# Expanded Access Investigational New Drug (IND) Protocol: Domestic Use of Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP; V920) for Pre-exposure Prophylaxis (PrEP) Vaccination of Adults (≥ 18 years of age) at Potential Occupational Risk for Exposure to *Zaire ebolavirus*

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## ABBREVIATIONS/DEFINITIONS

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| AE | Adverse event |
| CDC | Centers for Disease Control and Prevention |
| ELISA | Enzyme-linked immunosorbent assay |
| EU/mL | Endotoxin units per milliliter |
| EVD | Ebola virus disease |
| FDA | Food and Drug Administration |
| HIV | Human Immunodeficiency Virus |
| IgG | Immunoglobulin G |
| IM | Intramuscular |
| IND | Investigational New Drug |
| IP-10 | γ-inducible protein 10 |
| IRB | Institutional Review Board |
| MDV | Multi-dose vial |
| NHPs | Nonhuman primates |
| PCR | Polymerase chain reaction |
| PFU | Plaque-forming units |
| PrEP | Pre-exposure prophylaxis |
| PREVAIL | Partnership for Research on Ebola Virus in Liberia study |
| rVSV | Recombinant vesicular stomatitis virus |
| rVSVΔG-ZEBOV-GP | Recombinant vesicular stomatitis virus with envelope glycoprotein replaced by *Zaire ebolavirus* (Kikwit 1995 strain) glycoprotein (V920) |
| SAE | Serious adverse event |
| SDV | Single-dose vial |
| STRIVE | Sierra Leone Trial to Introduce a Vaccine against Ebola |
| VAERS | Vaccine Adverse Event Reporting System |

# 1 INTRODUCTION and BACKGROUND

Ebola virus is a zoonotic pathogen that causes severe hemorrhagic fever in humans known as Ebola virus disease (EVD). The virus is transmitted through contact with body fluids from infected patients. There are four species of Ebola virus that have been known to cause disease in humans. Of these, species *Zaire ebolavirus* is the most lethal with case fatality rates of 70-90% if left untreated.

Ebola Zaire Vaccine (also known as V920, rVSVΔG-ZEBOV-GP or rVSV-ZEBOV; brand name Ervebo®), manufactured by Merck Sharp & Dohme Corp., NJ, USA, is a replication-competent, live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine with the gene for the *Zaire ebolavirus* Kikwit strain glycoprotein (ZEBOV-GP) replacing the gene for the native VSV glycoprotein.[1] The vaccine was approved by the U.S. Food and Drug Administration (FDA) on December 19, 2019 for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older, based on the data from 12 clinical trials in which a total of 15,399 adults received a dose of $\geq 2x10^7$ (plaque-forming units) pfu. Clinical efficacy of the vaccine was supported by an open-label, randomized cluster (ring) vaccination study during the 2014-2016 outbreak in Guinea (Ebola Ça Suffit trial), in which 3,537 contacts and contacts of contacts of individuals with laboratory-confirmed EVD received either immediate or delayed (21 days or later) vaccination. Clinical immunogenicity was assessed in three studies conducted in Liberia, Sierra Leone, United States (U.S.), Canada, and Spain.

The rVSVΔG-ZEBOV-GP vaccine has been demonstrated to be a safe and effective vaccine for preventing EVD infection in well-controlled clinical trials. The vaccine has been shown to elicit rapid immune response in 14 days after a single dose. Seroconversion in adults peaked between 28 and 35 days for most clinical trial subjects.[2] However, the rVSVΔG-ZEBOV-GP vaccine does not provide cross protection against other species of *Ebolavirus* or *Marburgvirus*. Since the evaluation of clinical efficacy and immunogenicity has not been done in the same study, it is not possible to define a correlate of protection at the individual level. The duration of protection conferred by rVSVΔG-ZEBOV-GP is unknown, and effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin, and/or blood or plasma transfusion is also unknown.

Preliminary data from vaccine response during the 2018 outbreak in the Democratic Republic of Congo (DRC) confirm efficacy of rVSV-ZEBO-GP against disease.[3] Vaccine efficacy evaluation and safety monitoring during the vaccine response in DRC will provide additional data as they become available. See **Section 8, Efficacy and Safety Information of rVSVΔG-ZEBOV-GP for EVD** for a summary of efficacy and safety information from clinical studies and clinical experiences of the vaccine during the West Africa Ebola outbreak.

Importation of EVD to the U.S. from an epidemic region through an infected traveler or healthcare worker is a recognized risk with potential for secondary transmissions. During the 2014–2016 Ebola outbreak in West Africa, 11 people were treated for EVD in the U.S. Of the 11 domestically-treated EVD patients that resulted in 2 deaths, two were imported cases of EVD and seven were persons with EVD symptoms transported from West Africa to U.S. hospitals. Two domestic healthcare workers who cared for the first travel-associated EVD case diagnosed in the U.S., a man who traveled from West Africa to Dallas, Texas, tested positive for *Zaire ebolavirus*. The patient died but both healthcare workers recovered.[4]

The prior 2014–2016 Ebola outbreak in West Africa and the 2018 Ebola outbreak in DRC heighten the importance of pre-event preparedness and response, including vaccine availability and access to protect high-risk groups who may have potential occupational exposure to Ebola virus (e.g., laboratorians, healthcare workers, emergency responders) for pre-exposure prophylaxis (PrEP) against *Zaire ebolavirus*. On February 26, 2020, the Advisory Committee on Immunization Practices (ACIP) recommended PrEP vaccination with rVSVΔG-ZEBOV-GP for adults ≥ 18 years of age in the U.S. population who are at potential occupational risk of exposure to Ebola virus (species *Zaire ebolavirus*) because they are

responding or may respond to an outbreak of EVD; laboratorians or other staff working at biosafety-level 4 facilities in the U.S.; or healthcare personnel working at federally-designated Ebola Treatment Centers in the U.S.

## 2 EXPANDED ACCESS IND PROGRAM DESCRIPTION

With FDA's approval of rVSVΔG-ZEBOV-GP for prevention of EVD in adults (≥ 18 years) in December 2019, the manufacturing of licensed vaccine doses by Merck is actively underway and the delivery of licensed vaccine supply to the Strategic National Stockpile is expected to begin before the end of 2020. The rVSVΔG-ZEBOV-GP vaccine (Ervebo) is not planned for commercial marketing and domestic vaccine access will be facilitated through the U.S. government. Therefore, the Centers for Disease Control and Prevention (CDC) is sponsoring this expanded access IND program to provide domestic access to the investigational rVSVΔG-ZEBOV-GP vaccine (referred to as IND-labeled vaccine hereafter) for PrEP use in adults (≥ 18 years of age)* who are at potential risk of occupational exposure to Ebola virus (species *Zaire ebolavirus*) when licensed vaccine doses are unavailable or in limited supply to meet the PrEP vaccination needs.

Although the IND-labeled vaccine being made available under this IND protocol is produced using the same manufacturing process as the licensed vaccine, it was not produced at the specific manufacturing facility that renders the vaccine FDA-licensed (i.e., FDA-approved). Therefore, the regulatory status of the IND-labeled vaccine is differentiated from the FDA-licensed vaccine but is the same vaccine that was used and studied in over 15,000 people worldwide which provided scientific data to support the FDA's approval (i.e., licensure) of the vaccine. This IND is intended to facilitate interim vaccine access while the availability of licensed vaccine, Ervebo, is pending. Given the February 26th, 2020 ACIP recommendations, there is need for PrEP vaccination of individuals with occupational risk of Ebola virus exposure, especially for those deploying to areas with Ebola outbreaks, as there is no other means of domestic Ebola vaccine access (PREPARE study by National Institutes of Health is no longer enrolling new vaccinees).

The procedures set forth in this expanded access IND program are to help ensure that CDC, the sponsor of the IND, and the healthcare providers, their institutions/sites and affiliated personnel involved in the request receipt, handling, administration and disposal of IND-labeled vaccine are informed of and abide by the FDA regulations regarding IND and human subjects protections requirements (21 CFR Parts 312, 50, and 56). CDC will provide IND-labeled vaccine upon receipt of request by licensed healthcare providers from institutions/sites with identified individuals who meet the eligibility criteria under this IND protocol (see **Section 2.1, Inclusion Criteria/Eligibility**), aligned with the 2020 ACIP recommendations. Under this expanded access IND program, the requesting healthcare providers will serve as site investigators to assume the oversight responsibility, including any delegated activities, regarding vaccine receipt, handling and use at their institutions/sites, and monitoring and reporting of serious adverse events (SAEs) resulting from rVSVΔG-ZEBOV-GP administration. See **Section 5**, **Procedures**, and **Section 7, Program Responsibilities**, for further details.

