Protocol

Protocol for: Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. N Engl J Med 2023;388:2434-43. DOI: 10.1056/NEJMoa2215201

This trial protocol has been provided by the authors to give readers additional information about the work.

Supplement

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes

2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Original protocol: October 6, 2022

STUDY TRACKING AND REPORTING SYSTEM (STARS)
PROJECT DETERMINATION

Step 1: Project Description

Step 2: Regulation and Policy

Step 3: Funding Information

Step 4: External institution(s)

Step 5: Data Management Plan/Spatiality Information

STEP 1: PROJECT DESCRIPTION

Project Description Information

- **Project Title [150 characters max]:** Vaccine Effectiveness of JYNNEOS Against Symptomatic MPX Illness Using Electronic Health Record Data, 2022

- **Anticipated Start and Completion Dates:** October 17, 2022–December 31, 2022

- **Select the Priority of the project.**
  - ☐ Standard
  - ☒ Urgent
    - If 'Urgent,' Date Needed? October 14, 2022
    - Justification for "Urgent" priority: Key vaccine effectiveness project in the CDC Multi-National Monkeypox Response 2022

- **Provide Description of Project:**
  [3500 characters max. A short, clear description with sufficient detail to enable a reader to quickly understand whether the project or data set is of interest to them.]

From May 17, 2022, to September 30, 2022, >26,000 cases of confirmed or probable monkeypox (MPX) have been reported in the United States. Monkeypox infections can be acquired through close, sustained physical contact by all people, regardless of gender identity or sexual orientation. However, the current outbreak has disproportionally affected gay, bisexual, and other men who have sex with men (MSM) and transgender women.

JYNNEOS™, the Modified Vaccinia Ankara (MVA) vaccine, was approved in 2019 for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox.

On August 9, 2022, FDA issued an emergency use authorization (EUA) that allows healthcare providers to use the JYNNEOS vaccine by intradermal injection to increase the total number of doses available during the 2022 monkeypox outbreak.

CDC recommends vaccination with the JYNNEOS MPX and smallpox vaccine for people who have been exposed to MPX and certain people who may be more likely to get MPX. In support of this recommendation, CDC intends to estimate the effectiveness of the vaccine. This analysis aims to measure how well MPX vaccination protects people against symptomatic MPX infections under real-world conditions. This project is a proposed analysis of routinely collected electronic health record data included in COSMOS, a platform that allows EPIC investigators to analyze a dataset representing 162 million patients. CDC's role is to consult on the analysis and to contribute to writing. This project will examine the association of vaccination with JYNNEOS on symptomatic monkeypox by number of doses, dosing interval, immunocompromised status, age, route of administration, clinical endpoints. These data will provide actionable information to clinicians and the public health community on JYNNEOS vaccine for the prevention of monkeypox. This evaluation compliments other ongoing U.S. government efforts and is not duplicative.

Identifying a Project Associated with an IMS Activation and Type of Response

Note: COVID-19 related Projects and Funding should select 2019 Novel Coronavirus Response.

- **Is this submission associated with an IMS activation, Center, Institute or Office (CIO) Emergency Response, Epi-Aid (may or may not be associated with an IMS or CIO Emergency Response), or Assessment of Chemical Exposure (ACE).**
  - ☒ Yes
  - ☐ No

- **If 'Yes', provide type(s) of response and name(s):** _ Emergency Response: CDC Multi-National Monkeypox Response 2022_____

  Name of CIO: National Center for Immunization and Respiratory Diseases
  Name of the Epi-Aid: _____

  Name of Assessment of Chemical Exposure: _____

Primary Priority Related to the Project or Funding

- Select only one from the list below:
  - ☐ Transmission of SARS-CoV-2
  - ☐ Protection of healthcare personnel and patients
  - ☐ Natural history of SARS-CoV-2 infection
  - ☐ COVID-19 disease detection, burden, and impact
  - ☒ Prevention, mitigation, and intervention strategies
  - ☐ Social, behavioral, and communication science
  - ☐ Other Scientific Topic (If selected, the system requires a value for other)

  - ☐ Not Associated with a Scientific Topic

- **Indicate secondary priorities selections if appropriate.**
  If appropriate, select all that apply from the list below:

☐ Transmission of SARS-CoV-2
☐ Protection of healthcare personnel and patients
☐ Natural history of SARS-CoV-2 infection
☐ COVID-19 disease detection, burden, and impact
☐ Prevention, mitigation, and intervention strategies
☒ Social, behavioral, and communication science
☐ Other Scientific Topic

- **Task Forces Associated with Project**
  If appropriate, indicate Task Forces associated with the project.
  ☐ Chief Medical Officer Unit
  ☐ Community Interventions and Critical Populations
  ☐ Data, Analytics, and Modeling
  ☐ Epidemiology and Surveillance
  ☐ Global Migration
  ☐ Health Systems and Worker Safety
  ☐ International
  ☐ Joint Information Center (JIC)
  ☐ Laboratory and Testing
  ☐ STLT
  ☒ Vaccine Task Force
  ☐ Not Applicable

Goals/Purposes

- **Briefly describe the purpose of the project and how it addresses needs or priorities.**
  [3500 characters max]

  The goal of this project is to use a large electronic health record database to better understand vaccine effectiveness of JYNNEOS vaccine against symptomatic monkeypox infection. This could have important policy impact, including on recommendations for the use of JYNNEOS vaccine. There is limited information on the real-world vaccine effectiveness of JYNNEOS vaccine against symptomatic monkeypox by age, route of administration and dosing interval. The goal of this study is to help close that knowledge gap.

Objective(s)

- **Describe the specific objectives of the project and indicate if/how they relate to a public health emergency, or vaccines and immunization activities.**
  [3500 characters max]

Primary:

1. To estimate the effectiveness of JYNNEOS MPX vaccine in preventing laboratory-confirmed or probable symptomatic MPX infection.

Secondary (if statistically powered):

2. To estimate vaccine effectiveness by other factors of public health importance:
   - route of administration (subcutaneous vs. intradermal)
   - number of doses

- interval between doses
- age groups
- immunocompromised status
- clinical endpoints

Health Equity Questions

- Does this project include interventions, services, or policy change work aimed at improving the health of groups who have been excluded or marginalized and/or decreasing disparities?
  - ☒ Yes
  - ☐ No

Elements of Health Equity Science

- In what ways does this project incorporate elements of health equity science?
  [Select all that apply. A Minimum of one selection is required.]

☐ Project does not incorporate elements of health equity science. *[Note: If this item is selected, the system will not allow any other health equity selection as they do not apply.]*

☐ Measuring Disparities: Measuring or documenting one or more health disparities (in absolute and/or relative terms) or their change over time.

☐ Studying Social Determinants of Health (SDOH): Studying, measuring, or evaluating social determinants of health or their change over time (check all that apply)

☒ Assessing impact: Assessing the effectiveness or impact interventions, policies, programs, system or environment changes have on the health of groups that have been excluded or marginalized, or on social determinants of health (other than process evaluation)

☐ Methods to improve health equity research and practice: For example, developing methods, instruments, or other innovations to advance progress towards health equity or improve measurement of social determinants of health

☐ Other (Please summarize, e.g., economic analysis, ethical analysis, formative research)

_____

_____

Studying Social Determinants of Health (SDOH)

- In what ways does this project incorporate elements of health equity science?
  [Check all that apply. Minimum of one selection is required.]

☐ Economic Stability (e.g., Employment, Income, Wealth, Food Security, Housing Stability and Homelessness, Poverty).

☐ Education (All levels of education including Early Childhood Education and Development, also Language and Literacy)

☐ Health Care Access (e.g., Access to Health Care (including Insurance), Access to Primary Care, Health Literacy)

☐ Neighborhood and Environment (e.g., Access to Healthy Foods, Crime and Violence, Environmental and Climate Conditions, Housing Quality, Access to Broadband)

☐ Social and Community Context (Other characteristics of contexts within which people live, learn, work, and play. Examples include Discrimination (including Racism), Civic Participation, Incarceration, Social Cohesion, Workplace Conditions).

☐ Indices of SDOH (Measures that attempt to aggregate and quantify multiple social determinants of health). Specify determinants addressed [3500 characters max]:

_____

_____

☐ Other SDOH topics (SDOH-related areas that do not neatly in the above categories [3500 characters max]: _____

_____

☒ Assessing Impact: Assessing the effectiveness or impact interventions, policies, programs, system or environment changes have on health of groups that have been excluded or marginalized, or on social determinants of health (other than process evaluation).

☐ Methods to improve health equity research and practice: For example, developing methods, instruments, or other innovations to advance progress towards health equity or improve measurement of social determinants of health.

☐ Other (Please summarize. E.g., economic analysis, ethical analysis, formative research):

_____

_____

Working with Outside Institutions

- Will you be working with an outside Organization or Institution?
  - ☒ Yes
  - ☐ No

Submitting to the IRB Office

- Do you anticipate this project will be submitted to the IRB Office?
  - ☐ Yes [If "Yes", Step 2-Policy & Regulation will follow after Step 1 is completed.]
  - ☒ No [If "No", then Step-2-Policy & Regulation is not required.]

Data

- Will the project be collecting, generating, obtaining, or transferring data?
  - ☐ Yes
  - ☒ No

Activities or Tasks

- Select all activities or tasks applicable to this project.

