanderbilt, five CISA contributing sites are supported to lead CISA case reviews for COVID-19 vaccines.

3.3: Day On-Call Service Functions

The cornerstone of **CISA COVIDvax** will be the day on-call service. CDC and CISA sites are scaling up to provide clinical consultations to U.S. healthcare providers and health departments with complex vaccine safety questions. The day on-call service will operate during business hours Monday through Friday (Eastern Time). Much of the infrastructure needed for the day on-call service is already in place. Consults that are complex and less urgent may take 1-2 weeks to complete. For example, a consult request from a healthcare provider about whether it is safe to administer dose 2 of COVID-19 vaccine in a person who had a rash after dose 1 might take >1 week to complete, especially if a call with the healthcare provider and a CISA Project site allergist or dermatologist is needed. By the end of the first 2 weeks of start-up of the full-scale service, **CISA COVIDvax** could expect to carry about 20 active consults at a time in difference phases of the process. The volume of consults may vary, and it is anticipated that it may be higher during initial implementation of a widespread COVID-19 vaccination program in early 2021. Historically, interest in vaccine safety has also increased when a vaccine safety topic generates public visibility in the media or on social media.

Like the current CISA consultation service for routinely recommended vaccines, **CISA COVIDvax** is set up as a higher level (escalation) expert consult service unit and not as a frontline inquiry response service. Details about the CISA day on-call service are described below. CISA standard operating procedures (SOPs) are being updated or developed to support these operations and may adapt as the public health needs change. Information for healthcare providers about how to request a CISA consultation for routine vaccines is already available on the CDC CISA website;[19] this site will be updated to provide additional instructions for requesting a CISA COVID-19 vaccine safety consultation. The CDC CISA Project

Team will also receive inquiries that have been triaged by the ISO Inquiry Response Program and may require the CISA Project medical expertise (see below).

3.3.1: Inquiry Flow and Assignment of CISA Consults

During a COVID-19 vaccination program, we expect that CDC will receive most clinical inquiries about COVID-19 vaccine through CDC-INFO, which is CDC's national contact center and publication fulfillment system. CDC-INFO has live agents available by phone and email 24/7. Healthcare providers or health departments in the United States can request a consultation from **CISA COVIDvax** for a complex COVID-19 vaccine safety question that is (1) about an individual patient residing in the United States or vaccine safety issue and (2) not readily addressed by CDC or Advisory Committee on Immunization Practices (ACIP) guidelines by contacting CDC-INFO at 800-CDC-INFO (800-232-4636) or using the CDC-INFO webform. If they indicate that the request is for a CISA Project consultation for COVID-19 vaccine safety, then the request will be forwarded to the **CISA COVIDvax** clinicians for review. **CISA COVIDvax** will maintain an internal email box to receive requests for CISA COVID-19 vaccine safety consultations from CDC-INFO or other units in CDC. **CISA COVIDvax** CDC staff will also collaborate closely with the ISO Inquiry Response Program, which will receive clinical inquiries that may also be appropriate for CISA Project consultation. **CISA COVIDvax** will review clinical inquiries that involve COVID-19 vaccines with or without other vaccines. The CISAeval@cdc.gov email box described in section 1.4 will remain available for healthcare providers to use for requests for CISA vaccine safety consultations that are not about COVID-19 vaccines.

ISO-CDC staff currently plan to track all inquiries that come to ISO or **CISA COVIDvax** in a CDC REDCap database, housed in ISO (this is separate from the Vanderbilt database). This internal database will be used both to monitor assignments and completion status and to maintain summary data about each inquiry or CISA consult for COVID-19 vaccines. ISO-CISA staff will meet routinely to discuss inquiries with the ISO Inquiry Response Program and the ISO-CISA team will maintain a list of consults to assign to the CISA on-call physicians each day. ISO-CISA staff may also review cases with CISA site staff to help make assessments about whether consults are a good fit for **CISA COVIDvax**.

