

Expanded Access Investigational New Drug (IND) Protocol:
Ervebo[®] (Ebola Zaire Vaccine, Live) Booster Dose for Domestic 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
BSL-4	Biosafety level 4
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
HCP	Healthcare Personnel
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
IP-10	γ -inducible protein 10
IRB	Institutional Review Board
LRN	Laboratory Response Network
NHPs	Nonhuman primates
PCR	Polymerase chain reaction
PFU	Plaque-forming units
PPE	Personal Protective Equipment
PrEP	Pre-exposure prophylaxis
PREVAIL	Partnership for Research on Ebola Virus in Liberia study
rVSV	Recombinant vesicular stomatitis virus
rVSV Δ G-ZEBOV-GP	Recombinant vesicular stomatitis virus with envelope glycoprotein replaced by <i>Zaire ebolavirus</i> (Kikwit 1995 strain) glycoprotein (V920)
SAE	Serious adverse event
SDV	Single-dose vial
SNS	Strategic National Stockpile
SPTC	Special Pathogen Treatment Centers
STRIVE	Sierra Leone Trial to Introduce a Vaccine against Ebola
VAERS	Vaccine Adverse Event Reporting System
VRF	Vaccination Record Form

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 highly transmissible through contact with body fluids of infected individuals. There are four species of Ebola virus that have been known to cause disease in humans. The *Zaire ebolavirus* species is the most lethal, with case fatality rates of 70-90% if left untreated.

Importation of EVD to the United States (U.S.) from an epidemic region through an infected traveler or healthcare worker is a recognized risk with the potential for secondary transmission. During the 2014–2016 Ebola outbreak in West Africa, a total of 11 people were treated for EVD in the U.S., two of whom died. While the majority were infected with the Ebola virus in the outbreak region who entered the U.S. either as medical evacuation for treatment or as a regular airline passenger, two were domestic healthcare workers who carried for first travel-associated EVD case diagnosed in the U.S., marking the first known transmission of EVD in the US. Both recovered.¹ The 2014–2016 Ebola outbreak in West Africa and the series of Ebola outbreaks in the Democratic Republic of the Congo (DRC) since 2018 heighten the importance of pre-event preparedness and response, including vaccine availability and access for pre-exposure prophylaxis (PrEP) to protect high-risk groups (e.g., laboratorians, healthcare workers, emergency responders) who may have potential occupational exposure to Ebola virus against *Zaire ebolavirus*.

Ervebo[®] (Ebola Zaire Vaccine, Live; also known as V920, rVSVΔG-ZEBOV-GP or rVSV-ZEBOV), manufactured by Merck, was approved by the U.S. Food and Drug Administration (FDA) as a single dose administration for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older on December 19, 2019 as a single dose administration for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older.. However, booster doses are not part of the FDA-approved indication of Ervebo and FDA deems booster vaccination of Ervebo an unapproved use. Ervebo is not commercially marketed in the U.S., and its domestic availability limited to the stockpile supply by the US. Government. Therefore, the Centers for Disease Control and Prevention (CDC) is sponsoring this expanded access IND program to provide an umbrella regulatory mechanism for domestic access¹ to and use of Ervebo for booster vaccination in adults with prior Ebola vaccination history who are at potential occupational risk for exposure to *Zaire ebolavirus*.

Pre-event, domestic access to and use of Ervebo for PrEP is guided by [Advisory Committee on Immunization Practices \(ACIP\)](#) recommendations: for adults ≥ 18 years of age in the U.S. population who are at high risk for potential occupational exposure to Ebola virus (species *Zaire ebolavirus*) because they are responding or may respond to an outbreak of EVD; healthcare personnel working at federally-designated Ebola Treatment Centers, or involved in the care and transport of patients with suspected or confirmed EVD at special pathogens treatment centers in the U.S.; or laboratorians or other staff working at biosafety-level 4 facilities or at Laboratory Response Network (LRN) facilities that handle specimens that might contain replication-competent Ebola virus (species *Zaire ebolavirus*) in the U.S.^{5,6}

Ervebo 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.² FDA's approval of the vaccine was based on the data from 12 clinical trials in which a total of 15,399 adults received a dose of $\geq 2 \times 10^7$ 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, U.S., Canada, and Spain.