☐ New collection of information, data, or biospecimens
☒ Secondary data or specimen analysis
☐ Purchase, use, or transfer of information, data biospecimens or materials
☐ Research with humans
☐ Activity involving live vertebrate animals
☐ All work onsite at CDC facilities
☐ Programmatic work

Target Populations (Required)

- Select **all** target population(s) included/represented. Use the Population Guidance link (Population (cdc.gov) to view the population(s), definition(s), and source(s) for the population categories

X	**Check all that apply**		
	Adult 18-24 years		Impaired hearing or deaf
	American Indian or Alaska Native		Impaired mental
	Asian		Impaired physical
	Black or African American		International
	Businesses		Male
	Children		Native Hawaiian or Other Pacific Islander
	Older adults >64 years		Neonates
	Emancipated Minor		No human population
	Farmers		Other
	Females		Patient
	Fetuses		Pregnant women
X	General US Population		Prisoners
	Healthcare providers		Transgender
	Hispanic or Latino		White
	Immigrants or Refugees		Other (Describe):

Tags/Key Words

- **Provide tags/keywords under which the project could be indexed, cataloged, or searched under in biomedical and health-related databases such as MEDLINE/PubMed, NLM Catalog, etc. Examples might include population surveillance, communicable diseases, behavioral symptoms, sleep disturbances.**

  Monkeypox, MPX, vaccine effectiveness

CDC's Role

- **Describe the nature of CDC's involvement to include funding, technical assistance, development of concept, protocol, information collection instruments, data management, etc. Indicate whether the CDC has final decision authority over the project.**
  - ☒ Activity originated and designed by CDC staff, or conducted at the specific request of CDC, or CDC staff will approve study design and data collection
  - ☒ CDC employees will provide substantial technical assistance or oversight

☐ Activity originated and designed by CDC staff, or conducted at the specific request of CDC, or CDC staff will approve study design and data collection as a condition of any funding provided.
☐ Activity originated and designed by non-CDC staff (awardee or external collaborator)
☐ CDC employees or agents will obtain data by intervening or interacting with participants
☐ CDC employees or agents will obtain or use anonymous or unlinked data or biological specimens
☐ CDC employees or agents will obtain or use identifiable (including coded) private data or biological specimens
☒ CDC employees will participate as co-authors in presentation(s) or publications.
☒ OTHER (Describe):

_____CDC will not be receiving any data with PII.
_____

_____

_____

Method Categories

- **Select the Method Categories. This is the approach and plan to meet the objectives such as interventions, procedures, screening, etc. Multiple selections can be made.**

☐ Discussion Group
☐ Exposure Investigation
☐ Focus Group
☐ Genetic Sequencing
☐ Health Consultation
☐ Health Education
☐ Hybrid Study Design
☐ Individual Interviews (Qualitative)
☒ *Other:* Secondary data analysis

Methods

- **Describe the approach and plan to meet the objectives such as interventions, procedures, target population and respondent recruitment, screening and enrollment.**
- **Provide information to describe steps taken to ensure the quality of the project and if applicable, whether a review of the proposed statistical methods has been completed.**
- **3500 characters maximum**

A matched case-control design will be used, with cases individually matched (1:4) by calendar week of diagnosis, HHS region, and gender identify. Cases will be defined as individuals with MPX diagnosis and a documented in-person encounter between August 15, 2022 and September 30, 2022, and at least 2 in-person encounters in the prior 3 years. Controls will be individuals with a syphilis diagnosis, documented in-person encounter between August 15, 2022, and September 30, 2022, and at least 2 in-person encounters in the prior 3 years. Cases and controls will be identified by Epic Systems.

CDC is providing technical assistance to Epic Systems, a provider of electronic healthcare software for healthcare systems or facilities in all 50 U.S. states and the District of Columbia. Epic investigators analyze limited healthcare data using a data platform (COSMOS) and do not have access to identifiable health information. Aggregate summaries are produced from these analyses that can be used in reports and presentations. Epic investigators identify cases and controls, and then can analyze characteristics associated with receipt of JYNNEOS vaccination and monkeypox infection. Characteristics include vaccination, age, sex, race, ethnicity, social vulnerability index, underlying health condition categories, geographic region, and outpatient encounter type (e.g., televisit, in-person visit).

Information, Data, or Bio-specimens collection

- **Explain how information, data, or bio-specimens will be collected. Information refers to facts, statistics, opinions, observations and biological or genetic material provided or learned about human persons.**
- **Identify each collection activity for this project.**
- **Describe who the information will be collected from and what personally identifiable information will be used for the related activities.**
- **Provide information on the estimated burden (in hours) to respondents for each data collection activity proposed.**
- **3,500 characters max**

A data platform (COSMOS) allows Epic investigators to remotely analyze Epic data from participating health systems or facilities without directly accessing the limited data themselves. Epic investigators report that the data accessed and used by Cosmos users in their research activities were considered not to meet the definition of identifiable private information as defined at 45 CFR 46.102(f)(2). CDC only receives aggregate reports without identifiable data that can be used for presentations and publications.

Expected Use of Findings/Results and their Impact

- **Enter the expected use of findings/results and their impact.**
- **Describe how the information will be used and the results disseminated, including plans for peer-reviewed publication, conference presentations and/or web postings.**
- **3,500 characters max**

This project will estimate the effectiveness of JYNNEOS MPX vaccine in preventing MPX infection. If sufficiently powered, this project will also identify differences in effectiveness by number of doses, route of administration, interval between first and second dose, and by immunocompromised status, as well as against different clinical endpoints (e.g., hospitalization). Estimating the effectiveness of JYNNEOS vaccine in preventing symptomatic MPX infection by key strata will inform national JYNNEOS vaccine recommendations and outbreak response activities.

Findings will be disseminated to the scientific community in the form of CDC webpages, published papers and presentations at scientific conferences. No information with personally identifying information will be released in the form of a report or publication.

CDC/ATSDR HRPO/IRB Protocol Number & OMB Control #

- If available, provide the CDC/ATSDR HRPO/IRB Protocol # if this has a Protocol #: _____
- If available, provide the OMB Control # if this has a Control #: _____

Personally Identifiable Information (PII)

- Could individuals potentially be identified based on Information collected?
  - ☐ Yes
  - ☒ No

    If "Yes", Will PII be captured (including coded data)? Will the project collect, store, or transmit Personal Identifying information (PII) that can be used on its own or with other information to identify, contact, or locate a single person, or to identify an individual in context? This includes information in control of outside CDC partners and contractors.

    - ☐ Yes
    - ☒ No

    Does CDC have access to the identifiers (including coded data)?

    - ☐ Yes
    - ☒ No

Assurance of Confidentiality & Certificate of Confidentiality

- Is the project covered by an Assurance of Confidentiality? See the following link for guidance: Assurances of Confidentiality (cdc.gov).
  - ☐ Yes
  - ☒ No

- Does this activity meet the criteria for a Certificate of Confidentiality (CoC)? See the following link for guidance: Certificates of Confidentiality (cdc.gov).
  - ☐ Yes
  - ☒ No

- If the activity meets the CoC criteria, has the required language for the Certificate of Confidentiality been incorporated into the Protocol and/or Consent Form?
  - ☐ Yes
  - ☒ No

Formal Written Agreement

- Is there a formal written agreement prohibiting the release of identifiers?
  Is an agreement in place to prevent information from being disclosed to others which serves as a non-disclosure of identifiers (e.g., Key Agreement, Material Transfer Agreement, Technical Assistance Letter, Memorandum of Understanding, Data Use Agreement, Form 0.1375A, Form 0.1375B, etc.)?

  - ☐ Yes (If 'Yes', provide/upload the formal written agreement)
  - ☒ No

STEP 2: REGULATION AND POLICY – PROTOCOL INFORMATION

Regulation and Policy - IRB Office

- Do you anticipate this project will be submitted to the IRB Office? [This item was previously addressed in Step 1.]

  ☐ Yes [If "Yes", then Step 2-Policy & Regulation is required.]
  ☒ No [If "No", then Step-2-Policy & Regulation is not required. Skip to Section 3-Funding Information.]

Number of Study Participants, Populations Included

- Estimated # of study participants: _____0_____
  Report estimated counts rather than percentages.
  Include study subjects at domestic and foreign sites.

- Select ("x") the extent to which the following population(s) will be included, and the page # in the protocol if applicable.

  Children: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Minors: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Prisoners: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Pregnant Women: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Emancipated Minors: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

Suggested Level of Risk to Subjects

- Suggest level of risk to subjects:
  ☐ Minimal
  ☐ Greater than minimal

  NOTE: Select "Minimal" when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The definition varies slightly for research involving prisoners.

  NOTE: Select "Greater than Minimal" when the probability and magnitude of harm or discomfort anticipated in the proposed research are greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Any disclosure of illegal activities, sexual attitudes, genetics, religious beliefs, mental health that could place participants at risk of criminal or civil liability, be

damaging to the participants financial standing, employability, insurability, reputation, or be stigmatizing.

Exempt or Non-Exempt Research

- Do you anticipate this project will be exempt research or non-exempt research?
  - ☐ Exempt
  - ☐ Non-Exempt

- Select each category and the applicable options for all that apply to the protocol.
  Each option is also presented further below with details and information that appear in STARS.
  - ☐ Educational Practices
  - ☐ Educational Tests, Surveys, Interviews, or Observation of Public Behavior
  - ☐ Benign Behavioral Interventions and Collection of Information
  - ☐ Secondary Research for which Consent is not Required
  - ☐ Research and Demonstration Projects
  - ☐ Taste and Food Quality Evaluation and Consumer Acceptance Studies
  - ☐ Storage or Maintenance for Secondary Use for which Broad Consent is Required
  - ☐ Secondary Research for Which Broad Consent is Required

  NOTE:
  - Studies may be exempt from review when human participants conform to one of the categories from section 46.101(b) of 45 CFR 46.
  - Research may qualify for Exempt status if it involves very minimal or no risk.
  - Projects will not be given Exempt status if they include any degree of deception, involve more than very minimal risk to participants, involve sensitive information, or include protected classes or vulnerable populations.
  - Please note that researchers must always engage in practices that ensure privacy and that minimize the risks to participants, regardless of the level of review.

Exempt Research Category 1: Educational Practices

- If “Exempt” was selected above, check if the following applies:
  - ☐ Category 1: Educational Practices:
    - Normal educational practices in commonly accepted education settings.

    NOTE: Category 1: Educational Practices 45 CRF 46.104(d)(1) Research in Established or Commonly Accepted Education Settings that Involves Normal Educational Practices and Not likely to Adversely Impact Students' Opportunity to Learn or Assessment of Educator

Exempt Research Category 2: Educational Tests, Surveys, Interviews, or Observation of Public Behavior

- If “Exempt” was selected above, check if the following applies:
  - ☐ Educational tests, surveys, interviews, or observation of public behavior

- At least one of the criteria below must be met:
  - ☐ Recorded in such a manner that identity cannot readily be ascertained

☐ Disclosure outside the research would not reasonably place subjects at risk of liability or be damaging

☐ Adults only, identity can readily be ascertained

NOTE:
Category 2: Educational tests, surveys, interviews, or observation of public behavior 45 CFR 46.104(d)(2) Research only includes Educational Tests, Surveys, Interviews, Public Observation and Not Likely to Adversely Impact Students' Opportunity to Learn or Assessment of Educators if at least ONE of the following criteria met: (i) Recorded information cannot readily identify the subject (directly or indirectly/linked); Surveys & Interviews: No Children; Educational Tests or Observation of Public Behavior: Can Only include Children when Investigators Do Not participate in activities being observed OR (ii) Any disclosure of responses outside of the research would NOT reasonably place subject at risk (criminal, civil liability, financial, employability, educational advancement, reputation); Surveys & Interviews: No Children; Educational Tests or Observation of Public Behavior: Can Only include Children When Investigators Do Not Participate in Activities being Observed OR (iii) Information is recorded with identifiers & IRB conducts Limited Review; NO Children

Exempt Research Category 3: Benign Behavioral Interventions and Collection of Information

- If "Exempt" was selected above, check if the following applies:
  ☐ Benign Behavioral Interventions and Collection of Information

- Category 3: Benign Behavioral Interventions and Collection of Information:
  ☐ Information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot be readily ascertained directly or through identifiers linked to subjects.
  ☐ Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement or reputation
  ☐ Information obtained is recorded by the investigator in such a manner that the identity of human subjects can readily be ascertained directly or through identifiers linked to the subjects; Research involves deceiving the subjects regarding the nature or purposes of the research; Subject authorizes the deception through prospective agreement.

