V-safe Pregnancy Registry Protocol

Amendment to the V-safe Active Surveillance for COVID-19 Vaccine Safety protocol

Version 2

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V-safe pregnancy surveillance (amendment)

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Protocol amendment summary: V-safe is a novel smartphone-based active vaccine safety surveillance program that will be implemented at the start of an FDA Emergency Use Authorization (EUA) for COVID-19 vaccine use in the United States. As part of this novel public health surveillance activity established for COVID-19, information about pregnancy status at the time of vaccination and at defined follow up time points after vaccination will be collected. This protocol amendment will describe the defined time points and protocol for collecting information about pregnant persons exposed to COVID-19 vaccines and their infants. Given the lack of safety data from pre-EUA clinical trials of COVID-19 vaccines among pregnant persons, the v-safe pregnancy surveillance system will provide critical information to monitor the safety of COVID-19 vaccines administered under EUA and is intended to capture information about pregnant persons and their infants who have been vaccinated. This can inform clinical guidance regarding COVID-19 vaccination during pregnancy and can provide an additional method to detect adverse events that warrant further evaluation using existing safety and database systems.

Summary of updates:

1. Background was updated to acknowledge there are now three vaccines with FDA EUA.
2. Methods were updated to describe a new three question follow-up survey that will be administered to v-safe participants who report pregnancy.
3. Methods were updated to indicate the v-safe pregnancy registry will now receive full date of birth and race/ethnicity data for participants that may be pregnant from the v-safe survey system
4. Data Collection/Unreachable section (formerly Loss to follow-up) was updated to determine when a participant is considered unreachable.

Background:

Pregnancy was an exclusion from enrollment in pre-EUA clinical trials for COVID-19 vaccines (www.clinicaltrials.gov). In these pre-EUA clinical trials, pregnancy was screened for and pregnant persons were excluded based on urine pregnancy tests; clinical trial participants were recommended to avoid pregnancy during the trial through the use of reliable and effective contraception. While Pfizer and Moderna vaccine trials did include approximately 36 pregnant persons inadvertently vaccinated during pregnancy, these small numbers are not enough to establish the safety of maternal vaccination (1, 2). Safety data from infants exposed during pregnancy is not available because of the short length of follow up.

On December 1, 2020, the Advisory Committee on Immunization Practices (ACIP) voted that, when a COVID-19 vaccine is authorized by the FDA and recommended by ACIP, healthcare personnel should be offered vaccination in the initial phase of the COVID-19 vaccination program (phase 1a) (3). The healthcare workforce is predominantly female, and women account for 75% of full-time year-round healthcare personnel (4). Females also dominate the largest healthcare occupations, comprising 88% of registered nurses and 86% of healthcare support workers, which includes nursing, psychiatric, and personal and home health aides. Approximately 5% of women of reproductive age are estimated to be pregnant or postpartum at any time, translating to around 330,000 pregnant or newly postpartum women who are healthcare personnel and could be included in phase 1a

vaccine allocation. Furthermore, on December 20, 2020, the ACIP voted that phase 1c vaccine allocation includes persons aged 16-64 years with medical conditions that increase the risk for severe COVID-19, of which pregnancy is included (5).

Three COVID-19 vaccines have been FDA authorized and ACIP recommended, with permissive language indicating that pregnant women may choose to get any of the vaccines and should discuss risks and benefits with their healthcare providers (6-8). Although it is unknown at this time if FDA will authorize or ACIP will recommend additional COVID-19 vaccines for pregnant or breastfeeding persons, it is important that post-EUA surveillance systems exist to monitor the safety of all COVID-19 vaccines among known and inadvertently vaccinated pregnant persons.