### 2.1 Inclusion Criteria/Eligibility

In order to be eligible to receive rVSVΔG-ZEBOV-GP vaccine under this expanded access IND program, individuals must be adults (≥ 18 years of age) in the U.S. population who are at potential high risk of occupational exposure to Ebola virus (species *Zaire ebolavirus)* because they:

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* Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP; Ervebo) is FDA-approved for the prevention of disease caused by *Zaire ebolavirus* in individuals ≥ 18 years of age. While the use of the vaccine in the adult population will generally fall under its FDA-approved status, this expanded access IND enables the use of IND-labeled vaccine.

- Are responding or may respond to an outbreak of Ebola virus disease (e.g., persons who would be expected to provide care for Ebola patients or be deployed to an outbreak area)
  or
- Work as laboratorians or other staff at biosafety-level 4 facilities in the U.S.
  or
- Work as healthcare personnel** at federally-designated Ebola Treatment Centers in the U.S.

**Healthcare personnel refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to Ebola patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These healthcare personnel include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, physician assistants, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel). Adapted from https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.html

Please see the **Occupational Risk/Vaccine Eligibility Assessment Form** (Appendix A1) to help identify vaccine candidates and complete the **Ebola Vaccine Request and Use Agreement Form,** and **Form FDA 1572** (Appendix A2) to submit the vaccine request to CDC.

### 2.2 Exclusion Criteria

The rVSVΔG-ZEBOV-GP vaccine should not be given to individuals with any of the following:

- Known severe allergy, such as anaphylaxis, to any component of the vaccine, including rice protein
- Clinical evidence (e.g., oral temperature >38°C [100.4°F], systemic symptoms) of a systemic infection or other acute intercurrent illness at the scheduled time of vaccination†
- Presence of any clinically significant medical condition, past medical history, pre-existing illness (e.g., acute malignancy, history of Guillain-Barré syndrome, history of neurologic disorder that may increase risk, active autoimmune disorder or immunosuppression) that in the opinion of the healthcare provider (i.e., site investigator) may place the individual at an unreasonably increased risk by getting the vaccine
- Unwilling to complete the informed consent process and sign the consent form

†Vaccination may be rescheduled at a later date if the conditions resulting in ineligibility are no longer present.

While pregnancy and lactation are not absolute exclusion criteria for receiving rVSVΔG-ZEBOV-GP, live, attenuated vaccines are generally contraindicated during pregnancy. Women of reproductive age should be counseled on the potential fetal risk(s) of vaccination, and determination of whether to receive rVSVΔG-ZEBOV-GP should be made on an individual basis, in consultation with a healthcare provider, based on the risk/benefit of vaccination against the risk of exposure to Ebola virus.

Laboratory and healthcare workers at risk for occupational exposure to *Zaire ebolavirus* receiving IND-labeled vaccine must continue to adhere to recommended biosafety guidelines and infection prevention and control procedures. Individuals responding to an EVD outbreak must wear recommended personal protective equipment and follow proper procedures to prevent infection upon direct contact or contact with body fluids from a suspected or confirmed Ebola patient even if they received the IND-labeled vaccine.

# 3 PRECAUTIONS/SPECIAL POPULATIONS/ADVERSE EVENTS

## 3.1 Precautions

- Among the 15,399 adult subjects vaccinated with rVSVΔG-ZEBOV-GP during the clinical development of the vaccine, there were two reports of serious vaccine-related pyrexia and two reports of non-fatal anaphylaxis. Following vaccination with rVSVΔG-ZEBOV-GP, monitor the vaccinated individuals for signs and symptoms of hypersensitivity reactions. Appropriate medical treatment and supervision must be available in case of an anaphylactic event following the vaccine administration. Each vaccinated individual should be observed for a minimum of 30 minutes post-vaccination.
- Vaccination with rVSVΔG-ZEBOV-GP may not protect all individuals. Vaccinated individuals should continue to adhere to recommended infection control practices to prevent *Zaire ebolavirus* infection and transmission.
- The safety and effectiveness of rVSVΔG-ZEBOV-GP have not been assessed in immunocompromised individuals. The effectiveness of rVSVΔG-ZEBOV-GP in immunocompromised individuals may be diminished. To date, a small number of HIV-positive adult subjects have been vaccinated with rVSVΔG-ZEBOV-GP in the Partnership for Research on Ebola Virus in Liberia's (PREVAIL) first study (PREVAIL I).[5] Additional studies are ongoing to evaluate the use of rVSVΔG-ZEBOV-GP in HIV-positive subjects without severe immune compromise. The risk of vaccination with rVSVΔG-ZEBOV-GP, a live virus vaccine, in immunocompromised individuals should be weighed against the risk of disease due to *Zaire ebolavirus*.
- Because rVSVΔG-ZEBOV-GP is produced with rice derived recombinant human serum albumin, precaution should be taken with individuals allergic to rice. Individuals with a history of severe allergic reaction (e.g., anaphylaxis) to rice protein should not receive rVSVΔG-ZEBOV-GP.
- Vaccine virus RNA has been detected by reverse-transcription polymerase chain reaction in urine (up to 7 days post-vaccination), blood and saliva (up to 14 days post-vaccination), and fluid from skin vesicles (up to 20 days post-vaccination) of vaccinated adults.[2,6-10] Transmission of vaccine virus through close personal contact is a theoretical possibility. Healthcare providers administering vaccine should exercise appropriate infection control practices. Vaccine recipients should avoid:
    - sharing needles, razors, toothbrushes, eating utensils, drinking from the same cup, and open-mouth kissing for 2 weeks after vaccination; if oral sores develop after receiving vaccine, avoid these activities until the sores heal.
    - close contact and association with high-risk individuals (e.g., immunocompromised individuals, pregnant or breastfeeding women, infants (< 1year of age)) for up to 6 weeks following vaccination.
    - exposure of livestock to blood and bodily fluids for up to 6 weeks following vaccination.

  Additional post-vaccination instructions for vaccinated individuals are detailed in **Appendix B1, Informed Consent Form**.

## 3.2 Considerations for Special Populations

Pregnancy

There are no adequate well-controlled studies of rVSVΔG-ZEBOV-GP in pregnant women, and human data available from clinical trials with rVSVΔG-ZEBOV-GP are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy. In the randomized, unblinded Phase 2/3 Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) study that evaluated rVSVΔG-ZEBOV-GP vaccine, there were 84 pregnant women; 31 and 18 pregnant women in the immediate and deferred crossover vaccination arms, respectively, became pregnant within 60 days after vaccination, and 35 in the unvaccinated group became pregnant within 60 days of enrollment. Of the pregnant women with known

outcomes, no statistical difference in pregnancy loss, defined as spontaneous abortion and still birth, was observed between pregnant women in the immediate vaccination (14/31; 45%) and unvaccinated (11/33; 33%) arms. No external congenital anomalies were detected among 44 live-born infants examined (born to 28 vaccinated and 16 unvaccinated pregnant women).[11]

The World Health Organization recommends the use of rVSVΔG-ZEBOV-GP in pregnant and breastfeeding women during an active *Zaire ebolavirus* outbreak in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol.[12] Vaccination for pregnant women should consider the risk of exposure to *Zaire ebolavirus* against potential vaccine-related risk during pregnancy based on individual informed decisions.

Lactation
Human data are not available to assess the impact of rVSVΔG-ZEBOV-GP on milk production, its presence in breast milk, or its effects on the breastfed child. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for rVSVΔG-ZEBOV-GP and any potential adverse effects on the breastfed child from rVSVΔG-ZEBOV-GP or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

Older Adults
A total of 542 subjects ≥ 65 years of age received rVSVΔG-ZEBOV-GP during clinical development of the vaccine. Although this was inadequate to determine whether the immune response in older adults (≥ 65 years) is different from younger participants, the FDA-approval of Ervebo for prevention of disease caused by *Zaire ebolavirus* in adults (≥ 18 years) is inclusive of older adults without an upper age limit.