  NOTE:
  Category 3: Benign Behavioral Interventions and Collection of Information - 45 CRF 46.104(d)(3) Research involving Benign Behavioral Interventions through verbal, written responses, (including data entry or audiovisual recording) from adult subject who prospectively agrees and ONE of following met: May Not include Medical Interventions; Subject prospectively agrees (ii) Benign Behavioral Interventions must be: Brief in Duration, Painless/Harmless, Not Physically Invasive, Not Likely to Have a Significant Adverse Lasting Impact on Subjects, Unlikely that Subjects Will Find Interventions Offensive or Embarrassing (iii)No deception unless participant prospectively agrees. Recorded information cannot readily identify the subject (directly or indirectly/linked); ORB. Any disclosure of responses outside of the research would NOT reasonably place subject at risk (criminal, civil liability, financial, employability, educational advancement, reputation); ORC. Information is recorded with identifiers & IRB conducts Limited Review

Exempt Research Category 4: Secondary Research for which consent is not Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Secondary Research for Which Consent is Not Required

- Category 4: Secondary Research for Which Consent is Not Required
  - ☐ Identifiable private information or identifiable biospecimens are publicly available
  - ☐ Information, which may include information about biospecimens, recorded by investigator such that the identity of human subjects cannot readily be ascertained; Investigator does not contact subjects, and investigator will not re-identify subjects
  - ☐ Research use of identifiable health information which that use is regulated by HIPAA as health care operations, research or public health activities and purposes as those terms are defined in HIPAA
  - ☐ The research is conducted b, or on behalf of, a federal department or agency using government generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with applicable with applicable federal privacy standards found in the E-Government act, Privacy Act and the Paperwork Reduction Act.

NOTE:
Category 4, Secondary Research for which Consent is not Required **-** 45 CFR 46.104(d)(8) Secondary Research for Which Consent is Not Required: Use of Identifiable Information or Identifiable Biospecimen that have been or will be collected for some other 'primary' or 'initial' activity, if ONE of following criteria met: No Primary Collection from subjects for the research; Allows Both Retrospective and Prospective Secondary Use.(i) Biospecimens or Information is Publicly Available; OR(ii) Information recorded so subject cannot readily be identified (directly or indirectly/linked); Investigator does not contact subjects and will not re-identify the subjects; OR(iii) Collection and Analysis involving Investigators Use of Identifiable Health Information when use is regulated by HIPAA "health care operations" or "research" or "public health activities and purposes"; OR(iv) Research information collected by or on behalf of federal government using government generated or collected information obtained for non-research activities.

Exempt Research Category 5: Research and Demonstration Projects

- If "Exempt" was selected above, check if the following applies:
  - ☐ Research and Demonstration Projects

- Check if applicable:
  - ☐ Conducted or supported by a federal department or agency, or otherwise subject to the approval of department or agency heads designed to study, evaluate, improve or otherwise examine public benefit or service program

    NOTE:
    Category 5, Research and Demonstration Projects - 45 CFR 46.104(d)(5) Research and demonstration projects supported by a Federal Agency/Dept. AND Designed to study, public

benefit or service programs. Must be posted on a Federal Web Site. Federal website that will satisfy the consent form posting requirement: ClinicalTrials.gov

Exempt Research Category 6: Taste and Food Quality Evaluation and Consumer Acceptance Studies

- If "Exempt" was selected above, check if the following applies:
  - ☐ Taste and Food Quality Evaluation and Consumer Acceptance Studies
- Check if applicable:
  - ☐ Foods that are wholesome without additives
  - ☐ If a food is consumed that contains food ingredient at or below the level and for use found to be safe, or agricultural chemical or environmental contaminant at or below level food to be safe, by FDA or approved by EPA or Food Safety and Inspection Service of USDA.

Exempt Research Category 7: Storage or Maintenance for Secondary Use for which Broad Consent is Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Storage or Maintenance for Secondary Use for which Broad Consent is Required
- Check if applicable:
  - ☐ Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use

    NOTE:
    Category 7: 45 CFR 46.104(d)(7) Storage or Maintenance of Identifiable Private Information or Identifiable Biospecimens for Secondary Research which Broad Consent is required. Limited IRB review required under S46.111(a)(8).

Exempt Research Category 8: Secondary Research for Which Broad Consent is Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Secondary Research for Which Broad Consent is Required
- Check if applicable:
  - ☐ Broad consent for storage, maintenance and secondary research use of identifiable private information or identifiable biospecimens was obtained.

    NOTE:
    Category 8: 45 CFR 46.104(d)(8) Secondary research involving use of Identifiable Private Information or Identifiable Biospecimens for which Broad Consent was Required Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens was obtained in accordance with S46.116(a)(1) through (4), (a)(6) and (d)[S46.104(8) (i)]. Limited IRB review required under S46.111(a)(8). Note 1: [S46.104(8)(ii)] Documentation of informed consent or waiver of documentation of consent was obtained in accordance with S46.117 Note 2: [S46.104(8) (iv)] Investigator does not include returning individual research results to subjects as part of the study plan

Non-Exempt Research*

- Do you anticipate this project will be exempt research or non-exempt research? This item was also addressed above.
  - ☐ Exempt
  - ☐ Non-Exempt

  NOTE:
  Select **Non-Exempt** for any proposed research not qualifying for Exempt Research status requires IRB members review and vote on the proposal. These typically involve projects that place human subjects at more than minimal risk, or that involve sensitive topics or vulnerable populations such as prisoners, terminally ill patients, children, veterans, or cognitively impaired persons.

  A proposal that does not fulfill the criteria for Exempt status may undergo an Expedited review if it involves no more than minimal risk to the participants and meets other standards, such as not including protected classes or vulnerable populations, and not using intentional deception.

  If Non-exempt Research was selected, address the following as they pertain to Informed Consent, Clinical Trial and Other Considerations.

Non-Exempt Research/Informed Consent

- Check all that apply. Characterize requested changes to required features of the informed consent process. If a waiver is requested, enter the page number of the protocol where the waiver is justified:
  - ☐ Waiver or alteration of elements of informed consent for adults: Page # ____
  - ☐ Waiver of assent for children capable of providing assent: Page # ____
  - ☐ Waiver of parental permission: Page # ____
  - ☐ Waiver or alteration or authorization under HIPAA Privacy Rule: Page # ____

  NOTE:
  Which waivers to the consent process are requested: IRB may waive or alter the requirement of informed consent under 45 CFR 46.116(d), provided all the following four conditions are met: 1. research involves no more than minimal risk, 2. not adversely affect the rights and welfare, 3. research could not practicably be carried out without the waiver or alteration, and 4. subjects are provided with additional pertinent information after participation. Public benefit or service programs: 45 CFR 46.116(c). Research in emergency settings: 45 CFR 46.101(i). If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Non-Exempt Research/Informed Consent

- Which waivers to documentation of informed consent are requested?
  - ☐ Waiver of documentation of informed consent for adults: Page # ____
  - ☐ Waiver of documentation of assent for children capable of providing assent: Page # ____
  - ☐ Waiver of documentation of parental permission: Page # ____

  NOTE:

Which waivers to documentation of informed consent are requested? Potential participants, or the parents of children who are potential participants, are presented (either verbally or in writing) with the same information required in a written consent document, but documentation of the process (signing of the consent form) has been waived by the IRB. The FDA has not adopted this category so it cannot be used if the research is subject to the FDA regulations 21 CFR 50. If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Non-Exempt Research/Informed Consent

- How is it shown that the consent process is in understandable language?
  - ☐ Reading level has been estimated: Page # ____
  - ☐ Comprehension tool is provided: Page # ____
  - ☐ Short form is provided: Page # ____
  - ☐ Translation planned or performed: Page # ____
    - ☐ Certified translation/translator: Page # ____
    - ☐ Translation and back-translation to/from target language(s): Page # ____
    - ☐ Other Method: Page # ____
      Describe "Other Method": _____
      _____
      _____

NOTE: How is it shown that the consent process is in understandable language? Consent process in understandable language regulations are 45 CFR 46.116 and 45 CFR 46.117 and/or FDA regulations 21 CFR 50.25 and 21 CFR 50.27 apply. Subjects must be provided with both 1. A written consent document in a language understandable to them AND 2. An interpreter fluent in both English and the participant's spoken language to aid in the consent process. If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Regulation and Policy – Non-Exempt Research/Clinical Trial

- Clinical Trial - Check all that apply.
  - ☐ Does the study involve human participants?
  - ☐ Are the participants prospectively assigned to an intervention?
  - ☐ Is the study designed to evaluate the effect of the intervention on the participant?
  - ☐ Is the effect being evaluated a health-related biomedical or behavioral outcome?
  - ☐ This study is a registrable clinical trial. NOTE: If the study is a registrable clinical trial, enter the ID and/or select the ClinicalTrials.gov link to the route to the U.S. National Library of Medicine ClinicalTrials.gov for additional information.

    NOTE:
    1) 45 CFR 46.102(b) Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. 2) 45 CFR 46.102(e)(1) Human subject means a living individual

about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. 3) 45 CFR 46.102(2) Intervention includes both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. If the answer to any one of these questions is yes, then a Certificate of Confidentiality will apply to the research per subsection 301(d) of the Public Health Service Act. If you check all, then the study meets the definition of a clinical trial.

Non-Exempt Research/Other Considerations

- Other Considerations - Check all that apply.
  - ☐ Exception is requested to PHS, informing those tested about HIV serostatus: Protocol Page # _____
  - ☐ Human genetic testing is planned now or in the future.
  - ☐ This study involves long-term storage of identifiable biological specimens.
  - ☐ This study involves a drug, biologic, or device.
  - ☐ This study will be conducted under an Investigational New Drug (IND) exemption or Investigational Device Exemption (IDE).
    IND/IDE #: _____

NOTE:
1) 45 CFR 46.102(b) Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. 2) 45 CFR 46.102(e)(1) Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. 3) 45 CFR 46.102(2) Intervention includes both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. If the answer to any one of these questions is yes, then a Certificate of Confidentiality will apply to the research per subsection 301(d) of the Public Health Service Act. If you check all, then the study meets the definition of a clinical trial.