ISO-CISA will also be responsive to requests for consults from ISO or CDC leadership

3.3.2: Day On-Call Workflow

The **CISA COVIDvax** day on-call staffing model will ideally include: at least two on-call medical (or clinical) officers from CDC (primary medical officer and secondary medical officer(s)), a CDC **CISA COVIDvax** on-call medical supervisor, two on-call CISA site investigators with infectious disease or vaccine safety expertise (primary and back-up), and coordinators (from CDC, Vanderbilt [lead site], and the on-call CISA site); other clinical and operational staff may also participate as feasible. The CDC-CISA medical supervisor lead of the day will provide direction, with input from other CISA and CDC medical/clinical officers. CDC-CISA staff will also contribute to coordination. Experts at CISA sites, particularly at the lead site (Vanderbilt), may also provide consultation for the service when they are not on call if they have time and interest in this role. Six CISA sites (Vanderbilt, Boston, Cincinnati, Duke, Johns Hopkins, and Columbia) will participate in the day on-call pool. The teams have started training activities and are practicing day on-call processes by responding to vaccine safety clinical inquiries about routine vaccines.

The Monday–Friday schedule will have a rhythm that includes a daily check-in meeting in the morning and a sign-out communication in the afternoon or evening, which may be done by email when feasible. In addition, topical, educational or internal coordination calls may be scheduled during the day call hours. Consultation calls with the healthcare providers with clinical inquiries may also be scheduled.

CISA COVID-19 consults will be assigned in the morning and throughout the day. For non-urgent consults, CDC staff may make assignments within a few days after the day of receiving the inquiry, particularly if expertise at a specific CISA site in needed. Because the consults are expected to be complicated, when feasible, the CISA site physician will follow their consults through to closure and complete patient follow-up activities when indicated (see section 3.4.4). If this is not possible (e.g., the day on-call physician is going on vacation or clinical service the next day), then the consult (or selected action for the consult) can be signed out to other clinicians in the on-call pool, especially the night on-call staff (see below). Table 3 shows a sample weekly schedule for **CISA COVIDvax** daily calls.

Table 3: Sample CISA COVIDvax CISA site and CDC staff daily schedule* (subject to change)

Event/Time ET	Monday	Tuesday	Wednesday	Thursday	Friday
Night sign-out 8:30a	CDC on-call staff +/- CISA site night on-call physician as needed				
Day check-in** 10-11a	Day on-call CISA site(s) and CDC staff and Vanderbilt coordinators; other staff optional				N/A
Day check-in ** 10:30-11:30a	N/A	N/A	N/A	N/A	Same staff as Monday-Thurs calls
CISA WG calls 12-2p**	N/A	N/A	All CISA Sites	N/A	N/A
Sign-out 5-5:30p	CDC staff +/- CISA site on-call physician(s) as needed				

*Excludes federal holidays ** Vanderbilt to coordinate these calls

3.3.3: Night On-Call Responsibilities

The **CISA COVIDvax** night on-call service covers nights during the weekdays, and days and nights on weekends and federal holidays. Five CISA sites (Vanderbilt, Boston, Cincinnati, Duke, and Johns Hopkins) are participating in the night-on-call pool. CDC-CISA staff are conducting assessments to ensure that the CISA site physicians can rapidly receive and respond to calls after hours. Also, CDC medical officers will participate in the **CISA COVIDvax** night call pool. The primary function of the night on-call staff is to address COVID-19 vaccine safety emergencies that require clinical consultation (see below) that come in after hours and can't wait until the business next day.

The CDC-CISA on-call clinical officer will triage any emergency vaccine safety calls that come in after hours and they will contact the CISA site on-call physician if needed. When needed, the CDC **CISA COVIDvax** night on-call supervisor may also be contacted. The medical subject matter experts (specialists) at the CISA sites are expected to be available to assist with night on-call inquiries to the extent feasible (see section 3.3.6).

3.3.4: Day and Night On-Call Schedules

Tables 4 and 5 provide and Figure 3 provide sample on-call schedules for **CISA COVIDvax** CISA site physicians and CDC on-call clinical staff.