### 3.3 Possible Adverse Events with rVSVΔG-ZEBOV-GP
The most commonly reported injection-site adverse events among the adult subjects vaccinated with rVSVΔG-ZEBOV-GP during clinical development were injection-site pain (70%), swelling (17%), and redness (12%). The most commonly reported systemic adverse events following vaccination with rVSVΔG-ZEBOV-GP were headache (37%), feverishness (34%), muscle pain (33%), fatigue (19%), joint pain (18%), nausea (8%), arthritis (5%), rash (4%) and abnormal sweating (3%). The potential for previously not known, rare, serious events following vaccination may be possible. Monitor individuals for signs and symptoms of reactions following vaccination. Appropriate medical treatment and supervision must be available in case of an anaphylactic event.

## 4 PRODUCT DESCRIPTION
The rVSVΔG-ZEBOV-GP vaccine, manufactured by Merck Sharp & Dohme Corp., USA, is a live, attenuated recombinant Vesicular Stomatitis Virus (rVSV) with a deletion of the VSV envelope glycoprotein that is substituted with the *Zaire ebolavirus* (Kikwit 1995 strain) surface glycoprotein. The vaccine virus is grown in serum-free Vero cell cultures, harvested from the cell culture medium, and purified to produce bulk drug substance before being aseptically added to a drug product stabilizer solution. The filled final vaccine is supplied as single-dose vials containing a 1-mL dose and stored frozen at -80ºC to -60ºC (-112ºF to -76ºF) for long-term storage.

Each 1 mL dose contains a minimum of 72 million plaque forming units ($7.2 \times 10^7$ pfu) of vaccine virus in a stabilizer solution containing 10 mM Tromethamine (Tris) and 2.5 mg/mL rice-derived recombinant human serum albumin. Each 1 mL dose may contain residual amounts of host cell DNA (≤10 ng) and benzonase (≤15 ng). The vaccine may contain trace amounts of rice protein. The product contains no preservatives. The vaccine vial stopper is not made with natural rubber latex.

While licensed rVSVΔG-ZEBOV-GP and IND-labeled rVSVΔG-ZEBOV-GP vaccines are produced with the same ingredients and the same processes, they are produced at different manufacturing facilities and have different regulatory status with FDA.

Frozen vaccine will be shipped from Merck to the participating sites at ≤-60°C on dry ice in an insulated shipping container containing a temperature monitoring device. The preference is to maintain rVSVΔG-ZEBOV-GP frozen at -80ºC to -60ºC until use to the extent possible. The vaccine should be thawed completely **at room temperature** since it is sensitive to slow thawing at refrigerated temperature. Once thawed, vaccine can be stored refrigerated at 2-8ºC (35.6- 46.4ºF) for a total time of **no more than 13 days** or at room temperature (up to 25ºC; 77ºF) for a total time of **no more than 3 hours**. Please note that the maximum duration of post-thawed, IND-labeled vaccine storage at respective refrigerated and room temperatures is different from the durations noted for Ervebo in the package insert for the licensed Ebola vaccine.

## 5 PROCEDURES

The IND-labeled vaccine will be provided upon CDC's receipt and review of request from licensed healthcare providers for individuals with occupational risk of exposure to *Zaire ebolavirus*. After verifying requests, CDC will coordinate shipment of frozen vaccine(s) to participating sites directly from Merck. Also see **Section 7, Program Responsibilities,** for related information.

### 5.1 Vaccine Request and Release Decision

- Before requesting IND-labeled vaccine, identify individuals with occupational risk for *Zaire ebolavirus* using the **Occupational Risk/Vaccine Eligibility Assessment Form** (Appendix A1).
    - This form is provided for site use to aid in determining individuals for whom vaccination is appropriate. The vaccine eligibility under the IND is for the 3 occupational risk groups as indicated under Section 2.1 (EVD responders, BSL-4 workers, and Healthcare personnel).
- Complete and submit the **Ebola Vaccine Request and Use Agreement Form, and Form FDA 1572** (Appendix A2) with curriculum vitae (CV) to CDC by fax (404-471-2526) or a scanned copy via email (spathvax@cdc.gov).
    - By submitting the completed and signed forms in Appendix A2, the licensed healthcare providers at participating sites acknowledge that they understand and agree to assume oversight responsibility, including any delegated activities, regarding vaccine receipt, storage, handling, use and disposal under the CDC-sponsored IND program at their institutions/sites, including ensuring informed consent, monitoring and reporting of SAEs resulting from rVSVΔG-ZEBOV-GP administration, in accordance with this expanded access IND protocol and applicable FDA IND regulations.
- Upon receipt, CDC will review, verify and/or discuss the information with the requesting institution/site as needed to make a release decision, and initiate vaccine shipment, accordingly, which will be coordinated by Merck.
- CDC will not approve vaccine if upon review, eligibility criteria per the protocol are not met, or if there is incomplete information, any known or cited violation with FDA regulations, and/or any reason for which the requesting institution/site will not be able to comply with the requirements of the IND protocol.

### 5.2 Shipment of Vaccine

CDC will notify the requesting healthcare provider or designee once the vaccine release decision has been made.

- IND-labeled vaccine will be shipped by Merck to the address indicated in the **Ebola Vaccine Request and Use Agreement Form, and Form FDA 1572** (Appendix A2). Shipment information with estimated delivery date will be provided once arranged.

- The vaccine is maintained at -80ºC to -60ºC (-112ºF to -76ºF) for long-term storage. The vaccine will be shipped to requesting sites frozen at ≤-60ºC (≤-76ºF). A temperature monitoring device will be included in each vaccine shipment. See **Table 1** and **Section 5.3, Vaccine Receipt and Handling at Participating Sites**, for further information on storage conditions and durations.

### 5.3 Vaccine Receipt and Handling at Participating Sites

- Upon receipt of vaccine shipment, delivered by Merck frozen (≤-60ºC (≤-76ºF)), at the participating site, slowly open the insulated shipping container packed with dry ice and point the lid away from the body and others in the area.
- Remove the primary shipping box containing the vaccine vials from the outer, insulated shipping container and place immediately into a -80ºC to -60ºC (-112ºF to -76ºF) freezer, if available at the participating site. Preference is to maintain vaccine vials at -80ºC to -60ºC (-112ºF to -76ºF) until use to the extent feasible.
  - If -80ºC to -60ºC (-112ºF to -76ºF) freezer capacity is not available, then thaw vials completely at room temperature until no visible ice is present (approximately 10 to 15 minutes). Thaw vaccine vials **at room temperature only** as vaccine is sensitive to slow thawing at refrigerated temperature. Once fully thawed, store immediately at 2ºC to 8ºC (35.6ºF to 46.4ºF) and use within the use-by-period indicated in Table 1 below.

**Table 1:** Use-by-Period Once Thawed[2]

| Storage Temperature | Maximum Storage Duration |
|---|---|
| 2°C to 8°C (35.6°F to 46.4°F) | 13 days |
| 9°C to 25°C (48°F to 77°F) | 3 hours |

*Note: The maximum storage durations mentioned in this table are specifically for the IND-labeled vaccine and shorter than the maximum storage durations mentioned in the US package insert for the FDA-approved vaccine, Ervebo.*

  - Transfer time from dry ice of the shipper to the -80ºC to -60ºC (-112ºF to -76ºF) freezer at the participating site, if available, or thawing at room temperature followed by refrigeration, if no freezer at the participating site, should be kept to a minimum.
  - Protect vaccine from light. Do NOT re-freeze.
- After appropriately storing the vaccine into the freezer or refrigerator, locate the temperature monitoring device included in the shipment. Plug it into the USB port of a laptop or desktop computer immediately to stop the temperature recordings. The screen on the device may be blank as it warms up while plugged into the USB port. Do not wait to thaw the temperature monitoring device prior to plugging into a USB port as this can lead to potential inaccurate temperature recordings.
  - If a temperature excursion is indicated on the device, notify the CDC. CDC, in coordination with Merck, will provide clarification on if the vaccine can still be used or if it is unacceptable for administration and the appropriate next steps to take (e.g. discard on site).
- Similarly, notify CDC if a temperature excursion occurs at any time during vaccine storage at the participating site for determination on product impact and usability of the vaccine.