The CDC's Immunization Safety Office (ISO) will implement multiple systems to monitor the safety of COVID-19 vaccines (9). The Vaccine Adverse Event Reporting System (VAERS) receives passive reports on adverse events following vaccination from the public, medical providers, and manufacturers, and asks specific questions about pregnancy status at the time of vaccination. Pregnancy reports will be abstracted and supplemented with medical records when available. The Vaccine Safety Datalink (VSD) is a collaboration between CDC and nine integrated healthcare systems with demographic, vaccination, and healthcare utilization information on approximately 3% of the US population and 100,000 live births per year. The VSD has an electronic pregnancy episode algorithm that will monitor COVID-19 vaccine coverage and can be used to perform epidemiologic studies on pregnancy loss, acute adverse events, adverse pregnancy outcomes, and infant development and birth defects following exposure to COVID-19 vaccine in pregnancy. The Clinical Immunization Safety Assessment (CISA) project, a collaboration between CDC and seven academic centers, is planning to conduct a clinical trial examining the safety of vaccination during pregnancy. However, given the dearth of safety data of COVID-19 vaccines during pregnancy and the novelty of some COVID-19 vaccine candidate platforms (e.g. mRNA), it is essential that vaccine safety data among pregnant persons is comprehensive and captured in near real-time. A novel smartphone-based active surveillance vaccine safety monitoring system, v-safe, is currently being developed to supplement the ISO's immunization safety activities. As part of this surveillance activity, information on pregnancy status at the time of vaccination and at subsequent time points will be collected.

CDC plans to use the v-safe system to monitor non-male participants who received COVID-19 vaccines during pregnancy or in the periconception period (30 days before last menstrual period [LMP] through 14 days after LMP) through a pregnancy registry. This surveillance activity will be conducted in order to monitor the safety of COVID-19 vaccines during pregnancy and detect signals of adverse pregnancy and birth outcomes that warrant further investigation.

Objective:

To establish an enhanced active surveillance system for persons exposed to COVID-19 vaccine during pregnancy or in the periconception period to rapidly provide information about the safety of COVID-19 vaccines for pregnant persons and their infants.

Methods:

Surveillance Population and Inclusion Criteria

The population of pregnant persons eligible for surveillance through the pregnancy registry will include those exposed to COVID-19 vaccines during pregnancy or in the periconception period (30 days before LMP through 14 days after LMP) (Figure 1). Additional data will be collected on these pregnant persons; infants born to these persons will be monitored for the first three months of life to identify any newborn complications and diagnoses of major birth defects. Persons who are found not to be pregnant at the time of vaccination and are not identified as pregnant within 30 days after vaccination will not be included in the registry.

Identification of exposed pregnancies

V-safe is an opt-in text messaging and web-based surveillance system that will be offered to COVID-19 vaccine recipients. As part of the initial v-safe survey, all non-male participants (i.e., female, prefer not to say, other) will be asked questions about pregnancy status. In addition, screening questions to identify potential pregnancies will be asked at v-safe health check-ins that occur at days 21 and 42 after each vaccine dose (if applicable) and at 3, 6, and 12 months after the last vaccine dose (Figure 2). V-safe data managers at CDC will notify the pregnancy call center team (described below) of potential pregnant vaccine recipients daily. The pregnancy call center will be staffed by individuals trained to administer the questionnaire and also trained on the handling of PII. In order to identify as many pregnant persons as possible through v-safe, the follow up plan is:

- If a person answers "yes" to any pregnancy question, on the v-safe text messaging survey, she will be sent a follow-up survey by Oracle to respond to three questions. The first question is confirming pregnancy and the other two questions are related to interest in participating in the registry. All survey responses will be sent to the pregnancy call center.
- Those who responded “yes” to any pregnancy question, “yes” to being interested in being from the follow-up survey or who did not respond at all will be contacted by the pregnancy call center. During her initial call, she will be asked to participate in the pregnancy registry. If she declines, there will be no further contact by the pregnancy call center. She will remain enrolled in the v-safe text message monitoring system unless she elects to opt out.
- If she no longer participates in the v-safe survey questions (i.e., stops responding or opts out) after indicating “don’t know” to a pregnancy question, she will also be contacted by the pregnancy call center within 3 months of her last response to inquire about her pregnancy status.

The CDC v-safe pregnancy call center staff will be notified of participants who may be pregnant via a dataset that will be created from the v-safe survey system. The dataset will include the following variables:

- Unique v-safe id
- First Name
- Last Name
- Sex
- Full date of birth
- Phone Number
- Zip code

- Time zone
- Preferred language
- Race/ethnicity
- Vaccination dates
- Vaccine type
- Pregnancy response date
- Survey number that identified pregnancy

