Protocol Number VA-008

Version 2.6 2020-Jun-05

Clinical Study Protocol

Vaccinia Vaccination (ACAM2000®) of Plasma Donors for the Production of Vaccinia Immune Globulin Intravenous (VIGIV)

VA-008

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[redacted]

CONFIDENTIAL

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Study Sponsor:

[redacted]

Clinical Study Scientist:

[redacted]

Sponsor's Medical Expert:

[redacted]

Signatory Page

VA-008: Version 2.6

Vaccinia Vaccination (ACAM2000®) of Plasma Donors for the Production of Vaccinia Immune Globulin Intravenous (VIGIV)

Clinical Site(s):

Name:

Address:

Tel:

E-mail:

My signature below verifies that I have read and agree to this protocol. I accept my responsibilities as an investigator under the Good Clinical Practice (GCP) guidelines of ICH, the Declaration of Helsinki, local regulations (as applicable) and the study protocol, and I agree that I and my designees will conduct the study according to these regulations.

Site Principal Investigator:

Principal Investigator Name (print)	Title (print)
Principal Investigator Signature	Date (YYYY/MMM/DD)

Sponsor Signatory:

Emergent BioSolutions Canada Inc. [redacted]	Date (YYYY/MMM/DD)

VA-008 Protocol Synopsis

Title	Vaccinia Vaccination (ACAM2000®) of Plasma Donors for the Production of Vaccinia Immune Globulin Intravenous (VIGIV)
Sponsor	Emergent BioSolutions Canada Inc. [redacted] [redacted]
Sites and Investigators	Multiple plasma collection centers All investigators and site staff will be trained on ACAM2000 vaccine reconstitution and administration, vaccine risks, vaccine recipient education and care, and protocol requirements by Emergent BioSolutions
Study Start	September 2015
Objectives	To vaccinate plasma donors with the ACAM2000 smallpox vaccine thereby inducing an immune response resulting in high anti-vaccinia antibody titers. The collection of donor plasma will be used in the manufacturing of Vaccinia Immune Globulin Intravenous (VIGIV). To ensure the safety of plasma donors vaccinated with ACAM2000 through the implementation of risk factor screening procedures and the collection of post-vaccination safety data.
Subject Population	Healthy adult male and female volunteers who meet the requirements for source plasma donors and study entry criteria including previous immunization for smallpox.
Sample Size	Approximately 750 to 3000 plasma donors
Study Product	ACAM2000 (Smallpox (Vaccinia) Vaccine, Live) [Sanofi Pasteur Biologics LLC (formerly Acambis)]
Dosage	Percutaneous administration of a droplet (2.5 µL) of vaccine using a bifurcated needle.
Protocol Design	Open label, single arm, multi-center vaccination study
Inclusion Criteria	• Signed written informed consent

	• Age 18 to 65 • Normal and healthy (immune competent) as determined by medical history, physical exam, vital signs and clinical laboratory tests during the screening period • Subject must meet all required subject suitability criteria that pertain to normal source plasma donors. • Negative human immunodeficiency virus (HIV) serology during screening period (within 14 days prior to baseline) • Subject must have been previously immunized for smallpox, at ≥3 years prior to commencement of screening assessments, and vaccination history must be confirmed by oral or written history and the presence of a visible pathognomonic smallpox vaccination scar. • Female subjects of childbearing potential must agree to use highly effective birth control methods (e.g., hormonal contraception, intrauterine device (IUD), intrauterine system (IUS)) throughout the study[a], females of non-childbearing potential must be surgically sterile or meet postmenopausal requirements[b] and all women must be educated on risks of the ACAM2000 vaccine to an unborn child. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

Exclusion Criteria	• History of severe related adverse event(s) from previous participation in VA-001 or VA-006 studies or to any smallpox vaccination.
	• The subject, or a household contact or other close/intimate contact of the subject has ANY of the following:
	  • Eczema, history of eczema, exfoliative skin conditions, wounds, burns, or other skin conditions at the investigator's discretion
	  • A history of immune deficiencies
	  • Currently or has recently received radiotherapy or chemotherapy, adrenocorticotropic hormone (ACTH), corticosteroids, or immunosuppressive drugs
	  • Eye disease treated with topical steroids

	• Known or suspected disorders of immunoglobulin synthesis • Leukemia, lymphomas of any type, melanoma, or other malignant neoplasms affecting the bone marrow or lymphatic systems • Has been diagnosed with cancer and who will be undergoing chemotherapy or radiation therapy during the vaccination healing time • Is a transplant recipient (except for corneal transplant) • Is pregnant, planning pregnancy or breastfeeding(female subjects of childbearing potential must have negative pregnancy test prior to vaccination) • Household or other close/intimate contact(s) under the age of 12 months • History of allergies to phenol, any of the antibiotics listed in the vaccine content, or any other component of ACAM2000 or its diluents • Subjects with kidney disease (except kidney stones) • Subjects with abnormal electrocardiogram (EKG) at screening[c] • Subject has three (or more) of the following cardiovascular disease risk factors: • Severely or morbidly obese or higher obesity classification [body mass index (BMI) ≥36] • High blood pressure diagnosed by a doctor • High blood cholesterol diagnosed by a doctor • Diabetes or high blood sugar diagnosed by a doctor • A first degree relative (for example, mother, father, brother, sister) who had a heart condition before the age of 50 • Currently smokes tobacco (cigarettes)

	• Cardiovascular disease or heart condition diagnosed by a doctor at any time in the past, with or without symptoms, including:
	  • Arrhythmia
	  • Syncope related to cardiac disease
	  • Previous myocardial infarction
	  • Angina
	  • Coronary artery disease
	  • Congestive heart failure
	  • Cardiomyopathy
	  • Stroke or transient ischemic attack
	  • Myocarditis
	  • Pericarditis
	  • Chest pain or shortness of breath with activity (such as climbing stairs), peripheral edema, heart palpitations, dry cough, irregular heartbeat, excessive fatigue, unexplained syncope[e].
	  • Other heart conditions being treated by a physician

Assessments	**Screening [complete within 14 days before Baseline (Day 0)]** Prospective donors are presented with three informed consent forms: i) Plasma collection center's *Test Information and Donor's Consent*; ii) Plasma collection center's *Automated Plasmapheresis Information and Donor Consent*; iii) *VA-008 Study Specific Informed Consent* form. Potential plasma donors will be required to give written consent using the plasma collection center's *Test Information and Donor's Consent* form and asked to fill out a questionnaire to determine eligibility and identify risk factors for subject exclusion. • Potential plasma donors deemed eligible by questionnaire will be required to give written consent using both the plasma collection center's *Automated Plasmapheresis Information and Donor Consent* and the *VA-008 Study*

	Specific Informed Consent form. Potential plasma donors will then be screened to further ascertain their eligibility in this study and will be educated on ACAM2000 vaccination risks as well as study specific education.
	• All subjects who have signed the *VA-008 Study Specific Informed Consent* form will be documented on a screening log; the reason(s) for all screening failures will be captured.
	• Post-consent a subject number will be assigned and information including medical history, smallpox vaccination history, current medications (including birth control for females), detailed demographics (date of birth, race, ethnicity and gender), BMI (height and weight), physical exam, vital signs (body temperature, sitting blood pressure and pulse), and assessment for pericarditis/myocarditis symptoms will be collected to verify eligibility.
	• If subject is deemed eligible by the above screening, blood samples will be collected for:
	  • Hematology and blood chemistry
	  • HIV serology testing
	  • Immunologic assessment (IgA)[c]
	  • Serum pregnancy test for all female subjects of childbearing potential. Follicle-stimulating hormone (FSH) testing for postmenopausal women[a] (no menstrual cycle period for more than 12 months). As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.
	• Baseline EKG (if applicable)[b]
	• Once eligibility is confirmed, schedule baseline vaccination visit.
	• If a screened subject has not been vaccinated within 14 days of screening, the investigator must repeat the following assessments: subject eligibility; height and weight for BMI; pericarditis/myocarditis symptoms; immunodeficiency screening [immunoglobulin A

	(IgA)];pregnancy test (females); HIV serology testing; and concomitant medications as per the initial screening assessment. If a subject is not vaccinated within 30 days of the screening, a full screening evaluation must be performed. The subject will retain their Subject Number and details of the rescreening will be captured on the *Screening Log*. The most recent repeat assessment data will be captured. **Baseline (Day 0) prior to vaccination** • Update and verify subject eligibility assessment. • Review medical history. • Physical exam and vital signs. • Urine pregnancy test for all female subjects of child-bearing potential (must be negative prior to vaccination). As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. • Current medications. • Assessment for pericarditis/myocarditis. **Baseline (Day 0) vaccination and post-vaccination** • Following successful completion of the items above, vaccination with ACAM2000 as per the *Investigator's Brochure* by trained personnel. (Lot number, expiry date, location of injection site (right or left arm) and time of vaccination should be recorded). • Subjects must be observed for at least 30 minutes after vaccination. • Vaccination site inspection 30 minutes post-vaccination (or prior to subject's departure from plasma center). • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs). • Concomitant medications (if applicable).