STEP 3: FUNDING INFORMATION

Step 3: Funding

- **This step is designed to capture funding details associated with this project. If the project does not have any associated funding, select next to advance to Step 4.**
- **Items will include the following: Funding Type, Funding Title, Funding Number, Original Fiscal Year, Number of Years of Award, and Budget Amount**

- **NOTE: This step is designed to capture funding details associated with this project. If the project does not have any associated funding, select next to advance to Step 4.**

Funding – Funding Type and Title

- Select the Funding Type (Select one):
  - ☐ CDC Contract
  - ☐ CDC Cooperative Agreement
  - ☐ CDC Funding Intramural
  - ☐ CDC Grant
  - ☐ Cooperative Research and Development Agreement
  - ☐ FDA Funding
  - ☐ Funding from Another CIO
  - ☐ Gift
  - ☐ IMS Response
  - ☐ Other Federal Funding
  - ☐ Technical Assist-CDC Not Reimbursed
  - ☐ Technical Assist-CDC Reimbursed
  - ☐ Other (Specify): _____

- Funding Title (255 Characters):

- Funding #: _____
  [This is the award number assigned to the project (i.e., the NOFO number for a cooperative agreement, the contract number for a contract, or the spend plan unique ID for the IMS Response.]

- Original Fiscal Year: _____

- Number of Years of Award: _____

- Budget Amount: _____

STEP 4: EXTERNAL INSTITUTION(S)

Step 4: Adding Outside Organizations & Institutions

This section should be completed if "Yes" was the response for the following:

- Will you be working with an outside Organization or Institution?
  - ☒ Yes
  - ☐ No

If applicable, provide the following information for each awardee or collaborating institution involved in the project in any capacity.

Institution #1:

- Institution's Name: EPIC Systems
  [E.g., University of Tennessee-Chattanooga]

- Federal Wide Assurance Number (FWA #): *Will auto-populate in STARS*
  [STARS will auto-populate this # with Institution's name. The FWA is assigned to an institution for the Protection of Human Subjects.]

- FWA Expiration Date: *Will auto-populate in STARS*
  [STARS will auto-populate this date with Institution's name.]

- IRB Title: _____
  [This is the Internal Review Board for the Institution (if applicable and available). It will be provided in drop-down menu. For example, "U Tennessee Chattanooga IRB #1"]

- IRB Expiration Date: _____
  [This is the Institution's Internal Review Board Expiration Date. STARS will auto-populate this date with IRB Title.]

- Funding #: _____
  [This is the unique identifier assigned to the funding vehicle.]

STEP 5: DATA INFORMATON

Step 6: Data Management Plan

Proposed Data collection START Date: October, 17 2022

Proposed Data collection END Date: December 31, 2022

Select the Proposed Public Access Level (can choose multiple options):

☐ Public
☒ Non-public
☐ Restricted

Complete sections below according to how the above question was answered.

Non-Public Details

- **If "Non-Public" was selected, explain reason for not releasing the data**.
  (This may include information regarding access or restrictions based on privacy, security, or other policies of the owner of the data. As other examples: Removal of identifiers renders the remaining data of no value; Not sharable due to protection of intellectual property or trade secrets.)

  External co-investigators do not have access to identifiable data, but can analyze a limited dataset of routinely collected health information. CDC will not receive the data, only

summaries and reports of the data that do not contain identifiable information.

Restricted Details

- **If "Restricted" was selected, indicate the "Data Use Type":**
  NOTE: For a CDC Restricted dataset, this is the type of data use agreement that must be in place in order to receive this dataset (e.g., Data Sharing Agreement, Joint Statement of Understanding).

- **If "Restricted" was selected, provide the "Data Use Type URL":**
  NOTE: For a CDC Restricted dataset, this is the website where the process for requesting access to the dataset can be found.

- **If "Restricted" was selected, indicate the "Data Use Contact":**
  NOTE: Indicate the staff to contact about the data use understanding. If no contact is identified, go back to add New Staff Member and define that new staff member as a "Data Use Contact.")

Details for All Public Access Types, Regardless of Above Selection

- **Provide Public Access Justification:** [3,500 characters max]
  Please provide justification comment for your public access selection.

  Although this data is deidentified, it contains sensitive information regarding characteristics such as monkeypox diagnosis.

- **Explain how access will be provided to the data:** [3,500 characters max]
  In explanation, also include provisions for protection of privacy, confidentiality, security, intellectual property, proprietary, or other rights (e.g., suppression of person identifiers, etc.)

- **Describe plans for archival and long-term preservation of the data:** [3,500 characters max]
  (Please include justification for lack of storage or where storage will be and for how long. Also, the final DMP should include a link to the archived data with a description of when, how and by whom

the data can be accessed. Please indicate that all laws, regulations, and rights regarding data have been complied.)

Geographic Spatiality information:

NOTE: If the project takes place across the entire United States/Country, then the selection is United States only. In this case, you would not select State/Province or County/Region. Otherwise, further specify the project location.

Country	United States
State/Province	
County/Region	

Updated protocol: November 30, 2022

STUDY TRACKING AND REPORTING SYSTEM (STARS)
PROJECT DETERMINATION

Step 1: Project Description

Step 2: Regulation and Policy

Step 3: Funding Information

Step 4: External institution(s)

Step 5: Data Management Plan/Spatiality Information

STEP 1: PROJECT DESCRIPTION

Project Description Information

- **Project Title [150 characters max]:** Vaccine Effectiveness of JYNNEOS Against Medically-attended MPX Illness Using Electronic Health Record Data, 2022

- **Anticipated Start and Completion Dates:** October 17, 2022–December 31, 2022

- **Select the Priority of the project.**
  - ☐ Standard
  - ☒ Urgent
    - If 'Urgent,' Date Needed? October 14, 2022
    - Justification for "Urgent" priority: Key vaccine effectiveness project in the CDC Multi-National Monkeypox Response 2022

- **Provide Description of Project:**
  [3500 characters max. A short, clear description with sufficient detail to enable a reader to quickly understand whether the project or data set is of interest to them.]

From May 17, 2022, to September 30, 2022, >26,000 cases of confirmed or probable mpox have been reported in the United States. Mpox infections can be acquired through close, sustained physical contact by all people, regardless of gender identity or sexual orientation. However, the current outbreak has disproportionally affected gay, bisexual, and other men who have sex with men (MSM) and transgender women.

JYNNEOS™, the Modified Vaccinia Ankara (MVA) vaccine, was approved in 2019 for the prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox.

On August 9, 2022, FDA issued an emergency use authorization (EUA) that allows healthcare providers to use the JYNNEOS vaccine by intradermal injection to increase the total number of doses available during the 2022 mpox outbreak.

CDC recommends vaccination with the JYNNEOS mpox and smallpox vaccine for people who have been exposed to mpox and certain people who may be more likely to get mpox. In support of this recommendation, CDC intends to estimate the effectiveness of the vaccine. This analysis aims to measure how well mpox vaccination protects people against medically-attended mpox disease under real-world conditions. This project is a proposed analysis of routinely collected electronic health record data included in COSMOS, a platform that allows EPIC investigators to analyze a dataset representing 162 million patients. CDC's role is to consult on the analysis and to contribute to writing. This project will examine the association of vaccination with JYNNEOS on medically-attended mpox disease by number of doses, dosing interval, immunocompromised status, age, route of administration, and clinical endpoints. These data will provide actionable information to clinicians and the public health community on JYNNEOS vaccine for the prevention of mpox. This evaluation compliments other ongoing U.S. government efforts and is not duplicative.

Identifying a Project Associated with an IMS Activation and Type of Response

Note: COVID-19 related Projects and Funding should select 2019 Novel Coronavirus Response.

- **Is this submission associated with an IMS activation, Center, Institute or Office (CIO) Emergency Response, Epi-Aid (may or may not be associated with an IMS or CIO Emergency Response), or Assessment of Chemical Exposure (ACE).**
  - ☒ Yes
  - ☐ No

- **If 'Yes', provide type(s) of response and name(s):** _ Emergency Response: CDC Multi-National Monkeypox Response 2022_____

  Name of CIO: National Center for Immunization and Respiratory Diseases
  Name of the Epi-Aid: _____

  Name of Assessment of Chemical Exposure: _____

Primary Priority Related to the Project or Funding

- Select only one from the list below:
  - ☐ Transmission of SARS-CoV-2
  - ☐ Protection of healthcare personnel and patients
  - ☐ Natural history of SARS-CoV-2 infection
  - ☐ COVID-19 disease detection, burden, and impact
  - ☒ Prevention, mitigation, and intervention strategies
  - ☐ Social, behavioral, and communication science
  - ☐ Other Scientific Topic (If selected, the system requires a value for other)

  - ☐ Not Associated with a Scientific Topic

- **Indicate secondary priorities selections if appropriate.**
  If appropriate, select all that apply from the list below:

☐ Transmission of SARS-CoV-2
☐ Protection of healthcare personnel and patients
☐ Natural history of SARS-CoV-2 infection
☐ COVID-19 disease detection, burden, and impact
☐ Prevention, mitigation, and intervention strategies
☒ Social, behavioral, and communication science
☐ Other Scientific Topic

- **Task Forces Associated with Project**
  If appropriate, indicate Task Forces associated with the project.
  ☐ Chief Medical Officer Unit
  ☐ Community Interventions and Critical Populations
  ☐ Data, Analytics, and Modeling
  ☐ Epidemiology and Surveillance
  ☐ Global Migration
  ☐ Health Systems and Worker Safety
  ☐ International
  ☐ Joint Information Center (JIC)
  ☐ Laboratory and Testing
  ☐ STLT
  ☒ Vaccine Task Force
  ☐ Not Applicable

Goals/Purposes

- **Briefly describe the purpose of the project and how it addresses needs or priorities. [3500 characters max]**

  The goal of this project is to use a large electronic health record database to better understand vaccine effectiveness of JYNNEOS vaccine against medically-attended mpox disease This could have important policy impact, including on recommendations for the use of JYNNEOS vaccine. There is limited information on the real-world vaccine effectiveness of JYNNEOS vaccine against symptomatic mpox by age, route of administration and dosing interval. The goal of this study is to help close that knowledge gap.

Objective(s)

- **Describe the specific objectives of the project and indicate if/how they relate to a public health emergency, or vaccines and immunization activities. [3500 characters max]**

Primary:

1. To estimate the effectiveness of JYNNEOS mpox vaccine in preventing laboratory-confirmed or probable mpox illness.

Secondary (if statistically powered):

2. To estimate vaccine effectiveness by other factors of public health importance:
   - route of administration (subcutaneous, intradermal, heterologous)
   - number of doses

- interval between doses
- age groups
- immunocompromised status
- clinical endpoints

Health Equity Questions

- Does this project include interventions, services, or policy change work aimed at improving the health of groups who have been excluded or marginalized and/or decreasing disparities?
  - ☒ Yes
  - ☐ No

Elements of Health Equity Science

- In what ways does this project incorporate elements of health equity science?
  [Select all that apply. A Minimum of one selection is required.]