Data collection

CDC v-safe pregnancy call center and registry

The CDC v-safe pregnancy call center (referred to in this protocol amendment as call center) will be operated by CDC staff from ISO and other groups at CDC with obstetric and pediatric expertise (including the COVID-19 Epidemiology & Surveillance Task Force Pregnancy and Infant Linked Outcomes Team, which includes clinicians from the Division of Reproductive Health and the Division of Birth Defects and Infant Disorders). The call center staff will contact persons identified as pregnant or potentially pregnant in v-safe by calling or texting them using the mobile phone number provided during v-safe registration. The call center staff will be trained to conduct phone interviews with the pregnant participants, including: confirmation of the identity of the v-safe participant and whether the person was pregnant at the time of vaccination or within 30 days after vaccination, informing the pregnant person about the pregnancy registry, including risks, benefits, and alternatives, requesting consent for participation in the registry and for release of medical records from healthcare providers, and asking specific survey questions relevant to pregnancy. The call center staff will also be trained on how to handle challenging situations, such as pregnancy loss, neonatal or infant death, diagnosis of major birth defects and other severe outcomes and when to defer a call to one of the call center clinicians. Persons will be contacted once each trimester during pregnancy and at two time points in the postpartum period, once after delivery and once after the infant is 3 months old. Information collected from the v-safe pregnancy call center survey and medical records will include demographics, pre-pregnancy and gestational conditions, pregnancy history, COVID-19 vaccine information, pregnancy complications, pregnancy outcome and infant outcomes.

The initial contact will collect pregnancy history information, including outcomes of prior pregnancies, dating of current pregnancy, and pregnancy complications or comorbidities to date. Subsequent brief call center follow ups will occur once every trimester to identify any pregnancy complications. A longer call center follow up will occur at 4-8 weeks postpartum to obtain information on the delivery and any potential complications in the mother or infant. At this postpartum contact, the call center will also request consent from the person for release of her infant's medical records. A brief, final call center follow up will occur when the infant is 3 months old to inquire about any adverse events, including the diagnosis of any birth defects.

The call center staff will attempt to obtain medical records on all pregnant persons after the pregnancy conclusion (including medical records from obstetrical visits, ultrasounds, inpatient encounters, emergency room visits and notes from the delivery admission) and after the first 3 months of the infant's life (including well visits, genetic testing, subspecialty encounters, inpatient encounters) for all participants who consent to medical

record release, in order to verify diagnoses and complement information obtained over the phone. Medical record requests will be minimized to those required for development of clinical history and diagnosis verification.

Unreachable

The pregnancy call center might be unable to reach some pregnant persons exposed to COVID-19 vaccination for a variety of reasons. If there is a lack of response to a telephone call from the call center, the pregnant person receives a voicemail explaining the purpose of the call, in addition to a text message stating that the CDC pregnancy registry attempted to contact her. If the person does not respond to phone calls or text messages despite two separate attempts, performed 3 days apart at a different time of day, the pregnant person will be considered as unreachable and will no longer be included in the phone survey component of the registry. Any pregnant participant in the call center and registry may opt of out of the phone surveys or medical record release at any time. Opting out of the pregnancy phone surveys and/or medical record release does not preclude continued participation in v-safe.

Potential for duplication of data

Because the v-safe active surveillance program will also collect information on health impact events among participants that will result in a follow-up call and submission of a VAERS report, there is the potential for duplicative efforts among pregnant persons within v-safe and between the v-safe and VAERS pregnancy surveillance systems. V-safe and VAERS ISO staff will work closely together in order to minimize these duplicative efforts and to minimize the potential burden on pregnant persons and their healthcare providers. If a pregnancy is reported at the same time as a clinically important adverse event (defined by v-safe as a symptom or health condition that led to inability to work, led to inability to perform daily activities, or required care from a doctor or other healthcare professional), the event will first be reported to the VAERS call center per the v-safe protocol. After the pregnant person is contacted by the VAERS call center, she will then be contacted by the pregnancy call center team to inquire about her pregnancy and participation in the pregnancy registry. Additionally, if a pregnant person enrolls in v-safe and participates in the pregnancy registry and she or her healthcare provider independently submits a spontaneous VAERS report, the CDC v-safe pregnancy call center will only collect medical records that are not being collected via the standard VAERS procedures. This will be done to minimize the number of times a vaccine recipient is contacted, avoid duplicating efforts to obtain medical records, and avoid collecting overlapping information on the same vaccine recipients in multiple surveillance systems.