In well-controlled clinical trials in adults, Ervebo was demonstrated to be a safe and effective vaccine for preventing EVD. 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.³ However, Ervebo 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 Ervebo 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 DRC confirm efficacy of Ervebo against disease.⁴ 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 Ervebo 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.

2 EXPANDED ACCESS IND PROGRAM DESCRIPTION

There is need for PrEP vaccination of individuals with occupational risk of Ebola virus exposure, especially for those deploying to areas with Ebola outbreaks. Since Ervebo is not commercially marketed in the United States, the U.S. government is providing access to stockpiled vaccine in the SNS upon CDC's receipt, review, and approval of vaccine requests by licensed healthcare providers for vaccine eligible individuals. Ervebo requests for FDA-approved use as a single dose administration in Ebola vaccine naïve individuals are covered by the [FDA-approved labeling for Ervebo](#). CDC is sponsoring this expanded access IND program to facilitate access to and use of Ervebo for booster dose administrations, which is an not part of FDA-approved indication (i.e., unapproved use), requiring an IND regulatory coverage. through this IND.

The procedures set forth in this expanded access IND program for Ervebo booster doses 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 Ervebo for booster vaccination 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 Ervebo for booster vaccination upon receipt and review of requests by licensed healthcare providers from institutions/sites with identified individuals who meet the eligibility criteria under this IND protocol (see **Section 2.1, Ervebo Eligibility**). 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 Ervebo administration. See **Section 5, Procedures**, and **Section 7, Program Responsibilities**, for further details.

2.1 Ervebo Eligibility

Ervebo for booster vaccination under this expanded access IND protocol is for adults (≥ 18 years of age) in the U.S. population* who have previously been vaccinated with any Ebola vaccine (i.e., ≥ 6 months since prior vaccination) and are at potential occupational risk for exposure to *Zaire ebolavirus* for whom booster dose(s) may be appropriate:

- Responders** or individuals responding to an
- outbreak of EVD Ebola virus disease (e.g., persons who would be expected to provide care for Ebola patients or be deployed to an outbreak area).
 - **Laboratorians and support staff** working at biosafety level 4 (BSL-4) or Laboratory Response Network (LRN) facilities in the U.S. that handle specimens that contain or might contain replication-competent Ebola virus (species *Zaire ebolavirus*).

- **Healthcare personnel (HCP)*** at federally designated Ebola Treatment Centers or state-designated Special Pathogen Treatment Centers (SPTCs)** in the US involved in the care and transport of patients infected or suspected to be infected with Ebola virus (species *Zaire ebolavirus*). Healthcare personnel at other facilities may be eligible to receive Ervebo depending on specific circumstances of public health needs and the Ebola preparedness and/or response at such facilities.

* 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>

** Refers to healthcare facilities that intend to receive and are able to provide care for suspect or confirmed EVD patients for the duration of their illness, as assessed by the jurisdictional state health departments. In addition to EVD, these facilities may also be designated by the states to treat other high consequence pathogens.

Final eligibility and release decisions of Ervebo for booster dose administration, including dose interval (i.e., ≥ 6 months since prior vaccination), will be assessed on an individual case-by-case basis depending on clinical judgement of the risks and benefits and circumstances warranting booster dose administration (e.g., outbreak response, suspected waning immunity, vaccination strategy, and/or projected duration of elevated risk).

Please see the **Occupational Risk/Vaccine Eligibility Assessment Form** (Appendix A1) to help identify vaccine candidates. This is an optional form to aid in assessing occupational risk exposure for identifying individuals for vaccination, and does not need to be submitted to CDC. To request Ervebo booster vaccine, complete and submit the **Ervebo Request and Use Agreement Form** and **Form FDA 1572** (Appendix A2) to CDC.

2.2 Ervebo Ineligibility

Ervebo should not be given to individuals with any of the following:

- Known severe allergy, such as anaphylaxis, to Ervebo or any component of the vaccine, including rice protein.
- Clinical evidence of a systemic infection or other acute intercurrent illness at the scheduled time of vaccination[†] (e.g., oral temperature $>38^{\circ}\text{C}$ [100.4°F], systemic symptoms).
- 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 of a serious adverse reaction from the vaccination.
- 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 Ervebo, live, attenuated vaccines are generally contraindicated during pregnancy. Women of reproductive age should be counseled on the potential fetal risk(s) of vaccination, and the decision to receive Ervebo should be made on an

individual basis, in consultation with a healthcare provider, weighing the risks/benefits of vaccination against the risk of exposure to Ebola virus.