☐ Project does not incorporate elements of health equity science. *[Note: If this item is selected, the system will not allow any other health equity selection as they do not apply.]*

☐ Measuring Disparities: Measuring or documenting one or more health disparities (in absolute and/or relative terms) or their change over time.

☐ Studying Social Determinants of Health (SDOH): Studying, measuring, or evaluating social determinants of health or their change over time (check all that apply)

☒ Assessing impact: Assessing the effectiveness or impact interventions, policies, programs, system or environment changes have on the health of groups that have been excluded or marginalized, or on social determinants of health (other than process evaluation)

☐ Methods to improve health equity research and practice: For example, developing methods, instruments, or other innovations to advance progress towards health equity or improve measurement of social determinants of health

☐ Other (Please summarize, e.g., economic analysis, ethical analysis, formative research)

_____

_____

Studying Social Determinants of Health (SDOH)

- In what ways does this project incorporate elements of health equity science?
  [Check all that apply. Minimum of one selection is required.]

☐ Economic Stability (e.g., Employment, Income, Wealth, Food Security, Housing Stability and Homelessness, Poverty).

☐ Education (All levels of education including Early Childhood Education and Development, also Language and Literacy)

☐ Health Care Access (e.g., Access to Health Care (including Insurance), Access to Primary Care, Health Literacy)

☐ Neighborhood and Environment (e.g., Access to Healthy Foods, Crime and Violence, Environmental and Climate Conditions, Housing Quality, Access to Broadband)

☐ Social and Community Context (Other characteristics of contexts within which people live, learn, work, and play. Examples include Discrimination (including Racism), Civic Participation, Incarceration, Social Cohesion, Workplace Conditions).

☐ Indices of SDOH (Measures that attempt to aggregate and quantify multiple social determinants of health). Specify determinants addressed [3500 characters max]:

_____

_____

☐ Other SDOH topics (SDOH-related areas that do not neatly in the above categories [3500 characters max]: _____

_____

☒ Assessing Impact: Assessing the effectiveness or impact interventions, policies, programs, system or environment changes have on health of groups that have been excluded or marginalized, or on social determinants of health (other than process evaluation).

☐ Methods to improve health equity research and practice: For example, developing methods, instruments, or other innovations to advance progress towards health equity or improve measurement of social determinants of health.

☐ Other (Please summarize. E.g., economic analysis, ethical analysis, formative research):

_____

_____

Working with Outside Institutions

- Will you be working with an outside Organization or Institution?
  - ☒ Yes
  - ☐ No

Submitting to the IRB Office

- Do you anticipate this project will be submitted to the IRB Office?
  - ☐ Yes [If "Yes", Step 2-Policy & Regulation will follow after Step 1 is completed.]
  - ☒ No [If "No", then Step-2-Policy & Regulation is not required.]

Data

- Will the project be collecting, generating, obtaining, or transferring data?
  - ☐ Yes
  - ☒ No

Activities or Tasks

- Select all activities or tasks applicable to this project.

☐ New collection of information, data, or biospecimens
☒ Secondary data or specimen analysis
☐ Purchase, use, or transfer of information, data biospecimens or materials
☐ Research with humans
☐ Activity involving live vertebrate animals
☐ All work onsite at CDC facilities
☐ Programmatic work

Target Populations (Required)

- Select **all** target population(s) included/represented. Use the Population Guidance link (Population (cdc.gov) to view the population(s), definition(s), and source(s) for the population categories

X	**Check all that apply**		
	Adult 18-24 years		Impaired hearing or deaf
	American Indian or Alaska Native		Impaired mental
	Asian		Impaired physical
	Black or African American		International
	Businesses		Male
	Children		Native Hawaiian or Other Pacific Islander
	Older adults >64 years		Neonates
	Emancipated Minor		No human population
	Farmers		Other
	Females		Patient
	Fetuses		Pregnant women
X	General US Population		Prisoners
	Healthcare providers		Transgender
	Hispanic or Latino		White
	Immigrants or Refugees		Other (Describe):

Tags/Key Words

- **Provide tags/keywords under which the project could be indexed, cataloged, or searched under in biomedical and health-related databases such as MEDLINE/PubMed, NLM Catalog, etc. Examples might include population surveillance, communicable diseases, behavioral symptoms, sleep disturbances.**

  Mpox, MPX, vaccine effectiveness

CDC's Role

- **Describe the nature of CDC's involvement to include funding, technical assistance, development of concept, protocol, information collection instruments, data management, etc. Indicate whether the CDC has final decision authority over the project.**
  - ☒ Activity originated and designed by CDC staff, or conducted at the specific request of CDC, or CDC staff will approve study design and data collection
  - ☒ CDC employees will provide substantial technical assistance or oversight

☐ Activity originated and designed by CDC staff, or conducted at the specific request of CDC, or CDC staff will approve study design and data collection as a condition of any funding provided.
☐ Activity originated and designed by non-CDC staff (awardee or external collaborator)
☐ CDC employees or agents will obtain data by intervening or interacting with participants
☐ CDC employees or agents will obtain or use anonymous or unlinked data or biological specimens
☐ CDC employees or agents will obtain or use identifiable (including coded) private data or biological specimens
☒ CDC employees will participate as co-authors in presentation(s) or publications.
☒ OTHER (Describe):

_____CDC will not be receiving any data with PII.
_____

_____

_____

Method Categories

- **Select the Method Categories. This is the approach and plan to meet the objectives such as interventions, procedures, screening, etc. Multiple selections can be made.**

☐ Discussion Group
☐ Exposure Investigation
☐ Focus Group
☐ Genetic Sequencing
☐ Health Consultation
☐ Health Education
☐ Hybrid Study Design
☐ Individual Interviews (Qualitative)
☒ *Other:* Secondary data analysis

Methods

- **Describe the approach and plan to meet the objectives such as interventions, procedures, target population and respondent recruitment, screening and enrollment.**
- **Provide information to describe steps taken to ensure the quality of the project and if applicable, whether a review of the proposed statistical methods has been completed.**
- **3500 characters maximum**

A matched case-control design will be used, with cases individually matched (1:4) by calendar week of diagnosis, HHS region, and gender identify. Cases will be defined as individuals with mpox diagnosis or a positive orthopoxvirus or mpox virus laboratory test result and a documented in-person encounter between August 15, 2022 and November 19, 2022, and at least 1 in-person encounter in the prior 3 years. Controls will be individuals with an incident clinical HIV diagnosis or new positive HIV antibody or antigen/antibody test, or a new or refill prescription for HIV PrEP who also had a documented in-person encounter between August 15, 2022, and November 19, 2022, and

at least 1 in-person encounter in the prior 3 years. Cases and controls will be identified by Epic Systems.

CDC is providing technical assistance to Epic Systems, a provider of electronic healthcare software for healthcare systems or facilities in all 50 U.S. states and the District of Columbia. Epic investigators analyze limited healthcare data using a data platform (COSMOS) and do not have access to identifiable health information. Aggregate summaries are produced from these analyses that can be used in reports and presentations. Epic investigators identify cases and controls, and then can analyze characteristics associated with receipt of JYNNEOS vaccination and mpox infection. Characteristics include vaccination, age, sex, race, ethnicity, social vulnerability index, underlying health condition categories, geographic region, and outpatient encounter type (e.g., televisit, in-person visit).

Information, Data, or Bio-specimens collection

- **Explain how information, data, or bio-specimens will be collected. Information refers to facts, statistics, opinions, observations and biological or genetic material provided or learned about human persons.**
- **Identify each collection activity for this project.**
- **Describe who the information will be collected from and what personally identifiable information will be used for the related activities.**
- **Provide information on the estimated burden (in hours) to respondents for each data collection activity proposed.**
- **3,500 characters max**

A data platform (COSMOS) allows Epic investigators to remotely analyze Epic data from participating health systems or facilities without directly accessing the limited data themselves. Epic investigators report that the data accessed and used by Cosmos users in their research activities were considered not to meet the definition of identifiable private information as defined at 45 CFR 46.102(f)(2). CDC only receives aggregate reports without identifiable data that can be used for presentations and publications.

Expected Use of Findings/Results and their Impact

- **Enter the expected use of findings/results and their impact.**
- **Describe how the information will be used and the results disseminated, including plans for peer-reviewed publication, conference presentations and/or web postings.**
- **3,500 characters max**

This project will estimate the effectiveness of JYNNEOS mpox vaccine in preventing mpox disease. If sufficiently powered, this project will also identify differences in effectiveness by number of doses, route of administration, interval between first and second dose, and by immunocompromised status, as well as against different clinical endpoints (e.g., hospitalization). Estimating the effectiveness of JYNNEOS vaccine in preventing symptomatic mpox infection by key strata will inform national JYNNEOS vaccine recommendations and outbreak response activities.

Findings will be disseminated to the scientific community in the form of CDC webpages, published papers and presentations at scientific conferences. No information with personally identifying information will be released in the form of a report or publication.

CDC/ATSDR HRPO/IRB Protocol Number & OMB Control #

- If available, provide the CDC/ATSDR HRPO/IRB Protocol # if this has a Protocol #: _____
- If available, provide the OMB Control # if this has a Control #: _____

Personally Identifiable Information (PII)

- Could individuals potentially be identified based on Information collected?
  - ☐ Yes
  - ☒ No

    If "Yes", Will PII be captured (including coded data)? Will the project collect, store, or transmit Personal Identifying information (PII) that can be used on its own or with other information to identify, contact, or locate a single person, or to identify an individual in context? This includes information in control of outside CDC partners and contractors.

    - ☐ Yes
    - ☒ No

    Does CDC have access to the identifiers (including coded data)?

    - ☐ Yes
    - ☒ No

Assurance of Confidentiality & Certificate of Confidentiality

- Is the project covered by an Assurance of Confidentiality? See the following link for guidance: Assurances of Confidentiality (cdc.gov).
  - ☐ Yes
  - ☒ No

- Does this activity meet the criteria for a Certificate of Confidentiality (CoC)? See the following link for guidance: Certificates of Confidentiality (cdc.gov).
  - ☐ Yes
  - ☒ No

- If the activity meets the CoC criteria, has the required language for the Certificate of Confidentiality been incorporated into the Protocol and/or Consent Form?
  - ☐ Yes
  - ☒ No

Formal Written Agreement

- Is there a formal written agreement prohibiting the release of identifiers?
  Is an agreement in place to prevent information from being disclosed to others which serves as a non-disclosure of identifiers (e.g., Key Agreement, Material Transfer Agreement, Technical Assistance Letter, Memorandum of Understanding, Data Use Agreement, Form 0.1375A, Form 0.1375B, etc.)?