Table 4a: Sample Day On-Call Schedule for CISA Site Physicians (subject to change)

Role	Monday	Tuesday	Wednesday	Thursday	Friday
Primary CISA site	Site A	Site C	Site D	Site E	Site F
Back-up CISA site	Site B	Site D	Site A	Site B	Site C

Table 4b: Sample Night On-Call Schedule for CISA Site Physicians* (subject to change)

Role	Monday	Tuesday	Wednesday	Thursday		Friday	Saturday	Sunday
Times		5pm to 9 am ET Site A					24 hours Site A	

*Sites take night call about 1 week in 5; federal holidays are considered like a weekend day

Table 5a: Sample Day On-Call Schedule CDC Medical Officers* (subject to change)

Role	Monday	Tues	Wed	Thursday	Friday
Day On-Call Medical Supervisor	Day On-Call Medical Supervisor**				
Day On-Call Clinician 1	Officer A	Officer A	Officer D	Officer E	Office D
Day On-Call Clinician 2	Officer B	Officer C	Officer E	Officer D	Officer E

Table 5b: Sample Night On-Call Schedule for CDC Medical Officers (subject to change)

Role	Monday	Tues	Wed	Thursday	Friday	Sat	Sun
Night On-Call Medical Supervisor		Night On-Call Medical Supervisor**					
Night On-Call Clinician 1	Officer F	Officer B	Officer G	Officer C	Officer A	Officer H	Officer C
Night On-Call Clinician back-up	Officer H	Officer H	Officer H	Officer G	Officer G	Officer A	Officer E
Times		4 pm to 9 am				24 hours	

*8 on-call clinicians available for day or night on-call in this model.

** Supervisors usually will be covered each week by several experienced CDC-ISO medical officer staff

3.3.5: Vaccine Safety Emergencies

Clinical vaccine safety emergencies are not a common source of inquiries to CDC ISO, but it is important for the **CISA COVIDvax** to provide assistance when CDC receives an inquiry about vaccine safety that requires emergency clinical consultation. Two examples are provided to illustrate how an inquiry would be addressed. In example 1, a physician calls and requests guidance for a patient in the hospital with an adverse event who recently received COVID-19 vaccine. The call comes to CDC on Friday at 7pm ET. The calling physician wants an opinion on whether the vaccine may have caused the adverse event and wants to know if there are any specific labs to collect. In example 2, a health department calls Saturday morning because they received 3 calls in the past 48 hours about patients with the same type of symptoms shortly after COVID-19 vaccination. The health department is in the process of reporting to VAERS, but they want to know if this is being seen around the country and if they should do anything to work-up the patients. Both topics may also require collaboration with staff outside the CISA Project; the CDC-CISA clinical officers would coordinate that effort. Emergency calls that require CISA assistance during business hours will generally be assigned urgently to the day on-call person. Calls that come in after 5pm ET on weekdays or over the weekends or on holidays that cannot wait until the next business day will go to the night on-call CISA clinicians/physicians. They may be signed back over to the day on-call team in the morning or the night on-call clinicians/physicians may stay with the consult for continuity

3.4: Summary of Procedures for Responding to Requests for Consults

In the current CISA Project, three approaches are used to address vaccine safety requests for consult about a specific patient or vaccine safety clinical inquiries: 1. CISA Full Consultation; 2. CISA Mini Consultation; and 3. CISA enhanced inquiry response. These three ways of addressing complex vaccine safety consults and inquiries will be adapted to meet the needs of the COVID-19 vaccine safety response effort. CDC staff have started to review and update SOPs for these efforts. Details are beyond the scope of this work plan.

The 3 current methods are briefly summarized below, along with a short description of how the process may be adapted for use by **CISA COVIDvax** staff. When the **CISA COVIDvax** medical supervisor makes daily assignments, the inquiry response mechanism for review will be discussed. The goal of conducting (initiating) approximately 10 case consults per week through CISA **COVIDvax** anticipates that a mix of these methods will be used and that most will use the mini consult or enhanced inquiry approach. Some consults may require more than one mechanism. For example, a consult may need to be escalated from an enhanced inquiry response to a full review if the provider writes back with more detailed questions after receipt of the first email answering the inquiry. Regardless of the consult venue, the following applies: advice from CDC and CISA is meant to assist in decision-making, rather than provide direct patient management. Patient management decisions are the responsibility of the treating healthcare provider.