Laboratory and healthcare workers at risk for occupational exposure to *Zaire ebolavirus* receiving Ervebo 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 and transmission if they come into direct contact with body fluids from a suspected or confirmed Ebola patient, even if they have received Ervebo.

3 PRECAUTIONS/SPECIAL POPULATIONS/ADVERSE EVENTS

3.1 Precautions

- Among the 15,399 adult subjects vaccinated with Ervebo 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 Ervebo, 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 Ervebo 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 Ervebo have not been assessed in immunocompromised individuals. The effectiveness of Ervebo in immunocompromised individuals may be diminished. To date, a small number of HIV-positive adult subjects have been vaccinated with Ervebo in the Partnership for Research on Ebola Virus in Liberia (PREVAIL) first study (PREVAIL I) that evaluated two Ebola vaccines.⁷ Additional studies are ongoing to evaluate the use of Ervebo in HIV-positive subjects without severe immune compromise. The risk of vaccination with Ervebo, a live virus vaccine, in immunocompromised individuals should be weighed against the risk of disease due to *Zaire ebolavirus*.
- Because Ervebo 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 Ervebo.
- 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.^{3,8-11} 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 (< 1 year of age)) for up to 6 weeks following vaccination.
 - activity that may expose livestock to the vaccinated individual's 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 (ICF)**.

3.2 Considerations for Special Populations

Pregnancy

There are no adequate and well-controlled studies of Ervebo in pregnant women, and human data available from clinical trials with Ervebo 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 Ervebo, 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).¹³

The World Health Organization recommends the use of Ervebo 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.¹⁴ 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 Ervebo 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 Ervebo and any potential adverse effects on the breastfed child from Ervebo or from the underlying maternal condition. For preventative vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

Older Adults

A total of 542 subjects ≥ 65 years of age received Ervebo 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 Ervebo

The most commonly reported injection-site adverse events among the adult subjects vaccinated with Ervebo during clinical development were injection-site pain (70%), swelling (17%), and redness (12%). The most commonly reported systemic adverse events following vaccination with Ervebo were headache (37%), feverishness (34%), muscle pain (33%), fatigue (19%), joint pain (18%), nausea (8%), arthritis (5%), rash (4%) and abnormal sweating (3%). A limited number of adult subjects received a second dose 28 days after initial dose; reactogenicity at the injection site and systemic reactogenicity were less severe after the second dose than after the first dose. 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

Please refer to the [FDA-approved Ervebo package insert](#) for additional information. Ervebo, a sterile suspension for intramuscular injection, 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 (SDV) containing a 1 mL dose and stored frozen at -80°C to -60°C (-112°F to -76°F) for long-term storage.

Each 1 mL dose contains a minimum of 72 million plaque forming units (7.2×10^7 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.

The vaccine is maintained at -80°C to -60°C (-112°F to -76°F) for long-term storage in the SNS. Frozen vaccine will be shipped from the SNS to the receiving sites at -80°C to -60°C (-112°F to -76°F) on dry ice in an insulated shipping container containing a temperature monitoring device (TempTale[®] Ultra). The preference is to maintain Ervebo frozen at -80°C to -60°C 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 should be used immediately. If not used immediately, thawed vials can be stored refrigerated at 2°C to 8°C (35.6°F to 46.4°F) for a total time of **no more than 14 days** or at room temperature (up to 25°C ; 77°F) for a total time of **no more than 4 hours**.

5 PROCEDURES

Ervebo for booster vaccination will be provided upon CDC's receipt and review of request from licensed healthcare providers for individuals who have previously received Ervebo and/or any other Ebola vaccine (i.e., ≥ 6 months since prior vaccination) and with occupational risk of exposure to *Zaire ebolavirus*. After verifying requests, CDC will coordinate shipment of frozen vaccine(s) to receiving sites directly from the SNS. Also see **Section 7, Program Responsibilities**, for related information.