	• Review vaccination risks and post-vaccination care/study requirements with subject. • For all vaccinated subjects, electronic case report forms (eCRF) will be used to capture study data from screening to the end of study. • Provide vaccination site dressing kit and diary cards for each visit to capture any adverse events for the duration of the study. **Post-vaccination Day 3 (±1)** • Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy). • Assessment for pericarditis/myocarditis. • Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over video to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment. • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs). • Diary card review and verification against adverse events collection above. • Concomitant medications. • Review instructions for care of vaccination site and provide vaccination site dressing kit. **Post-vaccination Day 7 (±1)** • Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy). • Assessment of pericarditis/myocarditis symptoms. • Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent BioSolutions and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary

	measure, women of childbearing potential will not be included in the study temporarily. • If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment. Vaccination site inspection: • If subject does not have a cutaneous reaction (presence of induration, erythema and/or a characteristic papule lesion) at the vaccination site by Day 7, there is no confirmation of vaccination 'take'. As these subjects do not develop an immune response to the vaccination and are unlikely to be at risk of vaccination complications, further follow-up will be conducted by phone on Day 12, and Day 28. These non-responder subjects are not eligible for plasmapheresis. If non-responders are not able to attend End of Study (Day 35 ±3) visit in person at the site, the visit can be conducted over video conference or a phone call. For non-responders, no Final Safety Assessment at Day 90 (±3) will be necessary. All female subjects of childbearing potential must undergo a urine pregnancy test at Day 35 post-vaccination, regardless of 'take' status. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs). • Diary card review and verification against adverse events collection above. • Concomitant medications. • Review vaccination site care instructions and provide vaccination site dressing kit. **Post-vaccination Day 12 (±2), 21 (±3), and 28 (±3)**

	Plasmapheresis must not begin until at least 10 days after vaccination. Donors will undergo plasmapheresis according to FDA approved site procedures. Although plasmapheresis may occur up to biweekly during this period, the following study assessments will only be required once per week: • Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) • Assessment of pericarditis/myocarditis symptoms. • Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent BioSolutions and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. • Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over video to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment. • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs) • Diary card review and verification against adverse events collection above • Concomitant medications • Review vaccination site care instructions and provide vaccination site dressing kit. Post-vaccination weekly follow-up visits (can be scheduled to coincide with plasmapheresis i.e., Day 21 ±3, Day 28 ±3, Day 35 ±3). **End of study post-vaccination Day 35 (±3) or Early Withdrawal (if applicable)**

	• Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) (required only if the scab has not separated). • Vital signs. • Assessment of pericarditis/myocarditis symptoms. • Urine pregnancy test for female subjects of child bearing potential. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent BioSolutions and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. • Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment. • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs). • Diary card review and verification against adverse events collection above. • Concomitant medications. • Review vaccination site care instructions and provide vaccination site dressing kit (required only if the scab has not separated). After the end of study visit, eligible subjects have the option to continue donating plasma as per the plasma collection site's FDA approved standard operating procedure (SOP) for VIGIV plasma collection. **Extended follow-up weekly visits for unresolved related adverse reactions post-vaccination** All related adverse events (AEs) (serious and non-serious) will be followed to resolution or stabilization as applicable.

	If extended follow-up weekly visits are required, they will include: • Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) (required only if the scab has not separated). • Assessment of pericarditis/myocarditis symptoms. • Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent BioSolutions and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. • Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment. • Unanticipated problems. • All adverse events including all cardiovascular adverse events (symptoms and signs). • Diary card review and verification against adverse events collection above. • Concomitant medications. • Review vaccination site care instructions and provide vaccination site dressing kit (required only if the scab has not separated). **Final Safety Assessment Day 90 (±3) by telephone or in person** • Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) (required only if the scab has not separated). • Assessment for pericarditis/myocarditis. • Unanticipated problems.

	• All adverse events and all cardiovascular adverse events (symptoms and signs). **Additional assessments for subjects with symptoms of pericarditis and/or myocarditis** In the event that a subject presents at any assessment with symptoms or findings suggestive of pericarditis and/or myocarditis that may be related to vaccination, the investigator will conduct additional assessments as required to confirm or rule out a clinical diagnosis of pericarditis/myocarditis. If unable to assess in person subject will be referred to emergency room for further evaluation. Refer to section 6.9 and the algorithm provided in Appendix II for the required action steps if pericarditis and/or myocarditis are suspected.
Safety Parameters	Safety information will be collected and tabulated in the form of related Adverse Events which will be reported annually to the Central Institutional Review Board (IRB) according to the IRB reporting policies. Expedited Reports are submitted to the IRB as required.
Monitoring	Safety will be monitored using a risk-based monitoring approach. Sites will be monitored both remotely and in-person, a medical monitoring plan will be established and data will be reviewed on a monthly basis. A Data and Safety Monitoring Board (DSMB) will be established to ensure the safety of subjects participating in this study.

[a] Acceptable methods of birth control include: IUD (inserted at least seven days prior to vaccination), hormonal implant (inserted at least 30 days prior to vaccination), oral contraceptive (regimen started at least 30 days prior to vaccination) and injectable hormone (injected at least 30 days prior to vaccination). The decision to allow use of hormonal contraceptives should be based on the potential for interactions with concomitant medications. Birth control method must be used throughout the study until scab separates. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

[b] Postmenopausal is defined as either >12 consecutive months with no menses without an alternative medical cause or FSH ≥40 mIU/mL.; if these criteria are not met and the woman is >50 years, she may participate if she agrees to undergo pregnancy testing requirements and agrees to use an effective birth control method such as barrier contraception for 4 weeks post-vaccination or until scab separates, whichever is longer. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

[c] To mitigate the risk of enrolling subjects at higher risk of developing cardiac adverse events and potentially jeopardizing subject safety, an EKG will be performed prior to vaccination with ACAM2000 smallpox

vaccine in all potential subjects ≥50 years old and for all potential subjects <50 years old with two cardiovascular disease risk factors including severely or morbidly obese or higher obesity classification (BMI ≥36), high blood pressure diagnosed by a doctor, high blood cholesterol diagnosed by a doctor, diabetes or high blood sugar diagnosed by a doctor, a first degree relative who had a heart condition before the age of 50 and current tobacco smokers. EKG results will be reviewed by a third party board-certified cardiologist and will be reported to the site. All subjects with EKG interpreted as 'Abnormal, Significant' by the third party cardiologist will be excluded. Inclusion of subjects with 'Abnormal, Insignificant' EKG will be based on the Principal Investigator's discretion.

[d] If the lab results for quantitative IgA immunoglobulin level are lower than 15% below normal range, the subject may not proceed further in the screening process.

[e] Subjects will be solicited for symptoms suggestive of cardiovascular problems including chest pain, shortness of breath, peripheral edema, heart palpitations, dry cough, irregular heartbeat, excessive fatigue and unexplained syncope at screening and prior to vaccination. If subject has any of these symptoms, they will not be included in the study or if already included, they will not be vaccinated unless follow-up results confirm that the symptoms were isolated and not related to cardiovascular problems.

Schedule of Events

Assessment	Screening (Within 14 Days Before Baseline)[e]	Baseline (Day 0)	Day 3 (±1)	Day 7 (±1) [h]	Day 12 (±2)	Day 21 (±3)	Day 28 (±3)	End of Study Day 35 (±3) or Early Withdrawal	Follow-up Weekly Visits for Unresolved Adverse Reactions	Final Safety Assessment Day 90 (±3)
Eligibility Assessment	X	X								
Signed Informed Consent and Study Specific Education	X									
Medical History (including smallpox vaccination history)	X	X								
Demographics	X									
Height and Weight for BMI	X									
Physical Exam	X	X[a]								
Vital Signs	X	X						X		
Peri/myocarditis Symptoms[d]	X	X	X	X	X	X	X	X	X	X
EKG[i]	X									
Hematology and Blood Chemistry	X									
HIV Serology	X									
Immunologic Assessment (IgA)	X									
Pregnancy Test (Females) [c, g, h]	Serum[e]	Urine		Urine	Urine	Urine	Urine	Urine	Urine	
Vaccination		X								
Vaccination Site Inspection		X[f]	X	X	X	X	X	X	X	

Assessment	Screening (Within 14 Days Before Baseline)[e]	Baseline (Day 0)	Day 3 (±1)	Day 7 (±1) [h]	Day 12 (±2)	Day 21 (±3)	Day 28 (±3)	End of Study Day 35 (±3) or Early Withdrawal	Follow-up Weekly Visits for Unresolved Adverse Reactions	Final Safety Assessment Day 90 (±3)
Unanticipated Problems; All Adverse Events including all Cardiovascular Adverse Events		X	X	X	X	X	X	X	X	X
Diary card review and verification against adverse events			X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Vaccination Site Care and Instructions[b]		X	X	X	X	X	X	X	X	

[a] Physical exam is required at the baseline assessment in order to ensure that subject remains eligible for ACAM2000 vaccination.

[b] Provision of vaccination site care instructions and bandage kits are only required until scab separation.

[c] Pregnancy tests are required for all female subjects of childbearing potential (must be negative). In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent BioSolutions and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

[d] In the event that a subject presents at any assessment with symptoms or findings suggestive of pericarditis and/or myocarditis which may be related to vaccination, the investigator will conduct additional assessments as required to confirm or rule out a clinical diagnosis of pericarditis/myocarditis. Refer to the algorithm provided in Appendix II for the required action steps if pericarditis and/or myocarditis are suspected. If unable to perform additional assessments in person, subject will be referred to ER.