Clinical Review

Obstetric, neonatal and infant outcomes in the pregnancy registry will be reviewed by a panel of CDC clinical subject matter experts in order to accurately and consistently identify and classify potential pregnancy and infant clinical outcomes associated with exposure to COVID-19 vaccines. The review process will involve examination of all reported clinical data. Subject matter experts on the review panel may include obstetrician/gynecologists, pediatricians, pediatric infectious disease experts, vaccine safety experts, nurses, epidemiologists, analysts and others with extensive experience in birth defects surveillance. As needed, experts in specific areas not otherwise covered by the clinical review panel will be consulted (e.g. clinical geneticist, developmental specialist). Data will undergo review by multiple reviewers to ensure consistency in case classification, clinical review quality standards and ensure consensus in the interpretation of reported data and outcomes.

Analysis plan:

Data from the pregnancy registry will be analyzed monthly at a minimum; reports will include descriptive analyses of any adverse outcomes and rates of follow up among pregnant persons. Specifically, we will calculate rates of fetal demise (spontaneous abortion and stillbirth), pregnancy complications (pregnancy induced hypertension, gestational diabetes, pre-eclampsia), adverse birth outcomes (preterm delivery, small for gestational age, low birth weight, neonatal intensive care unit stays), major birth defects, and other outcomes of interest. These proportions may be compared to national averages, published background rates or estimates seen in other data systems. Adverse events may be analyzed in aggregate if rare (i.e., any major cardiac defect). Any potential signals will be compared to other surveillance systems, such as VAERS, and specifically for birth defects, the CDC's Metropolitan Atlanta Congenital Defects Program or the Texas Birth Defects Registry. Persistent signals will be evaluated in more robust database systems (such as the Vaccine Safety Datalink) that have denominator data of pregnant persons who received COVID-19 vaccines and comparison groups of pregnant persons who did not receive COVID-19 vaccines. For rare outcomes, evaluations may also be conducted in other database systems, such as the FDA or the Department of Defense (DOD), for appropriate follow up assessment.

Data quality, and management:

V-safe data will be collected, managed, and housed on a secure server by Oracle. Through Health and Human Services (HHS), Oracle has donated IT services to any agency conducting COVID-19 related activities. Oracle is providing IT support for v-safe. All VSAFE data is collected, stored, processed and transmitted in Federal Risk and Authorization Management Program (FEDRAMP) approved infrastructure environment (10).

CDC ISO data managers will create a dataset for the VAERS/v-safe pregnancy call center which includes only those participants who report potential pregnancies. V-safe pregnancy registry data obtained in phone calls and medical records will be stored on an internal CDC server. Data from all components of the v-safe pregnancy registry may be combined into a master dataset behind the CDC firewall using unique identification numbers assigned at registration.

Pre-approved CDC investigators and data managers, including CDC contractors, will be the only individuals with access to the full data. All electronic documents, data sets, and files relevant to the project will be stored on network folders with restricted access on CDC computers. The v-safe team at CDC will be primarily responsible for data management activities, including data extraction, documentation and archival of a final data set. The archive will include the protocol, statistical programs, human subjects review documents, statistical output, analytical data sets, and manuscripts. Data sharing plans will be developed at the completion of data collection.

Human subjects considerations and confidentiality

This protocol will require human subjects determination at CDC because CDC is the lead site and surveillance data will include collection of personal identifiable information (PII). This data will be collected for public health surveillance, not for research purposes. No PII will be included in any v-safe analyses, manuscripts, or datasets shared externally. Participation is voluntary and individuals self-enroll. Participants can opt-out of the v-safe pregnancy registry at any time and their data will only be used for the time they were considered an active participant. In addition, this activity presents minimal risk to subjects, and use of patient data for this purpose will not adversely affect subjects' rights or welfare.

Duration

The anticipated duration of an individual's and infant's inclusion of the v-safe pregnancy call center registry will be up to one year after vaccination, depending on the time point in pregnancy that a person is exposed to vaccine. The decision to discontinue the v-safe program or to modify v-safe procedures to scale back active telephone follow-up will be made in consultation with key stakeholders including the CDC COVID-19 Vaccine Task Force leadership and FDA.