### 5.4 Vaccination and Post-vaccination Procedures at Participating Sites

- IND-labeled vaccine administration at the participating sites will proceed with a designated licensed healthcare provider serving as a site investigator. Consultation with CDC Ebola subject matter experts is available as needed.
- Inform vaccinated individuals that if they choose to be vaccinated, then they will receive a brief voluntary electronic Post-Vaccination Adverse Events Survey from CDC via email or

text on or around days 7, 14, 21, and 28 after vaccination to monitor for specific adverse events. Show an example paper copy of **the CDC Post-Vaccination Adverse Events Survey** (Appendix B2) to eligible individuals with the informed consent form (ICF).

- For each eligible participant, conduct informed consent process (see **Appendix B1, Informed Consent Form**) and obtain a signed ICF prior to administering the vaccine. Provide a copy of the signed ICF to participants. On the day of vaccination, use the **Vaccination Record Form** (Appendix C) to assess and document vaccine eligibility, administration, and any or no occurrence of SAEs during the minimum 30-minute observation period following vaccination. The completed Vaccine Record Form for each vaccinated individual must be returned to CDC within 3 calendar days. Any subsequent AEs/SAEs experienced by the vaccinated individuals that the site investigator becomes aware of should be reported to VAERS.
- Remind vaccinated individuals of post-vaccination care and precautionary measures as outlined under the "**What you need to know AFTER you get the IND-labeled Ebola vaccine**" in the ICF (e.g., covering vaccination site, avoiding sharing razors, toothbrushes, eating utensils for 2 weeks after vaccine, avoid pregnancy for 8 weeks after vaccination by use of effective barrier prophylaxis and/or birth control, etc.).
- Within 14 calendar days of completing vaccination (i.e., having used received vaccines) or final vaccine disposition, complete the **Vaccine Product Accountability and Disposal Record Form** (Appendix D) and return to CDC by fax (404-471-2526) or a scanned copy via email (spathvax@cdc.gov). Failure to comply may result in further action and denial of future vaccine requests.

When the IND-labeled vaccine usage under the CDC-sponsored IND is determined no longer necessary (e.g., discontinuation of CDC-sponsored IND program), the participating sites will be notified with instructions to either discard or return the unused vaccines. Disposal and/or return must be appropriately documented in the **Vaccine Product Accountability and Disposal Record Form** (Appendix D).

## 6 DOSAGE AND ADMINISTRATION

Practice aseptic technique and standard precautions when preparing and administering IND-labeled vaccine intramuscularly (IM).

### 6.1 Preparation, Dosage and Administration

Supplies required:

- IND-labeled rVSVΔG-ZEBOV-GP (supplied as1-mL single dose vial containing $\geq 7.2 \times 10^7$ pfu)
- Sterile syringe (e.g., 3-mL syringe)
- Sterile needle for IM administration (e.g., 22-25 gauge, 1- to 1.5-inch length needle)

If frozen, thaw the vaccine vial completely **at room temperature** until no visible ice is present (approximately 10 to 15 minutes). Do not thaw the vial in a refrigerator as the vaccine is sensitive to slow thawing. Gently invert vial several times. The vaccine is a colorless to slightly brownish-yellow liquid with no particulates visible. Do not use if particulate matter or discoloration exist. Use the vaccine immediately after thawing. If not used immediately, the vaccine may be stored for up to 13 days at 2ºC to 8ºC (35.6ºF to 46.4ºF) or for up to 3 hours at room temperature (up to 25°C; 77°F) protected from light. **Do NOT re-freeze**.

Using aseptic technique, withdraw a 1 mL dose using a syringe with a sterile injection needle and administer the vaccine by IM injection in the deltoid area of the non-dominant arm at a 90º angle into the muscle tissue using a needle long enough to ensure IM deposition of the vaccine.

- Do not inject the vaccine intravascularly.
- No data are available for administration via the subcutaneous or intradermal routes.

After administration of the vaccine, the used vial and syringe should be disposed of as biohazardous waste in accordance with the participating sites' policy, as applicable. Used vials and syringes can be disposed of in normal biohazard containers, as the product does not contain Ebola virus.

## 7 PROGRAM RESPONSIBILITIES

CDC Principal Investigator

The CDC Principal Investigator is located at the CDC and has the oversight responsibility of this expanded access IND protocol to facilitate vaccine access for adults (≥ 18 years) with potential high risk of occupational exposure to EVD, and monitor appropriate use of rVSVΔG-ZEBOV-GP vaccine, including review of vaccination requests, evaluation of eligibility requirements and reported SAEs, and providing consultation to requesting healthcare providers (i.e., site investigators) as needed.

Licensed Healthcare Providers (Site Investigators)

By requesting and obtaining rVSVΔG-ZEBOV-GP vaccine under the CDC-sponsored IND 16337, the requesting licensed healthcare providers serve as site investigators for use of IND-labeled vaccine at their sites under this expanded access IND program and are responsible for ensuring appropriate handling, procedures and use of rVSVΔG-ZEBOV-GP at their institutions/sites in accordance with this IND protocol, and FDA IND regulations. By completing and signing the required **Ebola Vaccine Request and Use Agreement Form, and Form FDA 1572** (Appendix A2), the site investigator acknowledges and agrees to the responsibilities and also affirms the following to the best of their knowledge:

- The participating site has not been:
  i. Debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
  ii. Suspended by the Office for Human Research Protections as a clinical research site under 45 C.F.R. Part 46, and
- No persons performing activities in connection with the IND program has been disqualified as a clinical investigator under 21 C.F.R. Part 312.70 and/or convicted of a felony under federal law for conduct:
  i. Relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application, Pre-Market Application, 510(k) or IND or similar application; or
  ii. Otherwise relating to the regulation of any drug product or medical device under the Food Drug & Cosmetic Act.

### 7.1 Required Data Collection Forms, Monitoring and Safety Reporting

All required forms under this IND protocol must be completed and maintained at the institutions/participating sites and made available upon request by CDC or FDA. As mentioned in **Section 5, Procedures**, the following forms are provided for use, completion and/or return to CDC as specified below:

Appendix A1: **Occupational Risk/Vaccine Eligibility Assessment Form – Optional** for internal use by the vaccine-requesting institutions/participating sites to help identify individuals eligible for vaccine per occupational exposure risk assessment.

Appendix A2: **Ebola Vaccine Request and Use Agreement Form**, **and Form FDA 1572 – Required** in order to request vaccine. Must include the names of vaccine eligible individuals with their occupational risk categories. Submit the completed forms to CDC by email (spathvax@cdc.gov) or fax (404-471-2526).

Appendix B1: **Informed Consent Form (ICF) – Required and must be obtained prior to vaccination.** Provide participants a copy of their signed ICF. Retain the original, signed ICFs at the participating sites.

Appendix B2: **Example Copy of the CDC Post-Vaccination Adverse Events Survey – Required.** Inform the eligible individuals that they will receive a brief electronic survey from CDC via email or text on or around days 7, 14, 21, and 28 after vaccination to monitor for specific adverse events. The survey is expected to take less than 5 minutes to complete and will ask questions specific to the occurrence and severity of 5 specific adverse events (muscle pain, joint pain, joint swelling, skin lesions and/or oral lesions). Show an example paper copy of the survey to eligible individuals with the ICF.

Appendix C: **Vaccination Record Form (VRF) – Required**. Complete and return a VRF for each vaccinated individual to CDC within 3 calendars days of vaccination by email (spathvax@cdc.gov) or fax (404-471-2526). Retain copies at the participating sites. **All observed SAEs** during the **30-minute post-vaccination period must be recorded on the VRF and reported to CDC within 3 calendar days**, irrespective of whether the healthcare provider/site investigator considers the event to be vaccine-related or not. Any subsequent AEs/SAEs experienced by the vaccine recipients that the site investigator becomes aware of should be reported to VAERS (https://vaers.hhs.gov/).