[e] If a screened subject has not been vaccinated within 14 days of screening, the investigator must repeat the following assessments: subject eligibility; height and weight for BMI; pericarditis/myocarditis symptoms; immunodeficiency screening (IgA); pregnancy test (females); HIV serology testing; and concomitant medications as per the initial screening assessment. If a subject is not vaccinated within 30 days of screening, full screening evaluation must be performed. The subject will retain their Subject Number and details of the rescreening will be captured on the *Screening Log*. The most recent repeat assessment data will be captured.

[f] Vaccination site inspection 30 minutes post-vaccination (or prior to subject's departure from plasma center).

[g] Postmenopausal is defined as either >12 consecutive months with no menses without an alternative medical cause or FSH ≥40 mIU/mL; if these criteria are not met and the woman is >50 years, she may participate if she agrees to undergo pregnancy testing requirements and agrees to use an effective birth control

Assessment	Screening (Within 14 Days Before Baseline)[e]	Baseline (Day 0)	Day 3 (±1)	Day 7 (±1) [h]	Day 12 (±2)	Day 21 (±3)	Day 28 (±3)	End of Study Day 35 (±3) or Early Withdrawal	Follow-up Weekly Visits for Unresolved Adverse Reactions	Final Safety Assessment Day 90 (±3)

method such as barrier contraception for 4 weeks post-vaccination or until scab separates, whichever is longer. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

[h] If subject does not have a cutaneous reaction (presence of induration, erythema and/or a characteristic papule lesion) at the vaccination site by Day 7, there is no confirmation of vaccination 'take'. As these subjects do not develop an immune response to the vaccination and are unlikely to be at risk of vaccination complications, further follow-up will be conducted by phone on Day 12 and Day 28. These non-responder subjects are not eligible for plasmapheresis. All non-responders will attend End of Study (Day 35 ±3) visit in person at the site. For non-responders no Final Safety Assessment at Day 90 (±3) will be necessary. All female subjects of childbearing potential must undergo a urine pregnancy test at Day 35 post-vaccination, regardless of 'take' status. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

[i] To mitigate the risk of enrolling subjects at higher risk of developing cardiac adverse events and potentially jeopardizing subject safety an EKG will be performed prior to vaccination with ACAM2000 smallpox vaccine in all potential subjects ≥50 years old and for all potential subjects <50 years old with two cardiovascular disease risk factors including; severely or morbidly obese or higher obesity classification (BMI ≥36); high blood pressure diagnosed by a doctor; high blood cholesterol diagnosed by a doctor; diabetes or high blood sugar diagnosed by a doctor; a first degree relative who had a heart condition before the age of 50; and current tobacco smokers. EKG results will be reviewed by a third party board-certified cardiologist and will be reported to the site. All subjects with EKG interpreted as 'Abnormal, Significant' by the third party cardiologist will be excluded. Inclusion of subjects with 'Abnormal, Insignificant' EKG will be based on the Principal Investigator's discretion.

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Appendices

1 BACKGROUND INFORMATION

1.1 ACAM2000®

ACAM2000 (Smallpox (Vaccinia) Vaccine, Live) is a live, attenuated vaccinia virus derived from ACAM1000, a similar smallpox vaccine produced in cell culture by plaque-purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA). Dryvax was prepared from calf lymph, which was purified, concentrated and dried by lyophilization (1). It was prepared with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia.

Vaccinia vaccine is a highly effective immunizing agent that brought about the global eradication of smallpox. The last naturally occurring case of smallpox occurred in Somalia in 1977. In July 1979, the World Health Organization (WHO) certified that the world was free of naturally occurring smallpox (2).

Routine vaccinia vaccination was discontinued in 1971 (3). In 1976, the recommendation for routine vaccination of health care workers was also discontinued (4). In 1982, the only active licensed producer of vaccinia vaccine in the United States of America (USA), Wyeth-Lederle Vaccines and Pediatrics (subsidiary of American Home Products) discontinued production for general use, and in 1983, distribution to the civilian population was discontinued (5). For several years all military personnel continued to be routinely vaccinated; however, only selected groups of military personnel are currently vaccinated against smallpox (1). The Dryvax vaccine has now been replaced by ACAM2000, which is now kept by the Centers for Disease Control and Prevention (CDC) in Atlanta.

To ensure safe use of vaccinia vaccines, satisfactory stocks of vaccinia immune globulin (VIG) are necessary for managing specific vaccination complications (6). VIG is an isotonic sterile solution of the immune globulin fraction of plasma from persons vaccinated with vaccinia vaccine. The first commercially available VIG, manufactured by Baxter Healthcare, was originally approved by Center for Biologics Evaluation and Research (CBER) in 1968 but, like Dryvax, is no longer produced. Emergent BioSolutions Canada Inc. (Emergent) currently manufactures Vaccinia Immune Globulin Intravenous (VIGIV), which was approved by the Food and Drug Administration (FDA) in 2005.

1.2 Clinical Study Rationale

There is increased interest in building up the national stockpile of vaccinia vaccine as protection against the deliberate release of smallpox (variola virus), and VIGIV is necessary to treat potential serious vaccination-related complications. To produce VIGIV, a source of high titer anti-vaccinia plasma is required. However, plasma donors require booster vaccination to produce anti-vaccinia antibody titers required for successful production of VIGIV.

In previous plasma collection program study (VA-001) the Dryvax vaccine was used to elevate anti-vaccinia immune globulin titers in subjects and then plasma was collected to produce VIGIV. In a follow up study (VA-006), subjects were vaccinated using the ACAM2000 smallpox vaccine, and their plasma was collected to compare the VIGIV manufactured from plasma collected from donors

vaccinated with ACAM2000 to VIGIV manufactured from plasma previously collected from donors vaccinated with the Dryvax smallpox vaccine. ACAM2000 vaccinated donors produced plasma titres that were sufficient for pooling to manufacture VIGIV. In general, the key quality attributes of the ACAM2000 product fell within the range of results seen for VIGIV manufactured from Dryvax vaccinated donors.

In this study (VA-008), healthy adult male and female volunteers who meet the requirements for source plasma donors and study entry criteria will be vaccinated with the ACAM2000 smallpox vaccine for collection of plasma to be used in the manufacture of VIGIV. There are possible risks associated with ACAM2000 vaccination. To ensure the safety of plasma donors, risk factor screening procedures and the collection of post-vaccination safety data will be assessed throughout the study.

To reduce these possible risks the safety of each donor will be assessed throughout the study and the following safety measures will be taken:

- Training of the study staff on the possible related adverse events following ACAM2000 vaccination.
- Training of the study staff on vaccination site inspection (appearance and evaluation) at each study visit.
- Training of all investigators involved in the vaccination of subjects on administration of the ACAM2000 vaccine.
- Education of the study subjects on the possible risks involved with ACAM2000 vaccination and providing them with *ACAM2000 Medication Guide*.
- Thorough screening process to exclude subjects with higher risk of experiencing serious complications following vaccination e.g., excluding subjects with immunodeficiency, cardiovascular disease or heart condition, etc. (for a complete list see exclusion criteria section 4.2).
- Vaccination of subjects who were previously vaccinated with a smallpox vaccine (Dryvax or ACAM2000) and who do not have any unresolved adverse events from previous smallpox vaccination.
- Exclusion of subjects who are pregnant or are planning to become pregnantand performing pregnancy tests at each study visit for women of childbearing potential.
- Safety evaluation at each study visit by assessments of pericarditis/myocarditis symptoms, adverse events and subject reminders for vaccination site care.
- An algorithm (Appendix II) for suspected pericarditis/myocarditis will be followed to ensure subject safety and follow-up. If a subject who needs to have an EKG performed at BPL is not able to complete an in-person study visit due to COVID-19 restrictions, he/she will be instructed to go to the nearest emergency room (ER). The subject will be required to bring back the medical records to the next protocol scheduled visit. If a subject is not able to obtain the records or attend

the visit in person then the copy of the medical records is to be requested from the ER and sent to the Principal Investigator.

- A final safety assessment at Day 90 post-vaccination. All related adverse events (AEs) (serious and non-serious) will be followed to resolution or stabilization as applicable (may extend beyond Day 90 post-vaccination).
- Safety of subjects will be monitored throughout their study participation utilizing a combination of centralized and onsite monitoring (risk-based monitoring approach). Sites will be monitored and data will be reviewed on a monthly basis according to a Medical Monitoring Plan. A Data and Safety Monitoring Board (DSMB) will be established to meet at pre-defined intervals and have ad hoc meetings (if necessary) to review study data and independently ensure the safety of subjects participating in this study according to the DSMB charter.

1.3 Plasmapheresis

Blood is composed of plasma, blood cells, and platelets. Plasma is the clear, yellowish fluid portion of blood, lymph, or intramuscular fluid in which cells are suspended. It makes up about 55% of total blood volume. It is composed of mostly water and contains dissolved proteins, glucose, clotting factors, mineral ions, hormones and carbon dioxide.

Plasma will be collected by an automated plasmapheresis method, which involves a process whereby a needle is placed in the donor's arm, the device collects whole blood, separates the blood components by centrifugation, retaining the plasma portion of the blood and returning the remaining blood components to the donor through the same needle.

Plasmapheresis procedures will be conducted at FDA approved plasma collection sites, and will be conducted according to the site's FDA-approved standard operating procedures (SOPs) for plasma collection. The frequency of plasma donation and volume of plasma collected at each donation will vary by weight and will be conducted in accordance with the United States Code of Federal Regulations (CFR) Title 21 part 640.65.

Study subjects that have been vaccinated with ACAM2000 may not undergo plasmapheresis until at least 10 days after vaccination.