3.4.1: CISA Full Consultation

Current Routine non-COVID-19 CISA: In the routine CISA Project (non-COVID-19) activity, Vanderbilt (CISA lead site for clinical consultation) leads this effort, with technical input from CDC. A highly structured process is used to prepare a case for review on a CISA Work Group call (scheduled weekly). The calls have been described as a 'grand rounds' style teleconference. CISA experts across all the sites and the healthcare provider who requested the consultation are encouraged to join in the call. In addition, Vanderbilt obtains and reviews medical records, arranges for CISA site medical experts to join the call, and coordinates the call, minutes, and follow-up activities. A causality assessment is done using the CISA algorithm, for consults involving AEFI that occurred.[31] The healthcare provider is invited to the call and must agree to provide medical records and follow up information. The CDC medical lead for CISA clinical consultation activities is also highly involved in the content of the call and CDC provides review of VAERS data for use on the call. The call is conducted under a CDC Assurance of Confidentiality for the CISA Project.[32] A letter summarizing the call is sent out to the provider from Vanderbilt. Information about the case and follow-up is tracked in the Vanderbilt REDCap database. A CDC medical officer with an active U.S. medical license is required to be on the call. The time from receipt of the consult request to scheduling the call can be up to 3 months.

New CISA COVIDvax: Under the **CISA COVIDvax** it is expected that this Work Group process will still be used by the lead site for highly complex calls that require participation from multiple sites and experts. Some steps in the SOP may be shortened or removed for efficiency. Additionally, the contributing sites may provide heavier assistance. This forum may also be used to present several cases and discuss clinical themes or lessons or share follow-up outcomes data. It will generally continue to be held once a week, except for emergencies. For COVID-19 vaccine consults the response time goal will be within 1 month rather than 3 months. The routine non-COVID-19 processes and approach will also still be permissible under the **CISA COVIDvax**.

3.4.2: CISA Mini Consultation

Current Routine non-COVID-19: In the routine CISA work, Vanderbilt (CISA lead site for clinical consultation) leads this effort, with technical input from CDC. A structured process is used to prepare a case for review on a CISA WG-1 call (scheduled ad hoc). The mini consult calls include fewer experts than the full consult and can be scheduled more readily around the healthcare provider's (inquirer) schedule. The healthcare provider is invited to the call and must agree to provide medical records and follow up information. The CDC medical lead for CISA Clinical activities is also highly involved in the content of the call and CDC provides review of VAERS data for use on the call. A causality assessment is done using the CISA algorithm, for consults involving AEFI that occurred.[31] The call is conducted under a CDC Assurance of Confidentiality for the CISA Project.[29] A letter or email summarizing the call is sent out to the provider from Vanderbilt. Information about the case and follow-up is tracked in the Vanderbilt REDCap database. A CDC medical officer with an active U.S. medical license is required to be on the call. The time from receipt of the consult request to scheduling the call can be up to 3 months.

New CISA COVIDvax: Under **CISA COVIDvax** it is expected that this mini consultation process will be used by all sites participating in the day on-call pool. It will remain acceptable for Vanderbilt (lead site) to follow usual non-COVID-19 mini consult procedures. However, the following proposed changes are being implemented to make the process easier and allow contributing sites to lead mini consults; other changes may follow.