☐ Yes (If 'Yes', provide/upload the formal written agreement)
☒ No

STEP 2: REGULATION AND POLICY – PROTOCOL INFORMATION

Regulation and Policy - IRB Office

- Do you anticipate this project will be submitted to the IRB Office? [This item was previously addressed in Step 1.]

  ☐ Yes [If "Yes", then Step 2-Policy & Regulation is required.]
  ☒ No [If "No", then Step-2-Policy & Regulation is not required. Skip to Section 3-Funding Information.]

Number of Study Participants, Populations Included

- Estimated # of study participants: _____0_____
  Report estimated counts rather than percentages.
  Include study subjects at domestic and foreign sites.

- Select ("x") the extent to which the following population(s) will be included, and the page # in the protocol if applicable.

  Children: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Minors: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Prisoners: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Pregnant Women: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

  Emancipated Minors: ☐ Targeted, ☐ Allowed, ☐ Excluded, or ☐ N/A, Protocol Page # _____

Suggested Level of Risk to Subjects

- Suggest level of risk to subjects:
  ☐ Minimal
  ☐ Greater than minimal

  NOTE: Select "Minimal" when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The definition varies slightly for research involving prisoners.

  NOTE: Select "Greater than Minimal" when the probability and magnitude of harm or discomfort anticipated in the proposed research are greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Any disclosure of illegal activities, sexual attitudes, genetics,

religious beliefs, mental health that could place participants at risk of criminal or civil liability, be damaging to the participants financial standing, employability, insurability, reputation, or be stigmatizing.

Exempt or Non-Exempt Research

- Do you anticipate this project will be exempt research or non-exempt research?
  - ☐ Exempt
  - ☐ Non-Exempt

- Select each category and the applicable options for all that apply to the protocol.
  Each option is also presented further below with details and information that appear in STARS.
  - ☐ Educational Practices
  - ☐ Educational Tests, Surveys, Interviews, or Observation of Public Behavior
  - ☐ Benign Behavioral Interventions and Collection of Information
  - ☐ Secondary Research for which Consent is not Required
  - ☐ Research and Demonstration Projects
  - ☐ Taste and Food Quality Evaluation and Consumer Acceptance Studies
  - ☐ Storage or Maintenance for Secondary Use for which Broad Consent is Required
  - ☐ Secondary Research for Which Broad Consent is Required

  NOTE:
  - Studies may be exempt from review when human participants conform to one of the categories from section 46.101(b) of 45 CFR 46.
  - Research may qualify for Exempt status if it involves very minimal or no risk.
  - Projects will not be given Exempt status if they include any degree of deception, involve more than very minimal risk to participants, involve sensitive information, or include protected classes or vulnerable populations.
  - Please note that researchers must always engage in practices that ensure privacy and that minimize the risks to participants, regardless of the level of review.

Exempt Research Category 1: Educational Practices

- If “Exempt” was selected above, check if the following applies:
  - ☐ Category 1: Educational Practices:
    - Normal educational practices in commonly accepted education settings.

    NOTE: Category 1: Educational Practices 45 CRF 46.104(d)(1) Research in Established or Commonly Accepted Education Settings that Involves Normal Educational Practices and Not likely to Adversely Impact Students' Opportunity to Learn or Assessment of Educator

Exempt Research Category 2: Educational Tests, Surveys, Interviews, or Observation of Public Behavior

- If “Exempt” was selected above, check if the following applies:
  - ☐ Educational tests, surveys, interviews, or observation of public behavior

- At least one of the criteria below must be met:

☐ Recorded in such a manner that identity cannot readily be ascertained
☐ Disclosure outside the research would not reasonably place subjects at risk of liability or be damaging
☐ Adults only, identity can readily be ascertained

NOTE:
Category 2: Educational tests, surveys, interviews, or observation of public behavior 45 CFR 46.104(d)(2) Research only includes Educational Tests, Surveys, Interviews, Public Observation and Not Likely to Adversely Impact Students' Opportunity to Learn or Assessment of Educators if at least ONE of the following criteria met: (i) Recorded information cannot readily identify the subject (directly or indirectly/linked); Surveys & Interviews: No Children; Educational Tests or Observation of Public Behavior: Can Only include Children when Investigators Do Not participate in activities being observed OR (ii) Any disclosure of responses outside of the research would NOT reasonably place subject at risk (criminal, civil liability, financial, employability, educational advancement, reputation); Surveys & Interviews: No Children; Educational Tests or Observation of Public Behavior: Can Only include Children When Investigators Do Not Participate in Activities being Observed OR (iii) Information is recorded with identifiers & IRB conducts Limited Review; NO Children

Exempt Research Category 3: Benign Behavioral Interventions and Collection of Information

- If "Exempt" was selected above, check if the following applies:
  ☐ Benign Behavioral Interventions and Collection of Information

- Category 3: Benign Behavioral Interventions and Collection of Information:
  ☐ Information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot be readily ascertained directly or through identifiers linked to subjects.
  ☐ Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement or reputation
  ☐ Information obtained is recorded by the investigator in such a manner that the identity of human subjects can readily be ascertained directly or through identifiers linked to the subjects; Research involves deceiving the subjects regarding the nature or purposes of the research; Subject authorizes the deception through prospective agreement.

  NOTE:
  Category 3: Benign Behavioral Interventions and Collection of Information - 45 CRF 46.104(d)(3) Research involving Benign Behavioral Interventions through verbal, written responses, (including data entry or audiovisual recording) from adult subject who prospectively agrees and ONE of following met: May Not include Medical Interventions; Subject prospectively agrees (ii) Benign Behavioral Interventions must be: Brief in Duration, Painless/Harmless, Not Physically Invasive, Not Likely to Have a Significant Adverse Lasting Impact on Subjects, Unlikely that Subjects Will Find Interventions Offensive or Embarrassing (iii)No deception unless participant prospectively agrees. Recorded information cannot readily identify the subject (directly or indirectly/linked); ORB. Any disclosure of responses outside of the research would NOT reasonably place subject at risk (criminal, civil liability, financial, employability, educational advancement, reputation); ORC. Information is recorded with identifiers & IRB conducts Limited Review

Exempt Research Category 4: Secondary Research for which consent is not Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Secondary Research for Which Consent is Not Required

- Category 4: Secondary Research for Which Consent is Not Required
  - ☐ Identifiable private information or identifiable biospecimens are publicly available
  - ☐ Information, which may include information about biospecimens, recorded by investigator such that the identity of human subjects cannot readily be ascertained; Investigator does not contact subjects, and investigator will not re-identify subjects
  - ☐ Research use of identifiable health information which that use is regulated by HIPAA as health care operations, research or public health activities and purposes as those terms are defined in HIPAA
  - ☐ The research is conducted b, or on behalf of, a federal department or agency using government generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with applicable with applicable federal privacy standards found in the E-Government act, Privacy Act and the Paperwork Reduction Act.

NOTE:
Category 4, Secondary Research for which Consent is not Required - 45 CFR 46.104(d)(8) Secondary Research for Which Consent is Not Required: Use of Identifiable Information or Identifiable Biospecimen that have been or will be collected for some other 'primary' or 'initial' activity, if ONE of following criteria met: No Primary Collection from subjects for the research; Allows Both Retrospective and Prospective Secondary Use.(i) Biospecimens or Information is Publicly Available; OR(ii) Information recorded so subject cannot readily be identified (directly or indirectly/linked); Investigator does not contact subjects and will not re-identify the subjects; OR(iii) Collection and Analysis involving Investigators Use of Identifiable Health Information when use is regulated by HIPAA "health care operations" or "research" or "public health activities and purposes"; OR(iv) Research information collected by or on behalf of federal government using government generated or collected information obtained for non-research activities.

Exempt Research Category 5: Research and Demonstration Projects

- If "Exempt" was selected above, check if the following applies:
  - ☐ Research and Demonstration Projects

- Check if applicable:
  - ☐ Conducted or supported by a federal department or agency, or otherwise subject to the approval of department or agency heads designed to study, evaluate, improve or otherwise examine public benefit or service program

    NOTE:

Category 5, Research and Demonstration Projects - 45 CFR 46.104(d)(5) Research and demonstration projects supported by a Federal Agency/Dept. AND Designed to study, public benefit or service programs. Must be posted on a Federal Web Site. Federal website that will satisfy the consent form posting requirement: ClinicalTrials.gov

Exempt Research Category 6: Taste and Food Quality Evaluation and Consumer Acceptance Studies

- If "Exempt" was selected above, check if the following applies:
  - ☐ Taste and Food Quality Evaluation and Consumer Acceptance Studies
- Check if applicable:
  - ☐ Foods that are wholesome without additives
  - ☐ If a food is consumed that contains food ingredient at or below the level and for use found to be safe, or agricultural chemical or environmental contaminant at or below level food to be safe, by FDA or approved by EPA or Food Safety and Inspection Service of USDA.

Exempt Research Category 7: Storage or Maintenance for Secondary Use for which Broad Consent is Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Storage or Maintenance for Secondary Use for which Broad Consent is Required
- Check if applicable:
  - ☐ Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use

    NOTE:
    Category 7: 45 CFR 46.104(d)(7) Storage or Maintenance of Identifiable Private Information or Identifiable Biospecimens for Secondary Research which Broad Consent is required. Limited IRB review required under S46.111(a)(8).

Exempt Research Category 8: Secondary Research for Which Broad Consent is Required

- If "Exempt" was selected above, check if the following applies:
  - ☐ Secondary Research for Which Broad Consent is Required
- Check if applicable:
  - ☐ Broad consent for storage, maintenance and secondary research use of identifiable private information or identifiable biospecimens was obtained.

    NOTE:
    Category 8: 45 CFR 46.104(d)(8) Secondary research involving use of Identifiable Private Information or Identifiable Biospecimens for which Broad Consent was Required Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens was obtained in accordance with S46.116(a)(1) through (4), (a)(6) and (d)[S46.104(8) (i)]. Limited IRB review required under S46.111(a)(8). Note 1: [S46.104(8)(ii)] Documentation of informed consent or waiver of documentation of consent was obtained in accordance with S46.117 Note 2: [S46.104(8) (iv)] Investigator does not include returning individual research results to subjects as part of the study plan

Non-Exempt Research*

- Do you anticipate this project will be exempt research or non-exempt research? This item was also addressed above.
  - ☐ Exempt
  - ☐ Non-Exempt

NOTE:
Select **Non-Exempt** for any proposed research not qualifying for Exempt Research status requires IRB members review and vote on the proposal. These typically involve projects that place human subjects at more than minimal risk, or that involve sensitive topics or vulnerable populations such as prisoners, terminally ill patients, children, veterans, or cognitively impaired persons.