Donors who have been vaccinated with ACAM2000 under this protocol, who do not exhibit vaccine complications, should be deferred from participation in any blood donor program except for the specific collection of anti-vaccinia antibody until after the vaccination scab has separated spontaneously, or for 30 days post-vaccination, whichever is the later date. If scab is removed prior to spontaneous separation, FDA recommends that the donor be deferred for two months after vaccination.

For donors who have been vaccinated with ACAM2000 under this protocol, who have experienced complications of vaccination, FDA recommends that these donors be deferred from participation in

any other blood donor program until 14 days after all vaccine complications have completely resolved.

Sites must follow their FDA approved procedures for donor eligibility and deferral in addition to the eligibility requirements outlined in section 4.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Hypothesis

The protocol will allow for the safe use of ACAM2000 in a plasma donor vaccination program.

2.2 Primary Objective

This protocol is being conducted to vaccinate plasma donors with the ACAM2000 smallpox vaccine thereby inducing an immune response resulting in high anti-vaccinia antibody titers. The collection of donor plasma will be used in the manufacturing of Vaccinia Immune Globulin Intravenous (VIGIV). The objective of this protocol is to ensure the safety of plasma donors vaccinated with ACAM2000 through the implementation of risk factor screening procedures and the collection of post-vaccination safety data.

3 STUDY DESIGN

Open label, single arm, multi-center, vaccination program of plasma donors. Donor safety will be evaluated following administration of the ACAM2000 vaccine.

3.1 Anticipated Centers

Multiple FDA licensed plasma collection centers will be involved in this study.

3.2 Sample Size

Ongoing enrollment to fulfill VIGIV manufacturing requirements for current contracts.

3.3 Randomization and Blinding

There is no randomization or blinding in this study.

3.4 Criteria for Stopping or Terminating the Study

Emergent and the Principal Investigator may elect to terminate the study early as defined by the clinical study agreement. The study may be terminated at any or all sites for any of the following reasons:

- The safety data demonstrate or strongly suggest that the study treatment (or participation in the study) is unsafe. The Principal Investigator and sponsor, with input from the DSMB, will be responsible for ongoing review of safety data. The Principal Investigator will initially assess seriousness, causality and intensity (severity) of an adverse event.
- The protocol or conduct of the study is flawed such that the safety or rights of the study subjects may be adversely affected.
- The ethics committee has withdrawn the approval for the study and has denied reconsideration.
- Sponsor agrees with DSMB recommendation for stopping, terminating or suspending the study based on DSMB Charter.
- Poor recruitment.
- Relocation of the Principal Investigator or reallocation of Principal Investigator's responsibilities, or disqualification of the Principal Investigator by order of the regulatory authority.
- Non-adherence to the protocol or unavailability of the Principal Investigator or his/her staff for the sponsor's (or their authorized representative) monitoring personnel.
- Inadequate evidence of the Principal Investigator's personal conduct or supervision of the study.
- Change of research strategy or change of management priorities.
- Imposition of clinical hold by a regulatory authority.

Any decision to voluntarily suspend or terminate a clinical study will be carefully reviewed and fully justified. The sponsor will notify the FDA and the Central Institutional Review Board (IRB) of any suspension or termination, along with justification for restarting or terminating the study as applicable.

The Principal Investigator must notify the IRB in writing of the study's completion or early termination. Emergent must receive a copy of the notification letter from the IRB indicating receipt of the completion or early termination letter.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

Subjects must meet the inclusion criteria to participate in the study.

- Signed written informed consent.
- Age 18 to 65
- Normal and healthy (immune competent) as determined by medical history, physical exam, vital signs and clinical laboratory tests during the screening period

  - If the lab result for quantitative immunoglobulin A (IgA) is lower than 15% below normal range, the subject may not proceed further in the screening process.
- Subject must meet all required subject suitability criteria that pertain to normal source plasma donors as per 21 CFR 640.63.
- Negative human immunodeficiency virus (HIV) serology during screening period.
- Subject must have been previously immunized for smallpox, at ≥3 years prior to commencement of screening assessments, and vaccination history must be confirmed by oral or written history and the presence of a visible pathognomonic smallpox vaccination scar.
- Female subjects of childbearing potential must agree to use highly effective birth control methods. Acceptable methods of birth control include: IUD (inserted at least seven days prior to vaccination), hormonal implant (inserted at least 30 days prior to vaccination), oral contraceptive regimen (started at least 30 days prior to vaccination) and injectable hormone (injected at least 30 days prior to vaccination). The decision to allow use of hormonal contraceptives should be based on the potential for interactions with concomitant medications. Birth control method must be used throughout the study until scab separates. Females of non-childbearing potential are defined as being surgically sterile or meeting postmenopausal requirements and all women must be educated on risks of vaccine to an unborn child. Postmenopausal is defined as either >12 consecutive months with no menses without an alternative medical cause or FSH ≥40 mIU/mL or if these criteria are not met and the woman is >50 years, she may participate if she agrees to undergo pregnancy testing requirements and agrees to use an effective birth control method such as barrier contraception for four weeks post-vaccination or until the scab separates, whichever is longer. Written confirmation is required for surgical sterility and birth control methods. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.

4.2 Subject Exclusion Criteria

Subjects who have any of the exclusion criteria at screening and/or baseline will be excluded from participation in this study.

- History of severe related adverse event(s) from previous participation in VA-001 or VA-006 trials or to any smallpox vaccination.
- The subject, or a household contact or other close/intimate contact of the subject has ANY of the following:
  - Eczema, history of eczema, exfoliative skin conditions, wounds, burns, or other skin conditions at the investigator's discretion.
  - A history of immunodeficiency.

- Currently or has recently received radiotherapy or chemotherapy, adrenocorticotropic hormone (ACTH), corticosteroids, or immunosuppressive drugs. This includes any route of administration (including topical) for any duration of time at any dose for at least one month prior to vaccination.
  - Eye disease treated with topical steroids.
- Known or suspected disorders of immunoglobulin synthesis.
- Leukemia, lymphomas of any type, melanoma, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- Has been diagnosed with cancer and who will be undergoing chemotherapy or radiation therapy during the vaccination healing time.
- Is a transplant recipient (except for corneal transplant).
- Is pregnant, planning pregnancy or breastfeeding (female subjects must have negative urine pregnancy test prior to vaccination).

- Household or other close/intimate contact(s) under the age of 12 months.
- History of allergies to phenol, any of the antibiotics listed in the vaccine content, or any other component of ACAM2000 or its diluents (see section 5.1).
- Subjects with kidney disease (except kidney stones).
- Subjects with abnormal EKG at screening (if applicable).
  - To mitigate the risk of enrolling subjects at higher risk of developing cardiac adverse events and potentially jeopardizing subject safety an EKG will be performed prior to vaccination with ACAM2000 smallpox vaccine in all potential subjects ≥50 years old and for all potential subjects <50 years old with two cardiovascular disease risk factors as listed immediately below including severely or morbidly obese or higher obesity classification (BMI ≥36), high blood pressure, high blood cholesterol, diabetes or high blood sugar, a first degree relative who had a heart condition before the age of 50 and current tobacco smokers. EKG results will be reviewed by a qualified third party board-certified cardiologist and will be reported to the site.
  - All subjects with EKG interpreted as 'Abnormal, Significant' by the third party cardiologist will be excluded. Inclusion of subjects with 'Abnormal, Insignificant' EKG will be based on the Principal Investigator's discretion.
- Subject has three (or more) of the following cardiovascular disease risk factors:
  - Severely or morbidly obese or higher obesity classification (BMI ≥36)
  - High blood pressure diagnosed by a doctor
  - High blood cholesterol diagnosed by a doctor

- Diabetes or high blood sugar diagnosed by a doctor
- A first degree relative (for example, mother, father, brother, sister) who had a heart condition before the age of 50
- Currently smokes tobacco (cigarettes)

- Cardiovascular disease or heart condition diagnosed by a doctor at any time in the past, with or without symptoms, including:
  - Arrhythmia
  - Syncope related to cardiac disease
  - Previous myocardial infarction
  - Angina
  - Coronary artery disease
  - Congestive heart failure
  - Cardiomyopathy
  - Stroke or transient ischemic attack
  - Myocarditis
  - Pericarditis
  - Chest pain or shortness of breath with activity (such as climbing stairs), peripheral edema, heart palpitations, dry cough, irregular heartbeat, excessive fatigue, unexplained syncope
    - Subjects will be solicited for symptoms suggestive of cardiovascular problems (as stated above) at screening and prior to vaccination. If subject has any of these symptoms, they will not be included in the study or if already included, they will not be vaccinated unless follow-up results confirm that the symptoms were isolated and not related to cardiovascular problems.
  - Other heart conditions being treated by a physician

4.3 Subject Withdrawal

The subjects must be available, without coercion, for all parts of the study.

If continued participation jeopardizes the subject's health, the subject should be withdrawn from the study. The Principal Investigator is encouraged to consult the sponsor prior to the withdrawal of any subject, except in the event of a medical emergency. The reason for withdrawal of any subject must be clearly documented on the study source documents and the appropriate electronic Case Report Form (eCRF).