Appendix D: **Vaccine Product Accountability and Disposal Record Form – Required.** Complete and return to CDC within **14 calendar days** of completing vaccination (i.e., having used received vaccines) or final vaccine disposition by email (spathvax@cdc.gov) or fax (404-471-2526). Failure to comply may result in further action and denial of future vaccine requests.

### 7.1.1 Definitions of AEs and SAEs per 21 CFR 312.32

An **Adverse Event** (AE) is any untoward medical occurrence associated with the use of rVSVΔG-ZEBOV-GP in humans, whether or not considered related to rVSVΔG-ZEBOV-GP. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of rVSVΔG-ZEBOV-GP, without any judgment about causality.

A **Suspected Adverse Reaction** is any AE for which there is a reasonable possibility that rVSVΔG-ZEBOV-GP caused the AE. It is a subset of all AEs for which there is a reasonable possibility that rVSVΔG-ZEBOV-GP caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between rVSVΔG-ZEBOV-GP and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

An **Adverse Reaction** is any AE caused by rVSVΔG-ZEBOV-GP. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that rVSVΔG-ZEBOV-GP caused the event (i.e., in greater degree of certainty than "suspected" adverse reaction).

**Unexpected**: An AE is considered "unexpected" if it is not listed in this protocol or Package Insert, or is not listed at the specificity or severity observed.

**Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)**: An AE or suspected adverse reaction is considered "serious" if, in the view of either the treating physician or CDC, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

**Serious and Unexpected Suspected Adverse Reaction (SUSAR):** A suspected adverse reaction that is both unexpected (not consistent with the observed or expected risk information applicable to rVSVΔG-ZEBOV-GP) and also meets the definition of "serious" described above.

**NOTE**: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed.

**Life-Threatening**: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the treating physician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.

Healthcare providers (i.e., site investigators) must report SAEs with 48 hours of his or her awareness, irrespective of whether the healthcare provider considers the event to be vaccine-related or not. CDC will review all SAEs received and report serious, unexpected suspected adverse reactions to FDA within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1). CDC will report all serious and unexpected suspected adverse reactions and incidents to CDC IRB according to CDC IRB's policy and procedures.

### 7.2 Regulatory and Administrative Requirements

CDC, the sponsor of the IND, and all licensed healthcare providers (serving as site investigators) who request and receive IND-labeled vaccine under this IND protocol will abide by the Code of Federal Regulations (in particular, 21 CFR Parts 50, 56, and 312) and FDA good clinical practice guidelines. The IND protocol is subject to FDA's review and authorization as well as review and approval by an Institutional Review Board (IRB). CDC IRB will serve as central IRB for approval and continuing review of this IND protocol, which is determined non-research (i.e., does not constitute human subjects per 45 CFR 46.102(l)). Therefore, participating sites may use CDC IRB's approval of this protocol that meets the FDA's requirements regarding IRB review per 21 CFR Parts 50 and 56.

Any change or modification to this expanded access IND program that affects the purpose, procedures, or significant data or administrative aspects will require a formal amendment to the protocol. Such protocol amendments will be approved by the CDC IRB and submitted to FDA prior to implementation.

Information about specific site investigators (i.e., names, CVs, or Form FDA 1572) and/or participating sites may be shared with FDA, local public health jurisdictions, and the vaccine manufacture. Any information pertaining to site investigators and/or participating sites that are provided to the vaccine manufacturer is limited to use in the manufacturer's discussions with health authorities concerning this CDC-sponsored IND program.

### 7.3 Confidentiality

Although the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule generally prohibits the use or disclosure of private health information without the written authorization of the participant, there are several exceptions to this requirement, including an exception for public health. Representatives from CDC, FDA, and the vaccine manufacturer are eligible to review medical and program records related to the IND-labeled vaccine use as a part of their responsibility to protect persons in this expanded access IND program. No personal data will be used in any external communication or publication.

All proprietary and confidential information (e.g., Merck's Investigator's Brochure) provided under and/or in association with this expanded access IND protocol for rVSVΔG-ZEBOV-GP should only be used for the stated purpose and scope of the IND protocol in accordance with the applicable IND regulatory requirements. This protocol and its contents should not be further distributed or disclosed for any other purpose without prior authorization from the CDC. All proprietary and confidential information (e.g., Merck's Investigator's Brochure) provided under and/or in association with the CDC-sponsored IND program to the participating sites and site investigators must be regarded and kept as confidential information.

Should site investigators or participating sites plan any presentation, publication and/or press release using the data related to this IND protocol and/or the outcome of the CDC-sponsored IND program for rVSVΔG-ZEBOV-GP vaccine, they must notify CDC with a copy of any abstract, press release or manuscript prior to submission for publication to allow time (3 business days for abstracts, 5 business days for press releases and 25 business days for manuscripts) for preview and comments, including by the vaccine manufacturer regarding use of any confidential and proprietary information. The vaccine manufacturer may potentially request 30 additional business days for review, if necessary, to ensure presentation, publication and/or press release is free of vaccine manufacturer's confidential information.

### 7.4 Financial Remuneration and Insurance

CDC is providing rVSVΔG-ZEBOV-GP vaccine under this expanded access IND program at no cost. Participating sites that request, receive, handle, and administer the vaccines under the IND will be responsible for any cost or resources associated with vaccine administration. Should a participant be injured as a direct result of receiving rVSVΔG-ZEBOV-GP vaccination, he/she should be treated as indicated clinically and may be entitled to medical care for that injury. However, CDC does not set aside funds to pay for this kind of medical care. The participant or participant's insurer, Medicare, or Medicaid will have to pay for any care that is needed. The participant should understand that signing the consent does not constitute a waiver or release of legal rights. This is addressed in the Informed Consent.

## 8 EFFICACY and SAFETY INFORMATION of rVSVΔG-ZEBOV-GP for EVD

The summary of rVSVΔG-ZEBOV-GP efficacy and safety information can be found in the Ervebo package insert. Additional details of vaccine efficacy and safety information are also available in Merck's Investigator's Brochure, which can be made available upon request to CDC (spathvax@cdc.gov).

### 8.1 Immunogenicity and Efficacy of PrEP

Since the evaluation of clinical efficacy and immunogenicity has not been done in the same study, immune correlates for protection against *Zaire ebolavirus* infection are unknown. One study revealed strong and early innate immune activation following vaccination with rVSVΔG-ZEBOV-GP. A subset of early innate markers, encompassing interferon γ-inducible protein 10 (IP-10) and subsets of monocytes, dendritic cells, and NK cells as well as an early gene signature linked to the IP-10 pathway, were identified as innate immune signatures, that correlated with the GP-specific antibody response on day 28 and beyond.[13]

In the PREVAIL I study, there was a considerable increase in antibody titers in the vaccine groups (ChAd3-EBO-Z and rVSVΔG-ZEBOV-GP) 1-month post-vaccination (1090 EU/mL rVSVΔG-ZEBOV-G vs. 73 EU/mL placebo), and 83.7% of rVSVΔG-ZEBOV-GP vaccinated participants had an antibody response at one month (vs. 2.8% placebo). At 12 months the titer levels remained elevated (835 EU/mL rVSVΔG-ZEBOV-GP vs. 81 EU/mL placebo), and 79.5% in the rVSVΔG-ZEBOV-GP vaccinated group had an antibody response (vs. 6.8% in placebo).[5] However, the contribution of these long-term persistent ZEBOV-GP-specific IgG antibodies to the protection against disease caused by *Zaire ebolavirus* in humans is unclear so far.