A proposal that does not fulfill the criteria for Exempt status may undergo an Expedited review if it involves no more than minimal risk to the participants and meets other standards, such as not including protected classes or vulnerable populations, and not using intentional deception.

If Non-exempt Research was selected, address the following as they pertain to Informed Consent, Clinical Trial and Other Considerations.

Non-Exempt Research/Informed Consent

- Check all that apply. Characterize requested changes to required features of the informed consent process. If a waiver is requested, enter the page number of the protocol where the waiver is justified:
  - ☐ Waiver or alteration of elements of informed consent for adults: Page # ____
  - ☐ Waiver of assent for children capable of providing assent: Page # ____
  - ☐ Waiver of parental permission: Page # ____
  - ☐ Waiver or alteration or authorization under HIPAA Privacy Rule: Page # ____

NOTE:
Which waivers to the consent process are requested: IRB may waive or alter the requirement of informed consent under 45 CFR 46.116(d), provided all the following four conditions are met: 1. research involves no more than minimal risk, 2. not adversely affect the rights and welfare, 3. research could not practicably be carried out without the waiver or alteration, and 4. subjects are provided with additional pertinent information after participation. Public benefit or service programs: 45 CFR 46.116(c). Research in emergency settings: 45 CFR 46.101(i). If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Non-Exempt Research/Informed Consent

- Which waivers to documentation of informed consent are requested?
  - ☐ Waiver of documentation of informed consent for adults: Page # ____
  - ☐ Waiver of documentation of assent for children capable of providing assent: Page # ____
  - ☐ Waiver of documentation of parental permission: Page # ____

NOTE:
Which waivers to documentation of informed consent are requested? Potential participants, or the parents of children who are potential participants, are presented (either verbally or in writing) with the same information required in a written consent document, but documentation of the process (signing of the consent form) has been waived by the IRB. The FDA has not adopted this category so it cannot be used if the research is subject to the FDA regulations 21 CFR 50. If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Non-Exempt Research/Informed Consent

- How is it shown that the consent process is in understandable language?
  - ☐ Reading level has been estimated: Page # ____
  - ☐ Comprehension tool is provided: Page # ____
  - ☐ Short form is provided: Page # ____
  - ☐ Translation planned or performed: Page # ____
    - ☐ Certified translation/translator: Page # ____
    - ☐ Translation and back-translation to/from target language(s): Page # ____
    - ☐ Other Method: Page # ____
      Describe "Other Method": _____
      _____
      _____

NOTE: How is it shown that the consent process is in understandable language? Consent process in understandable language regulations are 45 CFR 46.116 and 45 CFR 46.117 and/or FDA regulations 21 CFR 50.25 and 21 CFR 50.27 apply. Subjects must be provided with both 1. A written consent document in a language understandable to them AND 2. An interpreter fluent in both English and the participant's spoken language to aid in the consent process. If a waiver is requested, enter the page number of the protocol where the waiver is justified. Check all that apply.

Regulation and Policy – Non-Exempt Research/Clinical Trial

- Clinical Trial - Check all that apply.
  - ☐ Does the study involve human participants?
  - ☐ Are the participants prospectively assigned to an intervention?
  - ☐ Is the study designed to evaluate the effect of the intervention on the participant?
  - ☐ Is the effect being evaluated a health-related biomedical or behavioral outcome?
  - ☐ This study is a registrable clinical trial. NOTE: If the study is a registrable clinical trial, enter the ID and/or select the ClinicalTrials.gov link to the route to the U.S. National Library of Medicine ClinicalTrials.gov for additional information.

    NOTE:
    1) 45 CFR 46.102(b) Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral

health-related outcomes. 2) 45 CFR 46.102(e)(1) Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. 3) 45 CFR 46.102(2) Intervention includes both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. If the answer to any one of these questions is yes, then a Certificate of Confidentiality will apply to the research per subsection 301(d) of the Public Health Service Act. If you check all, then the study meets the definition of a clinical trial.

Non-Exempt Research/Other Considerations

- Other Considerations - Check all that apply.
  - ☐ Exception is requested to PHS, informing those tested about HIV serostatus:
    Protocol Page # _____
  - ☐ Human genetic testing is planned now or in the future.
  - ☐ This study involves long-term storage of identifiable biological specimens.
  - ☐ This study involves a drug, biologic, or device.
  - ☐ This study will be conducted under an Investigational New Drug (IND) exemption or Investigational Device Exemption (IDE).
    IND/IDE #: _____

NOTE:
1) 45 CFR 46.102(b) Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. 2) 45 CFR 46.102(e)(1) Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. 3) 45 CFR 46.102(2) Intervention includes both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. If the answer to any one of these questions is yes, then a Certificate of Confidentiality will apply to the research per subsection 301(d) of the Public Health Service Act. If you check all, then the study meets the definition of a clinical trial.

STEP 3: FUNDING INFORMATION

Step 3: Funding

- **This step is designed to capture funding details associated with this project. If the project does not have any associated funding, select next to advance to Step 4.**

- **Items will include the following: Funding Type, Funding Title, Funding Number, Original Fiscal Year, Number of Years of Award, and Budget Amount**
- **NOTE: This step is designed to capture funding details associated with this project. If the project does not have any associated funding, select next to advance to Step 4.**

Funding – Funding Type and Title

- Select the Funding Type (Select one):
  - ☐ CDC Contract
  - ☐ CDC Cooperative Agreement
  - ☐ CDC Funding Intramural
  - ☐ CDC Grant
  - ☐ Cooperative Research and Development Agreement
  - ☐ FDA Funding
  - ☐ Funding from Another CIO
  - ☐ Gift
  - ☒ IMS Response
  - ☐ Other Federal Funding
  - ☐ Technical Assist-CDC Not Reimbursed
  - ☐ Technical Assist-CDC Reimbursed
  - ☐ Other (Specify): _____

- Funding Title (255 Characters):

- Funding #: _____
  [This is the award number assigned to the project (i.e., the NOFO number for a cooperative agreement, the contract number for a contract, or the spend plan unique ID for the IMS Response.]

- Original Fiscal Year: _____

- Number of Years of Award: _____

- Budget Amount: _____

STEP 4: EXTERNAL INSTITUTION(S)

Step 4: Adding Outside Organizations & Institutions

This section should be completed if "Yes" was the response for the following:

- Will you be working with an outside Organization or Institution?
  - ☒ Yes
  - ☐ No

If applicable, provide the following information for each awardee or collaborating institution involved in the project in any capacity.

Institution #1:

- Institution's Name: EPIC Systems
  [E.g., University of Tennessee-Chattanooga]

- Federal Wide Assurance Number (FWA #): *Will auto-populate in STARS*
  [STARS will auto-populate this # with Institution's name. The FWA is assigned to an institution for the Protection of Human Subjects.]

- FWA Expiration Date: *Will auto-populate in STARS*
  [STARS will auto-populate this date with Institution's name.]

- IRB Title: _____
  [This is the Internal Review Board for the Institution (if applicable and available). It will be provided in drop-down menu. For example, "U Tennessee Chattanooga IRB #1"]

- IRB Expiration Date: _____
  [This is the Institution's Internal Review Board Expiration Date. STARS will auto-populate this date with IRB Title.]

- Funding #: _____
  [This is the unique identifier assigned to the funding vehicle.]

STEP 5: DATA INFORMATON

Step 6: Data Management Plan

Proposed Data collection START Date: October, 17 2022

Proposed Data collection END Date: December 31, 2022

Select the Proposed Public Access Level (can choose multiple options):

- ☐ Public
- ☒ Non-public
- ☐ Restricted

Complete sections below according to how the above question was answered.

Non-Public Details

- **If "Non-Public" was selected, explain reason for not releasing the data**.
  (This may include information regarding access or restrictions based on privacy, security, or other policies of the owner of the data. As other examples: Removal of identifiers renders the remaining data of no value; Not sharable due to protection of intellectual property or trade secrets.)

External co-investigators do not have access to identifiable data, but can analyze a limited dataset of routinely collected health information. CDC will not receive the data, only summaries and reports of the data that do not contain identifiable information.

Restricted Details

- **If "Restricted" was selected, indicate the "Data Use Type":**
  NOTE: For a CDC Restricted dataset, this is the type of data use agreement that must be in place in order to receive this dataset (e.g., Data Sharing Agreement, Joint Statement of Understanding).

- **If "Restricted" was selected, provide the "Data Use Type URL":**
  NOTE: For a CDC Restricted dataset, this is the website where the process for requesting access to the dataset can be found.

- **If "Restricted" was selected, indicate the "Data Use Contact":**
  NOTE: Indicate the staff to contact about the data use understanding. If no contact is identified, go back to add New Staff Member and define that new staff member as a "Data Use Contact.")

Details for All Public Access Types, Regardless of Above Selection

- **Provide Public Access Justification:** [3,500 characters max]
  Please provide justification comment for your public access selection.

  Although this data is deidentified, it contains sensitive information regarding characteristics such as mpox diagnosis.

- **Explain how access will be provided to the data:** [3,500 characters max]
  In explanation, also include provisions for protection of privacy, confidentiality, security, intellectual property, proprietary, or other rights (e.g., suppression of person identifiers, etc.)

- **Describe plans for archival and long-term preservation of the data:** [3,500 characters max]

(Please include justification for lack of storage or where storage will be and for how long. Also, the final DMP should include a link to the archived data with a description of when, how and by whom the data can be accessed. Please indicate that all laws, regulations, and rights regarding data have been complied.)

Geographic Spatiality information:

NOTE: If the project takes place across the entire United States/Country, then the selection is United States only. In this case, you would not select State/Province or County/Region. Otherwise, further specify the project location.

Country	United States
State/Province	
County/Region	

Summary of protocol changes:

- Replaced the word “symptomatic” with “medically-attended” in the title and throughout the protocol to more accurately reflect the population captured in the analysis, (i.e. individuals seeking healthcare)
- Replaced the word “monkeypox” and abbreviation “MPX” with “mpox” per World Health Organization recommendations
- Updated the data through November 19, 2022 to more fully capture the span of the outbreak
- Modified the control group to better represent the source population (i.e. who was eligible for vaccination and who was at risk for mpox disease)
- Reduced the number of face-to-face health encounters from 2 to 1 in the prior three years, as part of the inclusion criteria to account for reduction in healthcare visits due to the pandemic
- Updated list of staff members involved in the study

Original Analytic Plan: October 13, 2022

JYNNEOS Vaccine Effectiveness Against Monkeypox Disease in the U.S.