4.3.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

In addition, subjects may be withdrawn from the study for any of, but not limited to, the following reasons:

1. The subject develops an intercurrent illness (adverse event) that prevents study completion.
2. The sponsor elects to stop the study.
3. The subject is not compliant with the requirements of the study to the satisfaction of the investigator and/or sponsor (withdrawn by the investigator).
4. The subject elects to stop further participation in the study (consent withdrawn).
5. Subject is lost to follow up.
6. The subject does not meet the entry criteria for the study but was erroneously entered into the trial, or no longer meets entry criteria after entry into the study per protocol.
7. The opinion of the Principal Investigator that it is unwise for the subject to continue in the study.

If a subject is withdrawn from the study, they will not be re-entered into the study for any reason.

4.3.2 Subject Replacement

If a subject is withdrawn from the study, these subjects will not be replaced as the sample size of the study accounts for withdrawn subjects.

4.3.3 Follow-up for Withdrawn Subjects

Every attempt will be made to ensure that subjects who are withdrawn, or who withdraw from the study during the active treatment or follow-up period, will complete all safety and assessments for the early withdrawal visit as outlined in this protocol. The Principal Investigator should inform the subjects that these assessments are for their own safety.

4.3.4 Subject Re-Entry into the Study

Subjects who have been previously vaccinated with ACAM2000 in VA-008 may be eligible to re-enter the study after three years providing that subjects meet all eligibility and screening assessments.

5 STUDY MEDICATION

5.1 Description, Packaging and Formulation

ACAM2000 is provided as a lyophilized preparation of purified live virus containing the following non-active excipients: 6 to 8 mM HEPES (pH 6.5 to 7.5), 2% human serum albumin USP, 0.5 to 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B. The vaccine is free from bacteria and fungi.

Diluent for ACAM2000 contains 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, supplied in 3 mL clear glass vials containing 0.6 mL.

After reconstitution, each vial of ACAM2000 vaccine contains 100 nominal doses (2.5 µL/dose). The concentration of vaccinia virus is 1.0 to 5.0 x 10^8 plaque-forming units (PFU)/mL or 2.5 to 12.5 x 10^5 PFU/dose determined by plaque assay in Vero cells. ACAM2000 is intended for multiple-puncture use, i.e., administered by the percutaneous route (scarification), into the superficial layers of the skin using a bifurcated needle. Bifurcated needles are supplied with vaccine.

For more information, please refer to the *Investigator's Brochure*.

5.2 Labeling

ACAM2000 will retain commercial labels, as per the manufacturer's specification and license.

5.3 Storage Conditions

ACAM2000 vaccine (lyophilized and/or reconstituted) must be stored inside a thermal isolation chamber (TIC) that has been properly pre-conditioned at 2 to 8°C (36 to 46ºF). The TIC containing the ACAM2000 vaccine (lyophilized and/or reconstituted) will be kept in a temperature monitored refrigerator at 2 to 8ºC (36 to 46ºF) and in a secure area. Once reconstituted ACAM2000 vaccine can be stored for only 14 days at 2 to 8°C (36 to 46ºF) after which it should be considered as unsuitable for use (ACAM2000 reconstitution day will be considered the first day of storage).

Reconstituted vaccine should be administered immediately after it is retrieved from refrigeration and should NOT be kept at room temperature except for the short period of time during a vaccination session [i.e., minimum amount of time required to vaccinate the subject(s)]. Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing the vaccine vial in the TIC inside the refrigerator between administrations.

Diluent for ACAM2000 should be stored at room temperature (15 to 30ºC, 59 to 86ºF).

Throughout the study, the Principal Investigator will keep an inventory and account of all ACAM2000 vaccine and diluent vials received using the *Site Inventory Log* and the *Drug Accountability Form*. Under no circumstances will the Principal Investigator allow the ACAM2000 to be used other than as specified in this protocol.

5.4 Reconstitution and Preparation

ACAM2000 is reconstituted by addition of 0.3 mL of diluent to the vial containing lyophilized vaccine. ACAM2000 should only be reconstituted with 0.3 mL of the diluent provided. Reconstitute as follows:

- Remove from cold storage and bring to room temperature before reconstitution.
- Remove flip-cap seals of the vaccine and diluents.
- Swab rubber stopper for the vaccine and diluent vials with an isopropyl alcohol swab and allow rubber stopper to dry thoroughly.
- Using aseptic technique, draw up 0.3 mL of diluent into a sterile 1 mL syringe fitted with a 25 gauge x 5/8" needle (provided), and transfer the entire contents of the syringe to the vaccine vial.
- Gently swirl to mix, but try not to get the product on the rubber stopper.

Reconstituted vaccine should be a clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Inspect reconstituted vaccine visually for particulate matter and discoloration upon reconstitution and prior to each administration. Each visual inspection must be recorded on the *Drug Accountability Log* for the VA-008 study. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be quarantined. See section 5.3 for storage requirements for reconstituted vaccine and section 5.5 for quarantine/disposal of expired and/or unsuitable vials.

Lot number and expiry date of ACAM2000 vaccine and its diluent, date of reconstitution, expiry date of reconstituted vaccine (once reconstituted ACAM2000 vaccine can be stored for only 14 days after which it should be considered expired) as well as visual inspection of reconstituted vial should be recorded on the VA-008 *Drug Accountability Log*.

For more information, please refer to the *Investigator's Brochure*.

5.5 Handling Precautions and Disposal

ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent.

Personnel preparing and administering the vaccine should wear a lab jacket, surgical or protective gloves and a mask or face shield and avoid contact of vaccine with skin, eyes or mucous membranes.

The vaccine vial, its stopper, the diluent syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be discarded in leak-proof, puncture-proof biohazard containers. These containers should then be disposed of appropriately.

Expired and/or unsuitable vaccine vials must be properly quarantined. All ACAM2000 vaccine vials must remain in quarantine and will not be destroyed until written authorization is provided by

Emergent and only at the site in the presence of a study monitor. Once approved, vials should be appropriately disposed of as biohazardous material.

5.6 Medication Shipment

ACAM2000 will be shipped in accordance with the temperature requirements to the site. The Principal Investigator or designate will be responsible for checking the number of vials and the condition of the vials received and entering this information into the drug accountability records, reporting the condition to Emergent and returning all shipping documentation. Drug will be released for use after the maintenance of temperature confirmation has been received and reviewed and written authorization has been issued to the investigator/designate by the sponsor or designate.

5.7 Drug Accountability

The Principal Investigator is responsible for maintaining accurate inventory records of ACAM2000, including overall inventory of ACAM2000 vials, as well as individual administration of vaccine to subjects participating in VA-008. The Principal Investigator or designate will inventory all ACAM2000 shipments upon receipt; acknowledge possession by signing all required documentation, and returning these to the sponsor. The Principal Investigator must ensure that all drug supplies are kept in a secure location at the site in accordance with recommended storage conditions.

This inventory and accountability record for the ACAM2000 will include:

- Protocol name and number.
- Product name and lot number.
- Name of qualified individual performing reconstitution and visual inspection of reconstituted vaccine.
- Name of qualified individual administering product, amount administered, route of administration, date administered.
- Subject identifier.

These records will be reviewed by representatives of the sponsor, and may be reviewed by regulatory agencies.

6 STUDY PROCEDURES

6.1 Screening [complete within 14 days prior to Baseline (Day 0)]

6.1.1 Consent Procedures and Subject Education

Prospective donors are presented with three informed consent forms: i) Plasma collection center's *Test Information and Donor's Consent;* ii) Plasma collection center's *Automated Plasmapheresis Information and Donor Consent*; iii) *VA-008 Study Specific Informed Consent* Form.

Prior to participation in the study, all subjects must be eligible plasma donors and screened in accordance with FDA approved SOPs (21 CFR 640.63). Potential plasma donors will be required to give written consent using the plasma collection center's *Test Information and Donor's Consent* Form and asked to fill out a questionnaire to determine eligibility and identify risk factors for subject exclusion.

For plasma donor screening, subjects will be consented according to FDA approved plasma collection sites procedures. Potential plasma donors deemed eligible by questionnaire will be required to give written consent using the plasma collection center's *Automated Plasmapheresis Information and Donor Consent* Form.

Following the aforementioned plasma center specific procedures, subjects who are eligible plasma donors will then undergo *VA-008 Study Specific Informed Consent* counseling by a study investigator. Once written informed consent is obtained, subjects will then be screened to further ascertain their eligibility in this study.

By the end of the screening process and prior to vaccination, the potential subject must:

- Have read, understood and signed all current and applicable informed consent forms listed above;
- Have been provided the *ACAM2000 Medication Guide* as educational material which clearly denotes the serious complications associated with this vaccine, which include serious heart problems, potential outcomes of fetal vaccination, vaccination of subjects with eczema and those with immune system deficiencies;
- Have been assigned a Subject Number and have been set up with a record file, along with any other administrative requirements.

6.1.2 Screening Assessment

- Eligibility assessment (review of inclusion and exclusion criteria).
- Confirmation of signed *Informed Consent Forms* (ICFs) and that the subject has been provided study specific education.

- All subjects who have signed the *VA-008 Study Specific Informed Consent Form* will be documented on a *Screening Log*; the reason(s) for all screening failures will be captured.