Another study found that at 360 days after vaccination, 174/175 (99%) study participants who received at least 10 million pfu of rVSVΔG-ZEBOV-GP vaccine and returned for follow-up were seropositive for ZEBOV-GP-specific IgG antibodies. At 730 days, 90/90 (100%) participants who received at least 10 million pfu of rVSVΔG-ZEBOV-GP vaccine and returned for follow-up were seropositive for ZEBOV-GP-specific IgG antibodies.[14]

The duration of protection following rVSVΔG-ZEBOV-GP vaccination is unknown. In unpublished animal studies, 2/6 nonhuman primates (NHPs) vaccinated with $3x10^6$ pfu and challenged with 1000 pfu of *Zaire ebolavirus* (Kikwit 7U) 3 months later survived; 3/7 NHPs vaccinated with either $3x10^6$ or $3x10^4$ pfu and challenged with 1000 pfu of *Zaire ebolavirus* 1 year later survived. At one-year post vaccination, there was no clear association between survival and pre-challenge antibody response as measured by ELISA or pseudovirion neutralization assay. It is unclear to what extent a similar waning of immune protection over time may be expected in humans receiving rVSVΔG-ZEBOV-GP vaccine. A follow-up study is in progress to assess durability of protection in NHPs vaccinated with one or two doses (60 days apart) of the full human vaccine dose (>$7.2x10^7$ pfu) that were challenged with 1000 pfu of *Zaire ebolavirus* four months after the last vaccine dose. Survival was 100% in the single-dose vaccine group, 88% in the two-dose vaccine group, and 0% in the saline control group. Histological and immunological sample testing results are pending.[2]

### 8.2 Safety

The clinical development program for rVSVΔG-ZEBOV-GP included 12 clinical studies conducted in North America, Europe, and Africa, in which a total of 15,399 adult subjects received a dose of rVSVΔG-ZEBOV-GP; 1,712 in double-blind, placebo-controlled trials and 13,687 in open label trials.
A report of four Phase 1, multi-center clinical trials of the rVSVΔG-ZEBOV-GP vaccine in 158 healthy adults in Africa and Europe reported mild to moderate early-onset reactogenicity including fever in 30% of vaccinees and vaccine viremia in 95% of vaccinees. Arthritis affecting one to four joints was reported in 22% of vaccinees at a study site in Geneva with onset approximately 7-14 days after vaccination. Pain lasted a median of 8 days and virus was identified in the synovial fluid aspirate and in skin vesicles of two other vaccinees. At six months, 10 of 11 participants with arthritis were symptom-free. Three vaccinees with arthritis also developed a mild maculopapular rash with rare vesicles on fingers and toes. Analysis of one papule identified the rVSVΔG-ZEBOV-GP vaccine strain by reverse transcriptase polymerase chain reaction (PCR).[7] Other phase 1 and 2 studies (total number vaccinated = 601) have also described similar vaccine reactogenicity, although rates of arthritis were lower in other studies.[8,15,16]

Although earlier analyses had revealed no association between the presence of arthritis and vaccine dose, age, sex, earlier arthralgia, or peak viremia, a more recent post-hoc multivariate analysis of risk factors for arthritis in rVSVΔG-ZEBOV-GP dose-tolerability studies was undertaken by Merck and evaluated the following factors: treatment dose, body mass index, age (18 to 45 years vs. 46 to 65 years), sex, medical history of arthritis (composite term), and race. The analysis identified an association with female sex and a past or current medical history of arthritis as two potential risk factors for the development of arthritis post-vaccination.[17]

A Phase 2/3 randomized, non-blinded trial with phased introduction of rVSVΔG-ZEBOV-GP vaccination in Sierra Leone (STRIVE) administered one IM dose of 2 x $10^7$ pfu of vaccine to healthcare and frontline response workers in 5 districts. Vaccine recipients were randomized to immediate or deferred vaccination and followed for 6 months post-vaccination. In total, 7,998 enrollees were vaccinated. No vaccine-related serious adverse events were reported. A vaccine safety substudy was conducted amongst 205 vaccinated participants. In this substudy population, vaccine reactogenicity was assessed, with the most commonly reported symptoms including pain at injection site (81%), headache (71%), subjective fever (50.7%), fatigue (50.7%), joint pain (31.7%), muscle pain (28.8%), and objective fever (20.5%). Skin vesicles were reported in seven (3.4%) vaccinees. The vaccine was generally well-tolerated, with most symptoms being mild to moderate in severity and resolving within 5 days.[18] Among 84 women inadvertently vaccinated in early pregnancy or that became pregnant $\leq$ 60 days after vaccination or enrollment, 45% (14/31) of women in the immediate vaccination group reported pregnancy loss, compared with 33% (11/33) of unvaccinated women with contemporaneous pregnancies (RR 1.35, 95% CI 0.73-2.52).[11] No congenital anomalies were detected among 44 live-born infants examined.

The Phase 2/3 randomized, double-blind, placebo-controlled PREVAIL I trial in Liberia compared ChAd3-EBO-Z (another vaccine under development) and rVSVΔG-ZEBOV. The trial enrolled 1,500 adult volunteers with 500 participants randomized to each of three arms: ChAd3-EBO-Z, rVSVΔG-ZEBOV, or placebo. As incidence of Ebola virus disease in Liberia declined, the study protocol was amended to focus on safety and longer-term 5-year immunogenicity. During the 12-month study period, 47 SAEs were reported in the rVSVΔG-ZEBOV-GP group compared to 59 in the placebo group (p=0.68); the majority of SAEs were attributable to malaria. Participants reported primarily grade 1 symptoms, with few grade 2 symptoms. The most commonly reported targeted symptoms in the rVSVΔG-ZEBOV-GP group were headache (31.9%), feverishness (30.5%), muscle pain (26.9%), and fatigue (15.4%). A two-week post-vaccination assessment for arthritis did not reveal a significant difference between the three groups.[5]

A Phase 3 ring vaccination trial of rVSVΔG-ZEBOV-GP in Guinea administered one IM dose of 2 x $10^7$ pfu of vaccine to 5,837 non-pregnant individuals > 6 years of age. Among all vaccinees (n=5837), the most frequently experienced solicited adverse events within 14 days of vaccination were: headache (33.3%), fatigue (25.4%), muscle pain (18.1%) arthralgia (17.9%), and myalgia (16.8%). Severity of these adverse events was also assessed. Among all vaccinees who experienced headache, 91% reported the headache as mild, 8.7% as moderate, and 0.4% as severe. Among all vaccinees who experienced fatigue within 14 days of vaccination, 84.3% reported the fatigue as mild, 14.2% as moderate, and 1.5% as severe. Amongst all vaccinees who experienced muscle pain within 14 days of vaccination, 83.3% reported muscle pain as mild, 15.7% as moderate, and 1% as severe. Amongst all vaccinees who experienced arthralgia within 14 days of vaccination, 89.1% reported the arthralgia as mild, 10.1% as moderate, and 0.7% as severe. Mean duration of arthralgia in adults was 2 days (interquartile range (IQR) 2-4). In addition, two serious vaccine-related adverse events were reported; one febrile reaction and one anaphylactic reaction, both of which resolved without sequelae.[19]

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# APPENDIX B1: Informed Consent Form

## Instructions:

- Prior to vaccination with *IND-labeled rVSVΔG-ZEBOV-GP vaccine*, Informed Consent must be obtained.

- Conduct informed consent process to help the vaccine-eligible individual to make an informed, voluntary decision on whether to get vaccinated based on information regarding risks and benefits of the vaccine and the purpose of the IND program regarding vaccine access, with opportunity to ask questions.

    - Print two copies of the signed ICF
    - Retain the original, signed ICF as part of the program records at the medical facility administering the vaccine
    - Provide one copy of the signed ICF to the individual to keep
    - Show the individual an example paper copy of **the CDC Post-Vaccination Adverse Events Survey** (Appendix B2)

Flesch-Kincaid Reading Level 8.8

# Use of Ebola Vaccine for Pre-exposure Prophylaxis of Ebola Virus Disease

Please read this consent form carefully and ask any questions that you may have. If you choose to get the Ebola vaccine, then you will be asked to sign this consent form. You will receive a copy of the consent form to keep.

## What is Ebola virus disease?

Ebola virus disease (EVD) is a rare disease caused by Ebola virus. It is severe and can cause death. Symptoms usually start 2 to 21 days after a person has contact with the virus. In most cases, symptoms start around days 8 to 10. First, a person may develop "dry" symptoms. These include fever, aches and pains, and fatigue. They may have "wet" symptoms (such as diarrhea and vomiting) as they get sicker. The most common Ebola symptoms are:

- Fever
- Aches and pains, such as severe headache, muscle and joint pain, and stomach pain
- Weakness and fatigue
- Diarrhea, vomiting, and stomach pain
- Unexplained bleeding or bruising

Other symptoms may include red eyes, skin rash, and hiccups.