Limitations and challenges

Limitations and challenges for v-safe pregnancy surveillance include the potential for limited enrollment and retention in the program given its voluntary nature. It might be difficult to contact pregnant and postpartum persons by phone, and to obtain medical records on all pregnant persons and infants. Furthermore, vaccinated pregnant persons who choose to participate in v-safe might be different from those who decline; therefore, rates of side effects and adverse events generated from v-safe might not be generalizable to the full population of pregnant vaccine recipients. Similarly, pregnant persons who choose to participate in the pregnancy registry might be those who are more likely to have concerns or have experienced adverse events. This potential bias will be minimized by the prospective nature of this surveillance system and by review of medical records and accurate characterization of events. Additionally, a sensitivity analysis examining only outcomes among those who were enrolled and monitored before an adverse pregnancy or birth outcome occurred will be performed. Finally, the information provided by v-safe pregnant participants for up to one year after vaccination might be impacted by recall bias, specifically among those on whom we are unable to obtain medical records.

Dissemination of information

Safety profile information from the registry may be presented to Advisory Committee on Immunization Practices (ACIP) subgroups (such as the Vaccine Safety Technical Subgroup [VaST]), ACIP meetings and other meetings that are requested. Further, at the conclusion of the registry, a final report will be written detailing the findings of this surveillance activity.