Description

From May 17, 2022, to September 30, 2022, >26,000 cases of monkeypox disease have been reported in the United States. Monkeypox disease can be acquired through close, sustained physical contact by all people, regardless of gender identity or sexual orientation. However, the current outbreak has disproportionally affected gay, bisexual, and other men who have sex with men (MSM) and transgender women.

JYNNEOS™, the Modified Vaccinia Ankara (MVA) vaccine, was approved in 2019 for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox disease. On August 9, 2022, FDA issued an emergency use authorization (EUA) that allows healthcare providers to use the JYNNEOS vaccine by intradermal injection to increase the total number of doses available during the 2022 monkeypox outbreak.

CDC recommends vaccination with the JYNNEOS vaccine for people who have been exposed to monkeypox and certain people who may be more likely to get monkeypox disease. In support of this recommendation, CDC intends to estimate the effectiveness of the vaccine. This analysis aims to measure how well monkeypox vaccination protects people against symptomatic monkeypox disease under real-world conditions.

This project will examine the association of vaccination with JYNNEOS on medically attended monkeypox by number of doses, age, immunocompromised status, and route of administration. A matched case-control design will be used, with cases individually matched (1:4) by calendar week of diagnosis, HHS region, and gender identity. We included case patients who had a monkeypox diagnosis code, or positive orthopoxvirus or monkeypox virus laboratory result, and control patients who had a syphilis diagnosis during August 15, 2022 – October 29, 2022.

The analysis will be conducted in partnership with Epic Systems using data from Epic's Cosmos platform, an integrated electronic health database containing records on over 169 million patients in all 50 states. These data will provide actionable information to clinicians and the public health community on JYNNEOS vaccine for the prevention of monkeypox disease.

Analysis Plan

Objective	Estimate the effectiveness of JYNNEOS monkeypox vaccine in preventing diagnosed, symptomatic monkeypox infection among U.S. adults seeking healthcare
Cases	Individuals with monkeypox diagnosis or positive orthopoxvirus or monkeypox virus laboratory test result and a documented in-person encounter between August 15, 2022 and October 29, 2022, and at least 2 face-to-face encounters in the prior 3 years
Controls	Individuals with a syphilis diagnosis between August 15, 2022 and October 29, 2022, and at least 2 face-to face encounter in the prior 3 years

Exclusions	Among cases: • Positive lab result for orthopox IgG • Telehealth encounter only at index event • <2 in-person encounters 3 years before index encounter Among controls: • Telehealth encounter only at date of index event • <2 in person encounters 3 years before index encounter • Monkeypox diagnosis or positive orthopoxvirus or monkeypox virus laboratory test result between August 15, 2021 and August 14, 2022
Design	Matched case-control design, 1:4 without replacement
Matching	Calendar week of diagnosis, HHS Census region, gender identity
Outcome	Monkeypox diagnosis or positive orthopoxvirus laboratory result or positive monkeypox virus laboratory result
Exposure	At least one dose of JYNNEOS vaccine*
Variables of interest	• Age • Legal sex • Gender identity • Race/ethnicity • Social vulnerability index • U.S. HHS Census region • Index event type • Source of index event • Duration of index hospitalization (associated with index event) • No. underlying conditions • No. encounters (face-to-face only) 1 year prior to index event • Immunocompromised (due to taking immunosuppressing medications or immunosuppressing conditions) • Tecovirimat (TPOXX) prescription • Pain medication (prescribed, IV meds) – prescribed on or after date of index event and is associated with index event • Vaccinated with ACAM2000 • Calendar week of diagnosis • JYNNEOS vaccine administration route
Analysis method	Conditional logistic regression, adjusting for *a priori* specified confounders (age, race/ethnicity, SVI, and immunocompromised status). Vaccine effectiveness = (1-OR) x 100
Strata for analysis	• Females • Males • Males aged 18-49 without ACAM2000 vaccination • Persons without immunocompromising conditions • Persons with immunocompromising conditions • Persons with HIV • Route of administration
Sensitivity Analyses	Repeat main analysis under following conditions: VE by route of administration based on the originally documented route of administration for vaccination on or after August 9th, 2022

*Fully vaccinated: Receipt of two doses of JYNNEOS vaccine ≥ 24 days apart and the second dose was ≥ 14 days before the index event. Partially vaccinated: Receipt of one dose ≥ 14 days before the index event, or the second dose was <14 days before the index event; patients who received one dose <14 days before the index event excluded as vaccination might represent post-exposure prophylaxis. Unvaccinated: No documented doses before the index event. For vaccinations before August 9, 2022, we recategorized route of administration from 'other' or 'missing' to 'subcutaneous' because JYNNEOS was authorized only for subcutaneous administration during this time. For vaccinations on or after August 9, 2022, we used dosage information to recategorize route of administration (if it was missing), as the standard (subcutaneous) vaccination dose is 0.5 mL and the EUA approved (intradermal) dose is 0.1 mL.

Final Analytic Plan: Last updated March 14, 2023

JYNNEOS Vaccine Effectiveness Against Mpox Disease in the U.S.

Description

From May 17, 2022, to September 30, 2022, >26,000 cases of mpox disease have been reported in the United States. Mpox disease can be acquired through close, sustained physical contact by all people, regardless of gender identity or sexual orientation. However, the current outbreak has disproportionally affected gay, bisexual, and other men who have sex with men (MSM) and transgender women.

JYNNEOS™, the Modified Vaccinia Ankara (MVA) vaccine, was approved in 2019 for the prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox disease. On August 9, 2022, FDA issued an emergency use authorization (EUA) that allows healthcare providers to use the JYNNEOS vaccine by intradermal injection to increase the total number of doses available during the 2022 mpox outbreak.

CDC recommends vaccination with the JYNNEOS vaccine for people who have been exposed to mpox and certain people who may be more likely to get mpox disease. In support of this recommendation, CDC intends to estimate the effectiveness of the vaccine. This analysis aims to measure how well mpox vaccination protects people against symptomatic mpox disease under real-world conditions.

This project will examine the association of vaccination with JYNNEOS on medically attended mpox by number of doses, age, immunocompromised status, and route of administration. A matched case-control design will be used, with cases individually matched (1:4) by calendar week of diagnosis, HHS region, and gender identity. We included case patients who had a mpox diagnosis code, or positive orthopoxvirus or mpox virus laboratory result, and control patients who had an incident HIV diagnosis, or a new or refill order for HIV pre-exposure prophylaxis during August 15, 2022 – November 19, 2022.

The analysis will be conducted in partnership with Epic Systems using data from Epic's Cosmos platform, an integrated electronic health database containing records on over 169 million patients in all 50 states. These data will provide actionable information to clinicians and the public health community on JYNNEOS vaccine for the prevention of mpox disease.

Analysis Plan

Objective	Estimate the effectiveness of JYNNEOS mpox vaccine in preventing medically-attended mpox disease among U.S. adults seeking healthcare
Cases	Individuals with mpox diagnosis or positive orthopoxvirus or mpox virus laboratory test result and a documented in-person encounter between August 15, 2022 and November 19, 2022, and at least 1 face-to-face encounter in the prior 3 years
Controls	Individuals with an incident HIV diagnosis, or a new or refill order for HIV pre-exposure prophylaxis between August 15, 2022 and November 19, 2022, and at least 1 face-to face encounter in the prior 3 years
Exclusions	Among cases: • Positive lab result for orthopox IgG

	• Telehealth encounter only at index event • No in-person encounters 3 years before index encounter Among controls: • Telehealth encounter only at date of index event • No in person encounters 3 years before index encounter • Mpox diagnosis or positive orthopoxvirus or mpox virus laboratory test result between August 15, 2021 and August 14, 2022
Design	Matched case-control design, 1:4 without replacement
Matching	Calendar week of diagnosis, HHS Census region, gender identity
Outcome	Mpox diagnosis or positive orthopoxvirus laboratory result or positive mpox virus laboratory result
Exposure	At least one dose of JYNNEOS vaccine*
Variables of interest	• Age • Legal sex • Gender identity • Race/ethnicity • Social vulnerability index • U.S. HHS Census region • Index event type • Source of index event • Duration of index hospitalization (associated with index event) • No. underlying conditions • No. encounters (face-to-face only) 1 year prior to index event • Immunocompromised (due to taking immunosuppressing medications or immunosuppressing conditions) • Tecovirimat (TPOXX) prescription • Pain medication (prescribed, IV meds) – prescribed on or after date of index event and is associated with index event • Vaccinated with ACAM2000 • Calendar week of diagnosis • JYNNEOS vaccine administration route
Analysis method	• Conditional logistic regression, adjusting for *a priori* specified confounders (age, race/ethnicity, SVI, and immunocompromised status). Vaccine effectiveness = (1-OR) x 100 • <u>Test for interactions for variables that may modify the effect of vaccination (immunocompromised status, age group)</u> • Calculate E-values for the primary outcome to assess the potential of unmeasured confounders to influence results.
Strata for analysis (if powered)	• Females • Males • Males aged 18-49 without ACAM2000 vaccination • Persons without immunocompromising conditions • Persons with immunocompromising conditions • Persons with HIV • Route of administration

Sensitivity Analyses	Repeat main analysis under following conditions: VE by route of administration based on the originally documented route of administration for vaccination on or after August 9th, 2022

*Fully vaccinated: Receipt of two doses of JYNNEOS vaccine ≥ 24 days apart and the second dose was ≥ 14 days before the index event. Partially vaccinated: Receipt of one dose ≥ 14 days before the index event, or the second dose was <14 days before the index event; patients who received one dose <14 days before the index event excluded as vaccination might represent post-exposure prophylaxis. Unvaccinated: No documented doses before the index event. For vaccinations before August 9, 2022, we recategorized route of administration from 'other' or 'missing' to 'subcutaneous' because JYNNEOS was authorized only for subcutaneous administration during this time. For vaccinations on or after August 9, 2022, we used dosage information to recategorize route of administration (if it was missing), as the standard (subcutaneous) vaccination dose is 0.5 mL and the EUA approved (intradermal) dose is 0.1 mL.

Summary of analysis plan changes:

- Updated the data through November 19, 2022 to more fully capture the span of the outbreak
- Modified the control group to better represent the source population (i.e. who was eligible for vaccination and who was at risk for mpox disease)
- Replaced the word “monkeypox” and abbreviation “MPX” with “mpox” per World Health Organization recommendations
- For inclusion criteria, reduced the number of face-to-face health encounters in the prior three years from 2 to 1 to account for reduction in healthcare visits due to the COVID-19 pandemic
- Added tests for interactions for variables that may modify the effect of vaccination (immunocompromised status, age group)
- Added calculation of E-values for the primary outcome to assess the potential of unmeasured confounders influencing results.