5.1 Vaccine Request and Release Decision

- Before requesting Ervebo, identify individuals with occupational risk for *Zaire ebolavirus* necessitating booster vaccination using the optional **Ervebo: Occupational Risk/Vaccine Eligibility Assessment Form** (Appendix A1).
 - This form is provided for vaccine requesting site's internal use to aid in determining individuals with potential risk for exposure to Ebola virus (species *Zaire ebolavirus*) for whom vaccination is appropriate. The vaccine eligibility occupational risk groups under this IND are mentioned under Section 2.1 (EVD responders, lab workers, and healthcare personnel). This form is for internal use by the vaccine requesting site at its discretion and does NOT need to be returned to CDC.
- Complete and submit the required **Ervebo 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, licensed healthcare providers at vaccine requesting sites acknowledge and agree to assume responsibility for the oversight and management of Ervebo receipt, storage, handling, use and disposal at their institutions/sites, including ensuring informed consent, monitoring vaccinated individuals, and reporting any SAEs resulting from Ervebo administration, in accordance with this CDC-sponsored EA-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 SNS.
 - CDC will not approve vaccine if upon review, vaccine eligibility per the protocol is 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.

- Ervebo will be shipped by SNS to the address indicated in the **Ervebo Request and Use Agreement Form**. Shipment information with estimated delivery date will be provided via email

from SNS once arranged.

- The vaccine will be shipped to requesting sites frozen at -80°C to -60°C (-112°F to -76°F) on dry ice in an insulated shipping container containing a temperature monitoring device (TempTale® Ultra). The vaccine shipment will come with instructions for the TempTale® Ultra device download and return procedure that should be followed. Below outlines the key instructions.

5.3 Vaccine Receipt and Handling at Participating Sites

- Upon receipt of vaccine shipment, delivered frozen (-80°C to -60°C (-112°F to -76°F)) by SNS, 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 TempTale Ultra Monitor from the top of the product and immediately deactivate it by pressing and holding the STOP button for 5 seconds until the “Stop Sign” icon (●) appears in the upper right corner of the display.
- Remove the frozen vaccine from the shipping container and place immediately into a -80°C to -60°C (-112°F to -76°F) freezer, if available at the participating site. Preference is to maintain vaccine vials at -80°C to -60°C (-112°F to -76°F) until administration, but if a -80°C to -60°C (-112°F to -76°F) freezer is not available:
 - The vaccine vials should be thawed completely at room temperature until no visible ice is present (approximately 10 to 15 minutes). Do not thaw the vials in a refrigerator as the vaccine is sensitive to slow thawing at refrigerated temperature.
 - Once fully thawed, the vials can be stored refrigerated at 2°C to 8°C (35.6°F to 46.4°F) and used within the use-by-period indicated in the table below.

Table 1: Use-by-Period Once Thawed

Storage Condition and Temperature		Maximum Storage Duration
Refrigerator	2°C to 8°C (35.6°F to 46.4°F)	14 days
Room Temperature	9°C to 25°C (48°F to 77°F)	4 hours

- Transfer time from the shipper to the participating site’s -80°C to -60°C (-112°F to -76°F) freezer, if available, or thawing at room temperature followed by refrigeration, if no freezer is available, should be kept to a minimum.
- Protect vaccine from light. Do NOT re-freeze.

5.3.1 Instructions for Handling Temperature Monitoring Device (TempTale Ultra)

Follow the instructions on the “TC-391 Packing Insert” that came with the product. Temperature recordings from the TempTale Ultra Monitor during shipment need to be reviewed by SNS to verify no temperature excursions occurred that impact vaccine usage. **The vaccine should not be administered until this temperature verification and vaccine release for usage is given by SNS.**

- To expedite SNS review, download the temperature recordings and email the files to SNS (sns.ops@cdc.gov; dsnsvaccine@cdc.gov) files before returning the TempTale monitor device:
 - After appropriately storing the vaccine in a -80°C to -60°C (-112°F to -76°F) freezer or 2°C to 8°C (35.6°F to 46.4°F) refrigerator, locate the TempTale Ultra device and plug it into the USB port of a laptop or desktop computer.
 - The screen on the TempTale Ultra device may be blank as it warms up while plugged into the USB port.
 - Do not unplug the device from the USB port while the RED light is blinking.
 - Email the PDF and TTV files to SNS as instructed above.
 - Return the TempTale® Ultra Monitor to SNS using the pre-addressed, FedEx/DHL envelope provided.