Figure 1. Entry into the v-safe pregnancy registry

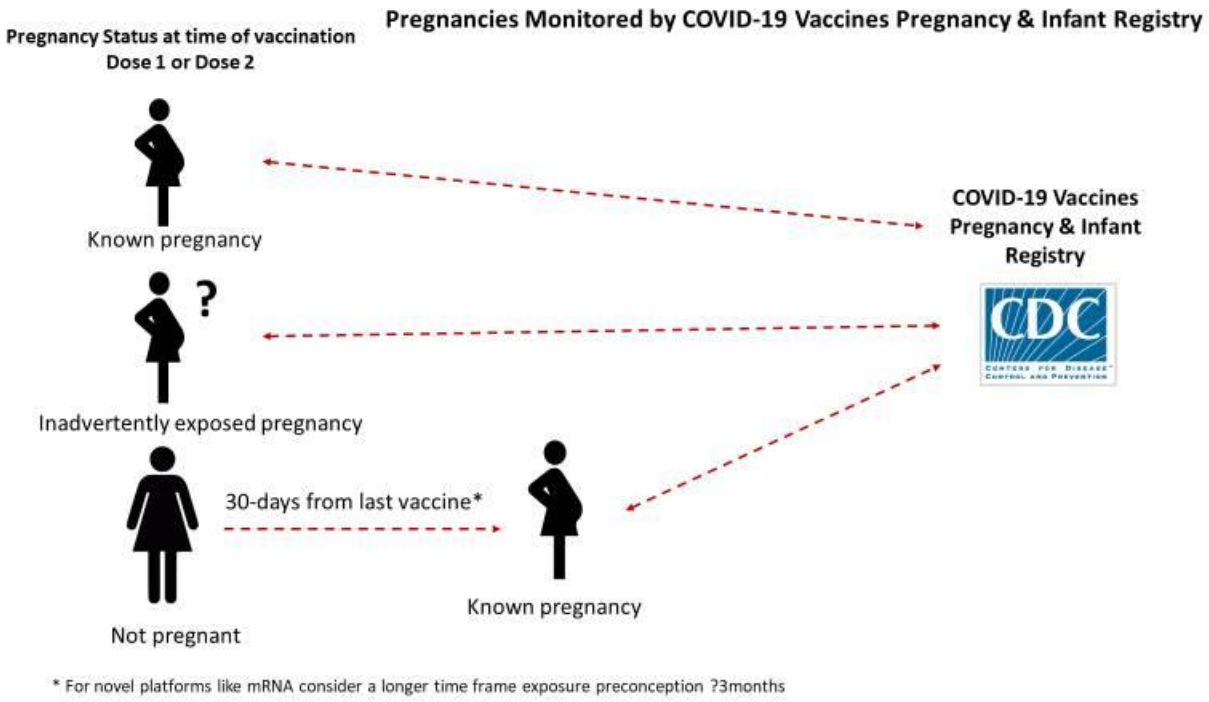
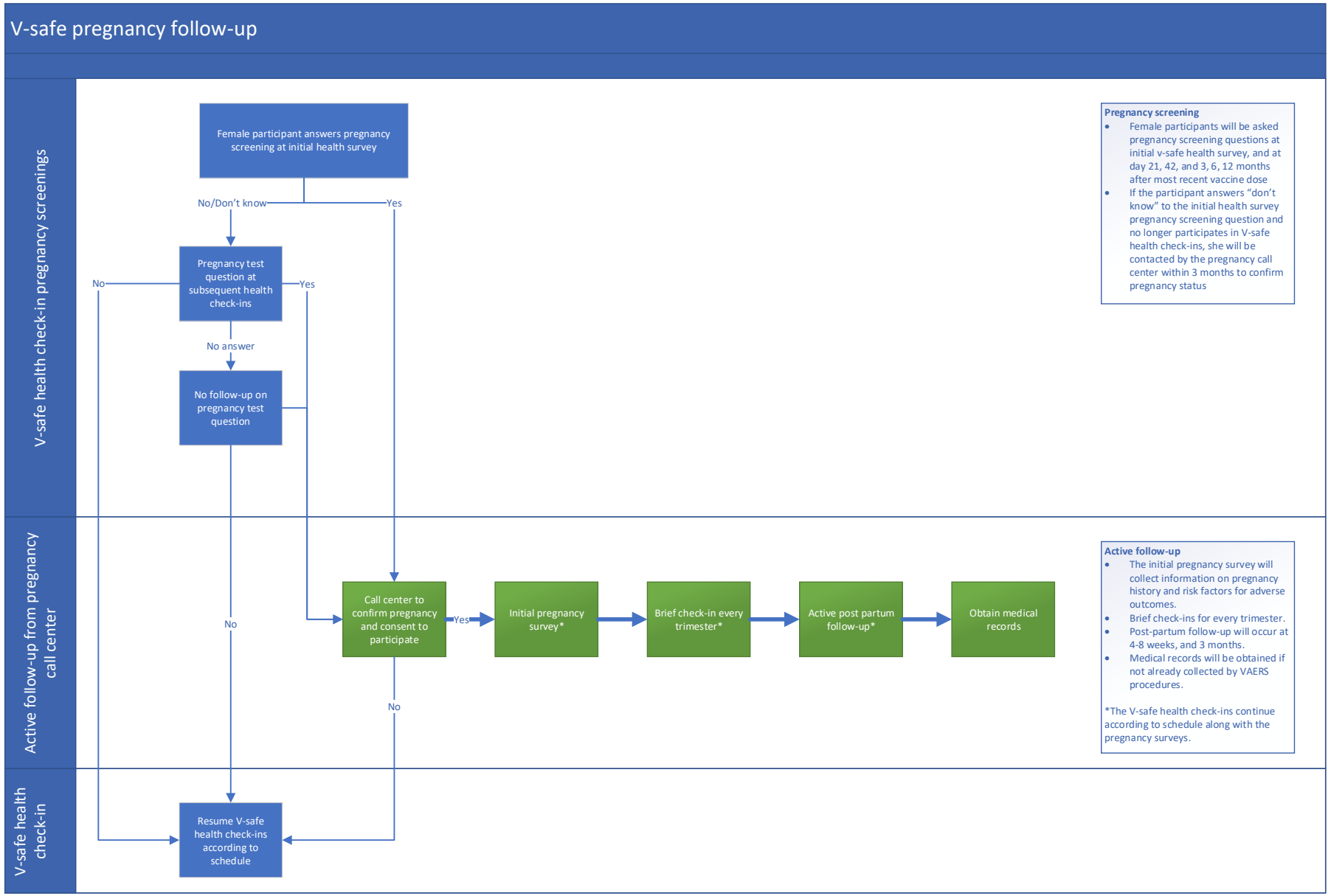


Figure 2. V-safe survey pregnancy ascertainment questions



References:

1. https://www.fda.gov/media/144337/download
2. https://www.fda.gov/media/144585/download
3. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/COVID-05-Vote.pdf
4. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-10/COVID-Wallace.pdf
5. https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e2.htm?s_cid=mm695152e2_w
6. https://www.fda.gov/media/144414/download
7. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html
8. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/slides-12-12/COVID-03-Mbaeyi.pdf
9. https://www.cdc.gov/vaccinesafety/ensuringsafety/index.html
10. *https://www.gsa.gov/technology/government-it-initiatives/fedramp)*