- All CISA site physicians in the call pool are anticipated to lead mini consults for consults that are on their assigned list. They may use their own site experts, if available. All sites will also have a coordinator to assist with this activity. The lead site coordinator may also be involved.
- While it is desired that a CDC medical officer participate in the mini consult call, this requirement may be removed to have more flexibility if there is high call volume. A CDC medical officer with a U.S. medical license should provide consultation for the case and back-up to CDC clinicians involved in the case as needed, but this person does not need to attend the call. Some steps in the process such as a VAERS review and detailed literature review, may be omitted if not clinically indicated.
- The mini consult may need to take place in a few stages. For example, if the on-call CDC medical officer (and CISA site physician if available) wants to call the provider requesting the consult to get information and then take some time to review the case with colleagues and schedule a follow-up call, that would be acceptable. Also, the causality assessment might be challenging for new investigators. It may be done as a second step, in consultation with more experienced CISA experts, if this is holding up case completion.
- The site conducting the mini consult should send out the email or letter to the provider. In **CISA COVIDvax** Vanderbilt will only have responsibility for sending communications for consults that they lead.
- For **CISA COVIDvax** consults, the response time goal will be within 2 weeks rather than 3 months.
- The contributing site that assessed the case will be responsible for securely obtaining and storing medical records and entering data about the case into the Vanderbilt REDCap database. Additional instructions about the data procedures will be provided by the lead site (Vanderbilt).
- The Contributing site that provided the consult will also lead the follow-up activities for assessing patient outcomes. The lead site (Vanderbilt) will provide assistance and training.

3.4.3: CISA Enhanced Inquiry Response

Current Routine non-COVID-19: The enhanced inquiry response is the shortest of the CISA consultation methods. It is also useful when the caller has a clinical question but is not directly taking care of a patient (such as from a health department) or when medical records are not needed or not available. As discussed above, ISO supports an Inquiry Response Program about vaccine safety for stakeholders, through the VAERS Project and Response Team (VPRT).[20] Staff from the ISO Inquiry Response Program receive inquiries from multiple sources (including CDC-INFO) and respond in an email to the inquirer. Some inquiries require additional clinical consultation and are referred to CISA for expert input. After the CISA Project team agrees to accept an enhanced inquiry, usually the CISA expert will review the inquiry and make suggestions on the response. CDC staff then incorporate this language into the inquiry response narrative, such as "an expert neurologist in the CISA Project reviewed the inquiry and provided this expert opinion…." The ISO-CDC staff review and approve the inquiry before it is sent out to the inquirer by the ISO inquiry service, through established procedures. The CISA-enhanced inquiries are not tracked in the Vanderbilt REDCap database. These inquiries are tracked by the ISO Inquiry Response Program.

New CISA COVIDvax: This process will be updated as needed to fit with any updated processes of the ISO inquiry response service. However, most elements are expected to be similar. It is expected that the **CISA COVIDvax** service could complete enhanced inquiries faster than mini consultations and a target goal for inquiry completion will be under 1 week. While the issue of causality may need to be considered to answer the inquiry, a formal CISA causality assessment is usually not provided.

3.4.4: Follow-up Activities for Patient Outcomes

An important function of the routine CISA clinical consultation service is to follow up with healthcare providers after the CISA consult to see if the provider followed the CISA guidance and to learn about outcomes of the patient. For example, if CISA advised to administer dose 2 COVID-19 vaccine to a patient that had a rash after dose one, it would be informative to see if the patient received the second dose and if they had any AEFI after vaccination. In the CISA process

for routine vaccine consultations, Vanderbilt obtains the follow-up for all consults. For the COVID-19 consultations, to the extent feasible, the CISA site that managed the COVID-19 clinical case review will also conduct follow-up to learn about the patient's outcomes. CDC-CISA clinicians will follow up on outcomes of enhanced inquires to the extent feasible to gain additional vaccine safety evidence.

3.5: Vaccine Safety Issues and Adjunct Scientific Functions

The current CISA Project clinical consulation activity for routine vaccines includes assessing vaccine safety issues, and this function will continue in **CISA COVIDvax**. There are many forms of vaccine safety issue assignments. For example, CISA reviewed vaccine safety issues that came up during a use of meningococcal B vaccines under an expanded access investigational new drug (IND) protocol at college campuses.[32] Possible issues arising in the COVID-19 response could include assisting ISO, CDC or the Advisory Committee on Immunization Practices (ACIP) evaluate a new safety issue. The CISA sites might review the literature and existing data about a vaccine safety topic and provide expert opinions. **CISA COVIDvax** staff might be asked to review a complex VAERS report. One example of an adjunct scientific function might be participating in a discussion about CISA research or serving as an expert on a safety review panel for a CISA Project clinical research study about COVID-19 vaccine safety. Conducting clinical research is not part of the **CISA COVIDvax** activity and is covered under the research arm of the CISA Project.