- Medical history including:
  - Smallpox vaccination history (name of the vaccine, the date and the location of the vaccination).
  - Record medical history of the following body systems: (1) head, eyes, ears, nose, mouth and throat (2) respiratory (3) cardiovascular (4) musculoskeletal (5) gastrointestinal (6) hematological (7) lymphatic (8) neurological (9) skin (10) allergies (including drug allergies).
  - Form of birth control confirmed in writing by primary care physician (females of childbearing potential). As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.
- Demographic information including date of birth, race, ethnicity and gender.
- Height, weight, and Body Mass Index (BMI).
- Full physical examination including evaluation of the following body systems: (1) general appearance (2) head, eyes, ears, nose, mouth and throat (3) lungs (4) heart (5) abdomen (6) extremities (7) lymph nodes (8) neurological (9) musculoskeletal (10) skin, allergies (including drug allergies).
- Vital signs (identifying clinical significance if applicable): including body temperature, sitting blood pressure and pulse.
- An EKG (if applicable) and assessment of pericarditis/myocarditis symptoms to provide a baseline against which any subsequent symptoms suggestive of pericarditis/myocarditis (from Day 3 onward) may be compared (see section 6.1.3).
- Hematology: complete blood count (CBC): hemoglobin, hematocrit, white blood cells (WBC) and differential, red blood cells (RBC), RBC indices [mean cell volume (MCV), mean cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)], mean platelet volume, and platelet count.
- Blood chemistry: random glucose, creatinine, blood urea nitrogen (BUN), alanine transaminase (ALT), aspartate transaminase (AST), and electrolytes (sodium, potassium, chloride, CO_2, and calcium).
- HIV serology (must be tested and found negative within 14 days prior to baseline).
- Immunologic assessment (IgA). Blood samples will be collected and sent to the central laboratory for analysis of quantitative IgA immunoglobulin level.
  - If the lab results for quantitative IgA immunoglobulin level are lower than 15% below normal range, the subject may not proceed further in the screening process.

  - Serum pregnancy test (females of childbearing potential) must be tested and found negative within 14 days prior to baseline. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.FSH testing for postmenopausal women (postmenopausal is defined as either >12 consecutive months with no menses without an alternative medical cause or FSH ≥40 mIU/mL or if these criteria are not met and the woman is >50 years, she may participate if she agrees to undergo pregnancy testing requirements and agrees to use an effective birth control method such as barrier contraception for four weeks post-vaccination or until scab separates, whichever is longer).
- List of medications currently taken by the subject (see section 6.10).
- Once eligibility is confirmed schedule baseline vaccination visit.
- If a screened subject has not been vaccinated within 14 days of screening, the investigator must repeat the following assessments: subject eligibility; height and weight for BMI; pericarditis/myocarditis symptoms; immunodeficiency screening (IgA); pregnancy test (females); HIV serology testing; and concomitant medications as per the initial screening assessment. If a subject is not vaccinated within 30 days of the screening, a full screening evaluation must be performed. The subject will retain their Subject Number and details of the rescreening will be captured on the Screening Log. The most recent repeat assessment data will be captured.

6.1.3 Assessment of Pericarditis/Myocarditis Symptoms (Screening)

- Solicit the subject for clinical symptoms of pericarditis/myocarditis (e.g., chest pain, heart palpitations, irregular heartbeat, excessive fatigue, peripheral edema, shortness of breath, unexplained syncope, dry cough).
  - Site personnel must be appropriately trained by a Principal Investigator or sub-Investigator who is a licensed physician, to recognize the symptoms of pericarditis/myocarditis, such as those listed above. This training must be documented on the site's training form, must be signed and dated by the person conducting the training and by the person receiving the training, and must be completed prior to allowing the trainee to solicit for symptoms of pericarditis/myocarditis.
- To mitigate the risk of enrolling subjects at higher risk of developing cardiac adverse events and potentially jeopardizing subject safety an EKG will be performed prior to vaccination with ACAM2000 smallpox vaccine in all potential subjects ≥50 years old and for all potential subjects <50 years old with two cardiovascular disease risk factors as listed in the exclusion criteria, including severely or morbidly obese or higher obesity classification (BMI ≥36); high blood pressure; high blood cholesterol; diabetes or high blood sugar; a first degree relative who had a heart condition before the age of 50; and current tobacco smokers. Subjects with three (or more) of these cardiovascular disease risk factors will be excluded from the study (see section 4.2).
- EKG results will be reviewed by a qualified third-party board certified cardiologist and will be reported to the site, a signed and dated checklist of the symptoms listed above and EKG results

(as applicable), as a minimum, will be maintained in the subject's chart to document that solicitation of these symptoms and further investigation for possible additional symptoms has occurred at the screening visit. If the Principal Investigator or sub-Investigator feels that further investigation is warranted, follow-up should be done with the subject's physician and/or cardiologist.

- For post-vaccination assessments where pericarditis/myocarditis is suspected refer to Appendix II.

6.2 Baseline (Day 0)

6.2.1 Prior to ACAM2000 Administration

- Verify and update eligibility assessment.
- Review medical history, and update if additional details or medical history conditions have arisen since the screening visit.
- Full physical examination including evaluation of the following body systems: (1) general appearance (2) head, eyes, ears, nose, mouth and throat (3) lungs (4) heart (5) abdomen (6) extremities (7) lymph nodes (8) neurological (9) musculoskeletal (10) skin.
- Vital signs (identifying clinical significance if applicable): including body temperature, sitting blood pressure and pulse.
- Urine pregnancy test (females of childbearing potential) (must be negative). As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. Review current medications (see section 6.10).
- Assessment for pericarditis/myocarditis (see section 6.1.3).

6.2.2 ACAM2000 Vaccination

Following the successful completion of baseline assessments, the ACAM2000 vaccine will be administered to eligible subjects, as per the *Investigator's Brochure*.

Reconstituted vaccine should be inspected visually prior to administration. Each vaccine reconstitution and visual vial inspection should be recorded on the Drug Accountability Log for the VA-008 study. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be quarantined. See section 5.5 for quarantine/disposal of unusable vials. If a vial of reconstituted ACAM2000 is deemed unusable, new vials of ACAM2000 and diluent can be reconstituted (see section 5.4) and vaccinations may continue. ACAM2000 must be administered only by a qualified medical practitioner who has received training by Emergent to safely and effectively administer the vaccine by the percutaneous route (scarification), as required by FDA. ACAM2000

should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route (for further information see the *Investigator's Brochure*).

- The ACAM2000 lot number, expiry date, location of injection site (right or left arm) and time of vaccination should be recorded.
- Subjects must be observed for at least 30 minutes after ACAM2000 vaccination.
- Vaccination site will be examined 30 minutes after ACAM2000 vaccination (or prior to subject's departure from plasma center).
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Concomitant medications (see section 6.10).

6.2.3 Subject Education and Vaccination Site Care

Study subjects will be explicitly instructed (oral and written) in care of the vaccination site in order to prevent spread of the vaccine virus to another person or to another part of the body (see Appendix I). Study subjects will be provided with a vaccination site dressing kit and medical waste disposal bag (to be returned to the site) and a detailed instruction sheet.

Subjects will be given diary cards for each visit after vaccination to capture any adverse events for the duration of the study.

6.3 Post-vaccination Day 3 (±1)

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy).
- Assessment of pericarditis/myocarditis (see section 6.9).
- Vaccination site inspection (the vaccination site will be inspected at each study visit until the site has healed and the scab has fallen off). If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment.
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Diary card review and verification against AE collection above.
- Concomitant medications (see section 6.10).
- Review instructions for care of vaccination site and provide vaccination site dressing kit (See section 6.2.3).

6.4 Post-vaccination Day 7 (±1)

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy).
- Assessment of pericarditis/myocarditis symptoms (see section 6.9).
- Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.
- Vaccination site inspection (see section 6.3). If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or video will be deleted after assessment.
    - If subject does not have a cutaneous reaction (presence of induration, erythema and/or a characteristic papule lesion) at the vaccination site by Day 7, there is no confirmation of vaccination 'take'. As these subjects do not develop an immune response to the vaccination and are unlikely to be at risk of vaccination complications, further follow-up will be conducted by phone on Day 12 and Day 28. These non-responder subjects are not eligible for plasmapheresis. All non-responders will attend End of Study (Day 35 ±3) visit in person at the site. For non-responders no Final Safety Assessment at Day 90 (±3) will be necessary. All female subjects of childbearing potential must undergo a urine pregnancy test at Day 35 post-vaccination, regardless of 'take' status. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Diary card review and verification against AE collection above.
- Concomitant medications (see section 6.10).
- Review vaccination site care instructions and provide vaccination site dressing kit (see section 6.2.3).

6.5 Post-vaccination Weekly Follow-ups Days 12 (±2), 21 (±3), 28 (±3) and Plasmapheresis

Plasmapheresis must not begin until at least 10 days after ACAM2000 vaccination. Donors will undergo plasmapheresis according to FDA approved site procedures.

Although plasmapheresis may occur up to biweekly during this period, the following study assessments will only be required once per week:

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy).

- Assessment of pericarditis/myocarditis symptoms (see section 6.9).
- Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment.
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Diary card review and verification against AE collection above.
- Concomitant medications (see section 6.10).
- Review vaccination site care instructions and provide vaccination site dressing kit (required if the scab has not separated) (see section 6.2.3).

6.6 End of Study Visit Day 35 (±3) or Early Withdrawal

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy).
- Vital signs (see section 6.1.2).Assessment of pericarditis/myocarditis symptoms (see section 6.9).
- Urine pregnancy test for female subjects of child bearing potential. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily. Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment.
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Diary card review and verification against AE collection above.
- Concomitant medications (see section 6.10).
- Review vaccination site care instructions and provide vaccination site dressing kit (required only if the scab has not separated) (see section 6.2.3). If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment.