The Ebola virus spreads between people. People can only spread the virus to other people after they develop Ebola symptoms. The virus spreads through direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth) with:

- the blood or body fluids of someone who is sick with or died from EVD. Body fluids can include urine, spit, sweat, feces, breast milk, or semen.
- objects (clothes, bedding, needles, or medical equipment) that has body fluids from a person who is sick with or has died from EVD on it.

Staff who work in labs and handle or have contact with patient samples or infectious materials containing the Ebola virus may also be at risk for EVD.

## What is the Ebola vaccine?

The Ebola vaccine (also known as rVSV-ZEBOV-GP) can help protect you from getting EVD if you come in contact with the Ebola virus. The Ebola vaccine helps the body's natural defense (immune) system fight off the Ebola virus. The vaccine contains a weakened part of the Ebola virus that will not make you sick with Ebola.

The vaccine only protects against Ebola virus disease due to *Zaire ebolavirus*. This Ebola vaccine was shown to be safe and protective against *Zaire ebolavirus* during previous outbreaks. These include the largest Ebola outbreak in West Africa in 2014-16 and the one in 2018 in the Democratic Republic of Congo.

The vaccine was approved by the U.S. Food and Drug Administration (FDA) in December 2019 to prevent disease caused by *Zaire ebolavirus* in adults 18 years of age and older. The vaccine might not protect everyone who gets it. This vaccine does not treat or cure people who are sick with EVD.

## What is the purpose of this program?

Only the Ebola vaccine doses produced at a specific factory are FDA-approved (known as "licensed" vaccine). These are not expected to be available until December 2020. So the Centers for Disease Control and Prevention (CDC) is providing this vaccine that was produced at a different facility (known as "investigational" vaccine) than the "licensed" vaccine. The investigational vaccine contains the same

ingredients and are made using the same process. The Ebola vaccine provided under this program is the same vaccine used and studied in over 15,000 people worldwide. This provided scientific data that supported the FDA's approval of the vaccine.

The investigational vaccine is offered under CDC's Investigational New Drug (IND) program to adults (≥ 18 years of age) who are at potential risk of Ebola due to their jobs. It is available to people who:

- Are responding or may respond to an outbreak of EVD such as people who care or may need to care for Ebola patients or could deploy to an Ebola outbreak
  or
- Work at a biosafety-level 4 lab in the U.S.
  or
- Work as healthcare staff at a federally designated Ebola Treatment Center in the U.S.

Use of the investigational vaccine (referred to as IND-labeled Ebola vaccine) has been reviewed and allowed by FDA and CDC's Institutional Review Board (IRB).

You can choose whether to receive the IND-labeled Ebola vaccine under this program. You may drop out at any time without penalty.

**Who should NOT receive the IND-labeled Ebola vaccine?**
The following people should not receive the Ebola vaccine:

- People who have an allergy, including anaphylaxis, to any component of the vaccine, including rice protein.
- People who are moderately or severely ill (such as those with an oral temperature >38°C (100.4°F)). However, these people can get the vaccine once they have recovered.
- People with a serious medical condition. These can include cancer, Guillain-Barré syndrome, history of brain disorder, active autoimmune disorder or weakened immune system. These conditions may place the person at an unreasonably increased risk by getting this vaccine.

**Who should get more advice before getting the IND-labeled Ebola vaccine?**
Tell the healthcare provider giving you the shot if you:

- have ever had a bad reaction to any vaccine.
- are pregnant or planning to become pregnant.
  - Ebola vaccine has not been studied in pregnant women. There are not enough data to know if there is a risk. It is also not known whether the Ebola vaccine is passed into breast milk. If you are pregnant, talk to your doctor about the risks of you getting ill with EVD and the potential benefits of the vaccine.
- have a weakened immune system or take medicines or treatments that might weaken your immune system.
- have close contact with anyone who has a weakened immune system.

**What happens if you choose to receive the IND-labeled Ebola vaccine?**
If you choose to get this vaccine, you will get one shot of the IND-labeled Ebola vaccine into the muscle of your upper arm. You will need to stay at the clinic for 30 minutes afterward. This will allow staff to monitor you for fainting or a serious allergic reaction. CDC will email or text you a brief survey on or around days 7, 14, 21, and 28 after receiving the vaccine. The survey will ask if any of five side effects occurred. If so, it will ask how severe they were. The survey should take about 5 minutes. An example of the survey will be shown to you before you sign this consent form. Responding to the survey is voluntary. However, we would appreciate it and it will help us monitor and assess side effects from this vaccine.

**What are the benefits of the IND-labeled Ebola vaccine?**
The vaccine may help protect you from getting EVD, but we do not know for sure. If the vaccine protects you against EVD, we do not know how long this protection might last.

**What are the risks/side effects of the IND-labeled Ebola vaccine?**
Side effects of the Ebola vaccine include:

- Pain, swelling, or redness at the injection site
- Fever
- Headache
- Chills
- Excessive sweating
- Nausea
- Feeling tired
- Muscle aches
- Joint pain
- Joint swelling
- Skin rash or blisters
- Mouth cuts or sores

The number of white blood cells someone has can decrease after vaccination. But this does not mean you are ill. They will go back to normal on their own.

Most side effects go away within a few days. Joint pain and swelling may last for weeks to years in some people. These symptoms may come back after going away.

The Ebola vaccine is made from a virus called vesicular stomatitis virus (VSV) that does not normally cause serious health problems in adults. Natural infection with VSV can cause mouth sores.

Fainting does not occur often. When it does, it is usually within the first 15 minutes after getting a vaccine. There may be other side effects from the vaccine that we do not know about yet.

Serious side effects:
Some people have had serious allergic reactions to the Ebola vaccine. Tell your healthcare provider promptly about any unusual or severe symptoms you have after getting this vaccine. See a doctor right away if you have signs of an allergic reaction, which may include:

- wheezing or difficulty breathing
- swelling of the face, lips, tongue, or other parts of the body
- all-over itching, redness, or itchy bumps on the skin
- a weak and rapid pulse
- nausea, vomiting or diarrhea
- dizziness or fainting

You will be observed for 30 minutes after receiving the vaccine for any immediate allergic reactions and will receive treatment for any reactions.

**What should you do if you have side effects?**

- If you have a severe allergic reaction, call 9-1-1, or go to the nearest hospital.
- Tell a healthcare provider right away that you just received the Ebola vaccine.
- Report any vaccine side effects that you have to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or http://www.vaers.hhs.gov and type "Ebola vaccine IND 16337" into "Vaccine (type and brand)" category.
- If you have muscle or joint pain, joint swelling, or skin or mouth sores, notify CDC on the surveys you will receive on days 7, 14, 21, and 28 after vaccination.

**Are there other options besides the IND-labeled Ebola vaccine?**
Not right now. The IND-labeled Ebola vaccine is being offered because the FDA-approved vaccine (Ervebo) is either not yet available or in limited supply. Whether you've received the vaccine or not, use

of recommended personal protection and infection control practices must also be followed for best prevention of Ebola virus infection and transmission of vaccine virus.

There is currently no FDA-approved treatment for EVD. Getting supportive care in a hospital is the only current treatment for patients who become sick from the Ebola virus.

**What you need to know AFTER you get the IND-labeled Ebola vaccine?**

- This IND-labeled Ebola vaccine may not protect everyone who gets it. You should still protect yourself from Ebola virus. Reduce contact with those who have EVD. Wear appropriate personal protective equipment (such as masks, gloves, etc.) when exposed to Ebola patients or infectious materials.
- Cover your shot site with a bandage (such as an adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact.
- If you develop a rash with blisters after receiving the vaccine, cover the blisters until they heal. The bandage may be removed when you can't see any fluid leaking.
- If you develop mouth sores after getting the vaccine, tell your healthcare provider.
- It has not been seen so far, but there is a possible risk that you could pass vaccine virus (not Ebola virus) to other people or animals. This is because the vaccine virus's genetic material (RNA) can stay in the body. The RNA has been found in urine for up to 7 days. It has been found in blood and saliva for up to 14 days after vaccination. Whether you may be infectious after vaccination and for how long are not known. To reduce possible risk to others, you should **avoid:**
    - sharing needles, razors, toothbrushes, eating utensils, drinking from the same cup, and open-mouth kissing for 2 weeks after vaccination. If you get mouth sores after getting the vaccine, avoid these activities until the sores heal.
    - close contact with people who have a condition that weakens the immune system or who take medicines that weaken the immune system.
    - close contact with pregnant or breastfeeding women, and infants (< 1 year of age) for up to 6 weeks after vaccination.
    - donating blood for at least 6 weeks after vaccination.
    - doing anything that may expose livestock to your blood and bodily fluids for up to 6 weeks following vaccination.
- Pregnancy should be avoided for 8 weeks following vaccination. Women of child-bearing potential should use an effective contraceptive method.
- Regardless of childbearing status or sexual orientation, use effective barrier protection, such as latex condoms, during any sexual interaction for 8 weeks after vaccination.
- If you are a healthcare worker caring for patients, adhere to recommended infection control standards.
- The IND-labeled vaccine may cause you to have a positive test for Ebola, even if you don't have the disease. Tell your healthcare provider that you received the IND-labeled vaccine.