3.6: Education and Training

Training and education are an important part of **CISA COVIDvax**. Clinicians at CISA sites with less experience leading CISA case consultations and CDC clinical officers new to CISA, need a quick way to get up to speed and work with the more experienced CISA investigators. Staff at CDC and CISA sites have started training for the **CISA COVIDvax** activities to ensure consistent processes and quality across all the on-call clinicians. **CISA COVIDvax** staff are developing training and education materials for their use and educational meetings are taking place. Ideally the staff will complete as much training as possible before COVID-19 vaccines are available. **CISA COVIDvax** staff are using influenza vaccine safety and other vaccine safety inquiries to practice conducting enhanced inquiries and case consultations and to test the

usefulness of the SOPs and training material. Staff may also consider mock COVID-19 clinical inquiry scenarios for training. After the actual COVID-19 vaccine safety consults have started, information learned from one or two complex inquiries might be relevant to future inquiries, and there might be standard approaches to evaluating certain types cases. **CISA COVIDvax** staff will contribute to updating education materials. As the service accumulates clinical expertise for COVID-19 vaccine safety, **CISA COVIDvax** staff may also contribute to CDC vaccine safety guidance, and educational materials for use by other CDC units in the response (such as the ISO Inquiry Response Program) or for the broader clinical community. Manuscripts and reports may also be considered to describe the work and clinical lessons learned.

3.7: CISA Database Functions

Under the routine CISA Project clinical consultation activity the Vanderbilt CISA lead site maintains a FISMA* moderate secure REDCap database.[29] The main function of the Vanderbilt database is to track clinical information for each full or mini clinical case consult, including the follow-up activities. As noted above, each CISA site participating in the **CISA COVIDvax** on-call consultation functions will be responsible for entering data from each completed consultation into the Vanderbilt REDCap database. Remote access to REDCap and training in access and data entry to the Vanderbilt REDCap database will be provided. Vanderbilt and CDC will have access to the data to run queries and reports. Vanderbilt will have staff with data management experience and will have capacity to generate daily, weekly, and ad hoc reports of CISA data as needed. CDC also needs ready access to the data off hours to help address vaccine safety emergencies or requests from leadership. In addition, reviewing data may be helpful to inform review of clinical consults, for example to see what happened to a patient with a similar situation. CDC will track COVID-19 vaccine safety inquiries that ISO receives, including CISA Project consult requests, in a separate CDC REDCap database. The CDC database will contain less clinical detail than the Vanderbilt database, but will also contain summaries of some clinical inquiry responses, such as

* Federal Information Security Management Act

the enhanced inquiry responses described above, that are not included in the Vanderbilt database. The CDC database may be useful for tracking themes of the clinical inquiries about vaccine safety, and numbers of inquiries completed.

3.8: Coordination Functions

CDC and CISA sites will have coordinators to assist the medical on-call staff with their clinical consultation activities. Coordinator functions will include tracking cases and progress, securely obtaining and storing medical records, scheduling meetings with physicians and other healthcare providers in need of consultation and scheduling other coordination meetings. Coordinators at the CISA sites may also enter data into the Vanderbilt REDCap database. The coordinator(s) at the lead CISA site (Vanderbilt) will coordinate the daily morning sign-in calls during the weekdays. The CDC **CISA COVIDvax** coordinator(s) will provide operational support to the CDC **CISA COVIDvax** Unit, including coordinating the schedules. They will also contribute to CDC data management activities for COVID-19 inquiries and the coordinators may have access to the Vanderbilt REDCap database. Coordinators may also help the lead medical staff with securely receiving medical records, conducting literature reviews, or supporting other technical assignments. As noted above, the CDC-CISA team has operational responsibility for assigning the day and night on-call schedule and facilitating communications with the CDC Emergency Operations Center staff about CDC on-call coverage for **CISA COVIDvax**.

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