- SNS will verify and provide notification on whether any temperature excursions occurred during shipment. If a temperature excursion occurred, SNS in coordination with CDC, will provide clarification on whether the vaccine can be used or if it is unsuitable for administration, as well as the appropriate next steps to take (e.g. discard on site).

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 Receiving Sites

- Ervebo 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 (e.g., vaccine eligibility, expected adverse events, clinical consideration for a booster dose).
- For each 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.
- Inform 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 (**Appendix B2: CDC Post-Vaccination Adverse Events Survey**).
- 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 Vaccination Record Form (VRF) for each vaccinated individual must be returned to CDC no later than 3 calendar days of vaccination. If any SAEs are observed, report to CDC by returning the completed VRF **as soon as possible** and **no later than 3 calendar days (72 hours)** of SAE occurrence. 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 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).
- 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.

6 DOSAGE AND ADMINISTRATION

The dose for Ervebo is 1 mL by intramuscular (IM) administration. Practice aseptic technique and standard precautions when preparing and administering the vaccine IM.

6.1 Preparation, Dosage and Administration

Supplies required:

- Ervebo (supplied as 1 mL SDV 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 needle length)

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. 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 14 days at 2°C to 8°C (35.6°F to 46.4°F) or for up to 4 hours at room temperature (up to 25°C; 77°F) protected from light. **Do NOT re-freeze.**

Gently invert the vial several times. Using aseptic technique, withdraw the 1 mL dose using a sterile needle and syringe. Administer a 1 mL dose of the vaccine by IM injection, at a 90° angle, preferably into the deltoid area of the individual's non-dominant arm.

- 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 allow Ervebo access and use for booster vaccination in adults (≥ 18 years) with potential high risk of occupational exposure to EVD who have previously received Ervebo and/or any other Ebola vaccine. The Principal Investigator will monitor the appropriate use of Ervebo, including review of vaccination requests, evaluation of eligibility requirements and reported SAEs, and provide consultation to requesting healthcare providers (i.e., site investigators) as needed.

Licensed Healthcare Providers (Site Investigators)

By requesting and obtaining Ervebo under the CDC-sponsored IND 16337 (i.e., completing and signing the required **Ervebo Request and Use Agreement Form**, and **Form FDA 1572** (Appendix A2)), the requesting licensed healthcare providers serve as site investigators for booster use of Ervebo at their sites under this expanded access IND program and are responsible for ensuring appropriate handling, procedures and use of Ervebo at their institutions/sites in accordance with this IND protocol, and FDA IND regulations.

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: Ervebo 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: Ervebo Request and Use Agreement Form, and Form FDA 1572 - Required.

Used 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: Copy of the CDC Post-Vaccination Adverse Events Electronic Survey

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 on the occurrence and severity of 5 specific adverse events (muscle pain, joint pain, joint swelling, skin lesions and/or oral lesions).

Appendix C: Ervebo Vaccination Record Form (VRF) – Required.

Complete and return a VRF for each vaccinated individual to CDC no later than 3 calendar 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 as soon as possible and no later than 3 calendar days (72 hours)** of SAE occurrence, 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: Ervebo Vaccine Product Accountability and Disposal Record Form – Required.

Complete and return to CDC within **14 calendar days** of completing vaccination (i.e., having used the 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 Ervebo in humans, whether or not considered related to Ervebo. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of Ervebo, without any judgment about causality.

A **Suspected Adverse Reaction** is any AE for which there is a reasonable possibility that Ervebo caused the AE. It is a subset of all AEs for which there is a reasonable possibility that Ervebo caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between Ervebo 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 Ervebo. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that Ervebo 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 [FDA-approved Ervebo 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 Ervebo) 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 **as soon as possible** and no later than 72 hours of observed occurrence or 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 Ervebo 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 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, and local public health jurisdictions, and the vaccine manufacturer. 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 may review medical and program records

related to the booster use of Ervebo 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 provided under and/or in association with this expanded access IND protocol for Ervebo 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 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.