**What are the costs?**

The IND-labeled Ebola vaccine is provided at no cost. Choosing to get the vaccine should not affect any health insurance that you have. This includes private insurance, Medicare, or Medicaid you use for routine medical costs not related to this program.

**What about your privacy?**

We will keep all facts about you private to the extent allowed by law. People who work for CDC, FDA, U.S. Department of Health and Human Services, local/state health departments, and the vaccine manufacturer may look at your medical records. This may, include your name and personal information. This is to monitor the proper and safe use of the Ebola vaccine. If this information is shared with anyone else, your name and personal information will not be used or listed. This includes reports or articles in

scientific journals. However, CDC can give your name to public health or medical people who, for example, need to find out how you may have contracted Ebola virus.

**What if you are harmed or have problems or questions?**
If you are harmed by being in this program, you will be treated. You (or your insurer, Medicare, or Medicaid) will have to pay for your care. If you feel you were harmed by your participation, please contact Dr. Mary Choi at 404-639-1155. If you have questions about the vaccine or the program, please call the CDC Viral Special Pathogens Branch (470-312-0094) to discuss your questions with an Ebola subject matter expert.

If you sign this consent form and agree to receive the Ebola vaccine, you are not giving up any rights. If you have questions about your rights in this program, please contact CDC's Human Research Protection Office at 800-584-8814. Please leave a message that includes your name, and telephone number, and refer to CDC IRB protocol #7298. Someone will return your call as soon as possible.

**Documentation of Informed Consent:** I have read this form, or it has been read to me. I have had a chance to ask questions and they were answered. I agree to get the Ebola vaccine. I have been given this consent form. I have been told that I will not lose any legal rights by being in this program.

| | |
|---|---|
| Name of Individual (Printed) | Date of Birth of Individual (mm/dd/yy) |
| Signature of Individual | Date/Time |
| Printed Name of Person Conducting Consent Interview | Signature of Person Conducting Consent Interview |

**Translator Documentation (if applicable)**
*Translator to document if informed consent process was given in another language other than English.*

| | |
|---|---|
| Name of Translator | Language |
| Signature of Translator | Date |

# APPENDIX B2: Example Copy of the CDC Post-Vaccination Adverse Events Survey

## Instructions:

- Inform vaccinees to expect the CDC post-vaccination adverse events survey via email or text on or around days 7, 14, 21 and 28 after vaccination. Show this example paper copy of the survey and encourage their participation in responding to the surveys.

- Inform vaccinated individuals that their responses to the Post-Vaccination Adverse Events Survey from CDC will be submitted to the Vaccine Adverse Event Reporting System (VAERS) and they will likely receive follow-up questions from VAERS in the future.

## Appendix B2: Example Copy of the CDC Post Vaccination Adverse Event Survey

***You're receiving this brief survey from the Centers for Disease Control and Prevention (CDC) regarding the investigational Ebola vaccine you received, which was provided under the CDC-sponsored program. At the time of vaccination, you were informed that CDC will be sending you a survey by email or text on or around days 7, 14, 21 and 28 after vaccination (a total of 4 times) to ask questions on 5 specific adverse events (side effects). The survey is expected to take less than 5 minutes. Your response to the survey is much appreciated and will greatly help monitor specific side effects regarding this vaccine. Please note that your responses to the survey that indicate adverse events will be added to the Vaccine Adverse Event Reporting System (VAERS). You may be contacted by the CDC VAERS team with follow-up questions.***

1. In the past 7 days, have you experienced any of the following adverse events?

| Adverse Events | *If yes,* when did it start? | *If yes,* has it resolved? |
|---|---|---|
| a. Muscle pain<br>☐ Yes ☐ No<br><br>*If yes*, how would you describe the muscle pain?<br>☐ Mild<br>☐ Moderate, some interference with daily activity<br>☐ Severe, prevents daily activity<br>☐ Requires medical attention/intervention | ___/___/____<br>MM/DD/YYYY<br><br>☐ Date unknown | ☐ Yes ☐ No<br><br>*If yes*, when did it resolve?<br>___/___/____ ☐ Date unknown<br>MM/DD/YYYY |
| b. Joint pain<br>☐ Yes ☐ No<br><br>*If yes*, which joints are affected?<br>_____<br><br>*If yes*, how would you describe the joint pain?<br>☐ Mild<br>☐ Moderate, some interference with daily activity<br>☐ Severe, prevents daily activity<br>☐ Requires medical attention/intervention | ***If yes,* when did it start? *(For each joint affected)***<br><br>___/___/____<br>MM/DD/YYYY<br><br>☐ Date unknown | ***If yes*, has it resolved? (*For each joint affected)***<br><br>☐ Yes ☐ No<br><br>*If yes*, when did it resolve?<br>___/___/____ ☐ Date unknown<br>MM/DD/YYYY |
| c. Joint swelling<br>☐ Yes ☐ No<br><br>If yes, which joints are affected?<br>_____ | ***If yes,* when did it start? *(For each joint affected)***<br><br>___/___/____<br>MM/DD/YYYY<br><br>☐ Date unknown | ***If yes*, has it resolved? (*For each joint affected)***<br><br>☐ Yes ☐ No<br><br>*If yes*, when did it resolve?<br>___/___/____ ☐ Date unknown<br>MM/DD/YYYY |
| d. Skin lesion (rash, pustule, vesicle)<br>☐ Yes ☐ No<br><br>If yes, where is the skin lesion?<br>_____ | ***If yes,* when did it start?**<br><br>___/___/____<br>MM/DD/YYYY<br><br>☐ Date unknown | ***If yes*, has it resolved?**<br><br>☐ Yes ☐ No<br><br>*If yes*, when did it resolve?<br>___/___/____ ☐ Date unknown<br>MM/DD/YYYY |

| | | |
|---|---|---|
| e. Oral lesion (blister, sore, vesicle)<br>☐ Yes ☐ No | ***If yes,* when did it start?**<br>____/____/____<br>MM/DD/YYYY<br>☐ Date unknown | ***If yes*, has it resolved?**<br>☐ Yes ☐ No<br>*If yes*, when did it resolve?<br>____/____/____ ☐ Date unknown<br>MM/DD/YYYY |
| f. Any other adverse events? If yes, describe. | ***If yes,* when did it start?**<br>____/____/____<br>MM/DD/YYYY<br>☐ Date unknown | ***If yes*, has it resolved?**<br>☐ Yes ☐ No<br>*If yes*, when did it resolve?<br>____/____/____ ☐ Date unknown<br>MM/DD/YYYY |

2. Have you missed work because of any of the adverse event(s) you experienced in the past 7 days? ☐ Yes ☐ No
   a. *If yes,* how many days of work did you miss? _____

3. Have you seen a healthcare provider for any of the adverse event(s) you experienced within the past 7 days? ☐ Yes ☐ No
   a. *If yes*, did you have any diagnostic testing performed? ☐ Yes ☐ No
      i. *If yes*, what diagnostic testing did you have? _____
   b. *If yes,* did you receive a diagnosis? ☐ Yes ☐ No
      i. *If yes,* please list the diagnosis(es) _____

***This is the end of the survey. Thank you for your participation! If any adverse events occur after completing all of the surveys (a total of 4 times), please report them to the VAERS at 1-800-822-7967 or http://www.vaers.hhs.gov. If you experience adverse events that you're concerned about or have questions on, consult a healthcare provider and inform them that you recently received the Ebola vaccine.***