7.4 Financial Remuneration and Insurance

CDC is providing Ervebo 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 Ervebo, 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 ERVEBO for EVD

The summary of Ervebo efficacy and safety information can be found in the [FDA-approved Ervebo package insert](#).

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 Ervebo. 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.¹⁵

In the PREVAIL I study, there was a considerable increase in antibody titers 1-month post-vaccination (GMT EU/ml [95% CI] of 1000 [910–1099] rVSV Δ G-ZEBOV-GP vs. 75 [69–80] placebo) with the antibody response rate of 83.7% in the Ervebo vaccinated group (vs. 2.8% placebo). At 12 months, the titer levels remained elevated but declined (818 [752–889] vs. 90 [83–96] placebo) with antibody response rate of 79.5% in the Ervebo vaccinated group (vs. 6.8% in placebo).⁷ In unpublished data of extended follow-up of the original PREVAIL I cohort, antibody titer levels decreased to 496 (442–557) and 65.1% sero-positive by three years. Additionally, antibody titer results in West African adults receiving single vs. boosted (day 56) Ervebo vaccination demonstrated short lived 4-month increase in serologic responses which return to same level of the single dose thereafter.

Another study found that at 365 days after vaccination, 77/77 (100%) study participants who received at least 1×10^7 pfu of Ervebo vaccine and returned for follow-up were seropositive (≥ 58.84 EU/mL) for ZEBOV-GP-specific IgG antibodies. At 730 days, 45/45 (100%) participants who received at least 1×10^7 pfu of Ervebo vaccine and returned for follow-up were seropositive for ZEBOV-GP-specific IgG antibodies.¹⁶ 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.

The duration of protection following a single dose of Ervebo is unknown. In unpublished animal studies, 2/6 nonhuman primates (NHPs) vaccinated with 3×10^6 pfu and challenged with 1000 pfu of *Zaire ebolavirus* (Kikwit 7U) 3 months later survived; 3/7 NHPs vaccinated with either 3×10^6 or 3×10^4 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 Ervebo. 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 ($>7.2 \times 10^7$ 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.¹²

Among the 673 EVD patients enrolled in the PALM trial, Ervebo vaccination status was available via self-report for 620 patients. Of these, 60 patients with EVD reported receiving the vaccine ≥ 10 days before their admission to an Ebola Treatment Center.¹⁷ Preliminary, unpublished data from an ongoing CDC study examining long-term immune responses found that antibodies against glycoproteins of both Ebola virus strains Mayinga 1976 and DRC2018 were detected in 44/45 (97.8%) samples collected 8–31 months after vaccination (median: 16 months). The majority of the samples tested negative for the presence of neutralizing antibodies using live virus focus-reduction neutralization assay.

Until additional data on the duration of protection following the initial vaccination becomes available, booster dosing should be considered on a case-by-case basis in individuals that were previously vaccinated ≥ 6 months and are at potential occupational risk for exposure to Ebola virus.

8.2 Safety

The clinical development program for Ervebo included 12 clinical studies conducted in North America, Europe, and Africa, in which a total of 15,399 adult subjects received a dose of Ervebo; 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 Ervebo 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 Ervebo vaccine strain by reverse transcriptase polymerase chain reaction (PCR).⁸ 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.^{9,18,19} Available clinical data suggest that a second dose of Ervebo may have an acceptable safety profile. A Phase 1 dose-escalation study included administration of two doses on Day 0 and 28 at three dosage levels (3×10^6 pfu, 2×10^7 pfu, and 1×10^8 pfu). Reactogenicity at the injection site and systemic reactogenicity were less severe after the second dose than after the first dose.²⁰

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 Ervebo 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.²¹

A Phase 2/3 randomized, non-blinded trial with phased introduction of Ervebo vaccination in Sierra Leone (STRIVE) administered one IM dose of 2×10^7 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.²² Among 84 women inadvertently vaccinated in early pregnancy or that became pregnant ≤ 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).¹³ 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 enrolled 1,500 adult volunteers with 500 participants randomized to each of three arms: ChAd3-EBO-Z, Ervebo, 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 Ervebo 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 Ervebo 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.⁷

A Phase 3 ring vaccination trial of Ervebo in Guinea administered one IM dose of 2×10^7 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.²³

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