After the End of Study visit, eligible subjects may have the option to continue donating plasma as per the site's FDA approved SOPs for VIGIV plasma collection.

Note: If a subject's vaccination site has not completely healed by the Early Withdrawal Visit then efforts will be made to follow up with the subject until the vaccination site is completely healed. In addition, efforts will be made to conduct the Day 90 safety follow-up with the subject.

6.7 Extended Follow-up Weekly Visits for Unresolved Adverse Reactions

All related AEs (serious and non-serious) will be followed to resolution or stabilization as applicable. Any vaccination scab that has not separated by 28 days after vaccination should be considered an AE.

If extended follow-up weekly visits are required, they will include:

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) (required only if the scab has not separated).
- Assessment of pericarditis/myocarditis symptoms (see section 6.9).
- Urine pregnancy test [females of childbearing potential (must be negative)]. In the event of a positive pregnancy test result, the pregnancy must be reported to Emergent and the *National Smallpox Vaccine in Pregnancy Registry*. As a COVID-19 precautionary measure, women of childbearing potential will not be included in the study temporarily.Vaccination site inspection. If the visit cannot be performed in person, the study subject should take a photograph of the vaccination site or show it over live video call to the Investigator who will document the assessment. Photo or live video call will be deleted after assessment.
- Unanticipated problems.
- All adverse events including all cardiovascular adverse events (symptoms and signs).
- Diary card review and verification against AE collection above.
- Concomitant medications (see section 6.10).
- Review vaccination site care instructions and provide vaccination site dressing kit (required only if the scab has not separated) (see section 6.2.3).

6.8 Final Safety Assessment Day 90 (±3)

A final safety assessment will be conducted (a phone interview is acceptable if an in-person visit cannot be arranged) for the following:

- Identify if any exclusion criteria have arisen (i.e. skin conditions, living conditions/close contacts, pregnancy) (required only if the scab has not separated).
- Assessment of pericarditis/myocarditis symptoms (see section 6.9).
- Unanticipated problems.

- All adverse events including all cardiovascular adverse events (symptoms and signs).

6.9 Additional Assessments for Subjects with Symptoms of Pericarditis and/or Myocarditis

In the event that a subject presents at any assessment with symptoms or findings suggestive of pericarditis and/or myocarditis (e.g., chest pain, heart palpitations, irregular heartbeat, excessive fatigue, peripheral edema, shortness of breath, unexplained syncope, dry cough) the investigator will conduct additional assessments (e.g., physical exam including pericardial rub, assess for diminished heart sounds, pleural effusion, and peripheral edema) as required to confirm or rule out a clinical diagnosis of pericarditis/myocarditis. If unable to perform additional assessments in person, subject will be referred to the ER for further evaluation.

If isolated symptom(s) is/are mild and not likely to be pericarditis and/or myocarditis the site will follow up with the subject after 24 to 48 hours to assess if the symptom(s) persists. If resolved, the subject may continue in the study according to the scheduled visits. Subjects should be instructed to report reoccurrence, worsening of, or presentation of additional symptoms immediately to the site physician.

If the subject symptom(s) is/are indicative of pericarditis and/or myocarditis at any visit or if after 24 to 48 hours the reassessment suggests the symptom(s) is/are persisting and/or worsening, the site will perform an EKG. The EKG will be interpreted by an off-site board certified cardiologist provided by the EKG supplier. If a subject is not able to make the in-person visits due to COVID-19 related travel restrictions, then the subject exhibiting potential symptoms of pericarditis/myocarditis needing an EKG will be referred to ER.

If following off-site cardiologist EKG review the subject is not likely to have pericarditis and/or myocarditis, the site will follow-up with the subject after 24 to 48 hours to assess if the symptom(s) persists. If resolved, the subject may continue in the study according to the scheduled visits. If after off-site cardiologist EKG review pericarditis and/or myocarditis is likely, the subject should immediately be referred to a local board-certified cardiologist for further assessment and follow-up where national criteria for evaluation and treatment based upon local standards of care will be applied.

If at any visit the subject symptom(s) is/are severe and indicative of pericarditis and/or myocarditis, the subject should immediately be referred to a local board certified cardiologist for further assessment and follow-up where national criteria for evaluation and treatment based upon local standards of care will be applied i.e., site EKG and off-site cardiologist review should not occur. For these expedited cases, EKG(s) should be interpreted by a local board-certified cardiologist who is aware of the patient's history and physical exam results.

The subject will be followed as described above for unresolved related adverse events. Subject should be made aware that any symptoms of pericarditis and/or myocarditis should be reported to the site physician immediately.

Refer to the algorithm provided in Appendix II for the required action steps if pericarditis and/or myocarditis are suspected.

6.10 Concomitant Medications

The use of concomitant medication that the investigator considers unnecessary will be discouraged in the subjects by the investigator; noncompliance with this measure could be grounds for withdrawal of the subject from the study.

Study subjects will be questioned about all concomitant medications including all herbal preparations and non-prescription medications that they are receiving, and this information will be recorded by the investigator (or designate) on the appropriate data forms.

7 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The Principal Investigator is responsible for the evaluation and documentation of events meeting the criteria and definition of an adverse event (AE)/adverse drug reactions (ADR) or serious adverse event/reactions (SAE/SAR) as provided in this protocol.

All AEs are to be elicited by the Principal Investigator.The causality relationship of an AE with the study drug is to be determined by Principal Investigator.

Diary cards will be utilized to help subjects record and track AEs between study assessments. All adverse events/reactions on diary cards will be reviewed with subjects by the Principal Investigator and/or designateat the regularly scheduled visits. The reviewer will sign the diary card to document this review. If unable to sign the diary card, the Principal Investigator will document review of the diary card in the corresponding visit source document. If the subject is unable to attend in person, an image of the diary card will be transmitted to the Principal Investigator by photo or live video call. If possible, an image of the diary card will be printed and filed in the subject's source document file. Adverse events from the diary card will then be entered into the electronic case report form (eCRF) that is within data capture (EDC) system.

All adverse events/reactions will be examined by the investigator for assessment of both severity and causality using the criteria described in sections 7.6 and 7.7.

The definitions for adverse events/adverse drug reactions, as well as serious events/reactions provided below follow definitions provided by ICH, 21 CFR 312 and Office for Human Research Protection (OHRP) Guidance documents.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related as per 21 CFR 312.32.

An AE can therefore be any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of ACAM2000, whether or not it is considered related to ACAM2000.

Examples of AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition including an existing sign or symptom (i.e., worsening).
- Significant or unexpected worsening or exacerbation of the condition/indication under the study.
- A new condition detected or diagnosed after ACAM2000 administration even though it may have been present prior to the start of the study (congenital anomalies diagnosed after ACAM2000 administration would not be considered an AE).
- Signs, symptoms, or clinical sequelae of a suspected overdose of either ACAM2000 or a concurrent medication ("overdose" per se, should not be reported as an AE/SAE).
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures.

An AE does not include:

- Expected vaccination reactions that are mild in nature (see section 7.8.1).
- Medical or surgical procedures (e.g., colonoscopy or biopsy) occurring while on study; the medical condition that leads to the procedure is considered an AE.
- Social or convenience hospital admissions where an untoward medical occurrence did not occur.
- Day-to-day fluctuations of a pre-existing disease or conditions present or detected at the start of the study that do not worsen.

Any AEs that are considered serious (section 7.5) (SAEs) must be reported to Emergent either by fax or E-mail according to section 7.10.

The safety information to be collected includes the nature, date and time of onset, intensity, duration, causality, and outcome of the event. Even if the AE/SAE is assessed by the physician and/or healthcare provider as not reasonably attributable to ACAM2000, its occurrence must be recorded in the source documents and into the EDC.

7.2 Adverse Drug Reaction(s) (ADRs)

An adverse drug reaction is defined as an unwanted noxious and unintended response to a therapeutic drug. ADRs are characterized by a suspected causal relationship between the product and the occurrence of the reaction.

The phrase "unwanted noxious and unintended response" means that a causal relationship between the medicinal product and the onset of an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Causal relationships should be assessed according to section 7.7.

7.3 Expected/Unexpected AEs/ADRs

An expected adverse drug reaction/event is an adverse reaction/event that is consistent by nature or severity (see section 7.6), specificity, or outcome with the *Investigator's Brochure*.

An expected ADR with a fatal outcome should be considered unexpected unless the *Investigator's Brochure* specifically states that the ADR might be associated with a fatal outcome.

An unexpected adverse drug reaction/event is an adverse reaction/event that is **not** consistent by nature or severity (see section 7.6), specificity, or outcome with the *Investigator's Brochure*.

7.4 Adverse Events of Special Interest

Adverse events of special interest that need to be reported to the sponsor are: autoinoculation, cardiomyopathy, central nervous system disease, contact transmission of vaccinia, death, eczema vaccinatum, fetal vaccinia, generalized vaccinia, ischemic heart disease, ocular vaccinia, potential myocarditis and pericarditis, progressive vaccinia, Stevens-Johnson Syndrome, and superinfection of vaccination site.

These events can be non-serious and unrelated to the product.

7.5 Serious Adverse Events

An AE should be classified as a SAE if it meets one of the following criteria:

- Results in death.
- It is life-threatening. An event is considered life-threatening if, in the view of the physician or healthcare provider, its occurrence places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Note: complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is considered serious. Any stable condition for which hospitalization is planned before study inclusion or in-hospital treatment as outpatient is not considered an SAE. Hospitalization during the study for social reasons (transport difficulties, respite, etc.) or observation in the emergency room for no more than 24 hours is not considered an SAE.

  Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Results in persistent or significant disability or incapacity. The term disability is defined as substantial disruption of a person's ability to conduct normal life functions, physically or mentally. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Constitutes a congenital anomaly or birth defect.
- Any other medically significant event. Any other medically significant event includes an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.6 Assessment of Severity (intensity)

Assessments of AE/ADR severity are to follow the guidelines provided below:

Table 1 AE/ADR Severity Assessment

Intensity	Description
Mild	Awareness of a sign or symptom but subject can tolerate.
Moderate	Discomfort enough to cause interference with normal daily activity.
Severe	Resulting in an inability to do work or do usual daily activity.

7.7 Assessment of Causality

Causality is an established relationship between the occurrence of an adverse event/reaction and the concomitant or previous intake of medications.

Adverse events may be caused by one or more of the following:

1. The product and/or procedures involved in the research study.
2. An underlying disease, disorder, or condition of the subject.
3. Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) would be considered unrelated to participation in the research.

The various causality categories are listed in Table 2.

Table 2 General Definitions of Causality Categories

Certain (Definitely Related)	• Event or laboratory test abnormality, with plausible time relationship to the study drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable (Probably Related)	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible (Possibly Related)	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unrelated	• No temporal association to study product. • An alternate etiology has been established. • The event does not follow the known pattern of response to study product. • The event does not reappear or worsen with re-challenge.
Conditional/ Unclassified[a]	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable[a]	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

[a] This is a temporary assessment to be used within the initial SAE report, since stringent timelines might not allow the collection of all the information necessary for making proper causality assessment. In this case, investigators must actively seek all available data on the event and provide a causality assessment of certain (definite)/ probable/ possible/ unlikely in a follow-up SAE report.

7.8 Description of Known Adverse Event Profile for ACAM2000

The following information has been described within a 'black box warning' for ACAM2000; for complete information on the known AE profile of ACAM2000, see the *Investigator's Brochure*.

- Suspected cases of pericarditis and/or myocarditis have been observed in healthy adult primary vaccinees (at an approximate rate of 5.7 per 1000, 95% CI: 1.9 to 13.3) receiving ACAM2000.
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, and erythema multiforme major (including STEVENS-JOHNSON SYNDROME) and eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness, and fetal death have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines.

These risks are increased in vaccinees with the following conditions and may result in severe disability, permanent neurological sequelae and/or death:

- Cardiac disease or a history of cardiac disease
- Eye disease treated with topical steroids
- Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications
- Eczema and persons with a history of eczema or other acute or chronic exfoliative skin conditions
- Infants less than 12 months of age
- Pregnancy

ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee.

The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

In addition to the boxed warning common adverse events associated with ACAM2000 are those expected following vaccinia vaccination, including inoculation site signs and symptoms, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, and headache. These adverse events are less frequent in revaccinated persons (due to pre-existing immunity) than in primary vaccinees.

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus. Self-limited skin rashes not associated with vaccinia replication in skin, including urticaria and folliculitis, may occur following vaccination.

7.8.1 Anticipated Vaccine Reactogenicity and Adverse Events

The expected responses to re-vaccination with ACAM2000 are similar to the expected responses of primary vaccinia vaccination, except typically with less severity and shorter duration. In general, the shorter the interval between first-time vaccination and revaccination, the more likely it is that there will be no “take” or major reaction. Among those for whom 25 years or more has elapsed since last vaccination, essentially all should experience a "major reaction" indicative of a vaccination “take”. Rarely, in some individuals, seemingly appropriate vaccination techniques may result in no reaction; these are considered as ‘non-takes’.

The expected responses to vaccination “take” include:

- Reddening of the injection site within 30 minutes of administration.
- The development of a papule at the site of vaccination two to five days after percutaneous administration of vaccinia vaccine.
- The papule becomes vesicular, then pustular and reaches its maximum size in eight to ten days.
- The pustule dries and forms a scab, which separates within 14 to 21 days, leaving a scar.
- Local reactions at the inoculation site are expected, including redness, swelling, tenderness, pain and itchiness.
- Fever (approximately 15% of vaccinees are expected to develop a fever >100ºF upon re-vaccination).

These reactions are typically mild (Table 1) and do not interfere with daily function. Any clinical observation that fit these criteria will not be characterized as adverse events.

Variations of expected reactions may occur in a small number of vaccinees including:

- Local satellite lesions (that are normal in appearance) and are within 2.5 cm (1 inch) of the vaccination site
- Lymphangitis
- Local edema
- Robust “take” (intense inflammation surrounding the papule)

None of these expected variations of normal reactions require any treatment other than symptomatic relief (7).

However, if an expected vaccine reaction is of greater intensity or duration (i.e., moderate or severe pain (Table 1), requires medication or interferes with daily life), these observations should be characterized as an adverse event.

Regardless of whether these observed vaccine site reactions are characterized as adverse events or not, the clinical observation should be noted in the donor record file.

If study subjects are diagnosed with complications of vaccinia vaccination that are treatable with VIGIV (eczema vaccinatum, progressive vaccinia, ocular vaccinia resulting from inadvertent implantation, or severe generalized vaccinia), refer to section 7.8.2 on how to obtain VIGIV from the CDC for treatment of these complications and sections 7.9 and 7.10 for reporting requirements.

7.8.2 Treatment of Complications of Vaccinia Vaccination

The only product currently approved for the treatment of complications of vaccinia vaccination is VIGIV. VIGIV is an isotonic sterile solution of the immune globulin fraction of plasma from persons vaccinated with vaccinia vaccine. VIGIV is indicated for treatment of the following complications of smallpox vaccination:

- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia
- Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy, or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions
- Aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard

VIGIV must be administered as per the VIGIV Package Insert and should be administered as early as possible after the onset of symptoms.

The CDC is the only source of VIGIV for civilians. Please contact: the CDC Director's Emergency Operations Center (DEOC) at 770-488-7100 should any vaccination complications arise that would necessitate treatment with VIGIV. This number is accessible 24 hours a day, seven days a week.

Note: If complications of vaccinia vaccination develop requiring treatment with VIGIV, these should be recorded and/or reported to Emergent as described in section 7.10 and to CDC and/or Local/State Health Authorities as described in section 7.8.

7.9 Adverse Event/Reaction Reporting

The following are adverse events of special interest that need to be reported to the sponsor's Pharmacovigilance department by phone (see section 7.10) within 24 hours of knowledge of the event: autoinoculation, cardiomyopathy, central nervous system disease, contact transmission of vaccinia, death, eczema vaccinatum, fetal vaccinia, generalized vaccinia, ischemic heart disease, ocular vaccinia, potential myocarditis and pericarditis, progressive vaccinia, Stevens-Johnson Syndrome, and superinfection of vaccination site.

Occurrence of adverse events will be reported into the eCRF and monitored throughout all phases of the study at all visits and will cover all participating subjects. Study subjects will be provided with a 24-hour telephone number to contact study personnel in case of an untoward reaction.

The Principal Investigator(s) will follow all adverse events for at least four weeks after the administration of ACAM2000 and throughout all phases of the study up to the final study visit. The related adverse events will be followed until resolution or stabilization as applicable.

According to CDC Reporting Guidelines (8) "Any adverse reaction that requires treatment with VIGIV should be reported immediately, and adverse events that meet the regulatory criteria for "serious" (i.e., those resulting in hospitalization, permanent disability, life-threatening illness, or death) should be reported within 48 hours; all other events should be reported within 1 week by the Principal Investigator." Vaccinia complications, including those in section 7.8.2, are also reportable to CDC.

If smallpox vaccination/vaccinia-related AEs are required to be reported to the site's State or Local Health Authority(ies), the Principal Investigator will be responsible for such reporting. If a complication arises, such as a second scab or satellite lesions close to the vaccination site, these AEs may not be considered reportable. The complications that arise within the area under the bandage can be handled according to instructions in this protocol for vaccination site care. Such expected vaccination reactions may only be considered reportable at the investigator's discretion considering subject and close contact safety, specifically the risk of vaccinia spread to self or others. Please review your site's relevant State and Local Health Authority reporting requirements as most states require reporting immediately or within 24 hours.

7.10 Reporting of Serious Adverse Events/Reactions and Adverse Events of Special Interest

The healthcare provider/investigator will report all SAEs, including deaths, and adverse events of special interest (AESI) to Emergent by phone within 24 hours of knowledge of the event. A completed SAE Form must be submitted to the sponsor (including medical summary of the SAE and AESI) within three calendar days of the physician or healthcare provider's knowledge of occurrence of the SAE or AESI.

Emergent will contact the investigator (or designee) for the SAE or AESI follow-ups.

All reports should be made to:

[redacted]

Emergent will report all unexpected Serious Adverse Reactions (SARs) to the Central Institutional Review Board (IRB) that would be responsible for the study and to the appropriate regulatory agencies according to established regulatory reporting guidelines. Emergent will also report Serious Adverse Reactions (SARs) to the DSMB according to the terms of the DSMB Charter.

All clinical site investigators will be notified of the occurrence of any SAEs considered related to product exposure at other investigational sites.

7.11 Unanticipated Problems

As outlined by the Office for Human Research Protection (OHRP), unanticipated problems must be reported to the IRB according to the requirements of 45 CFR Part 46. Unanticipated problems are considered to include any incident, experience, or outcome that meets all of the following criteria:

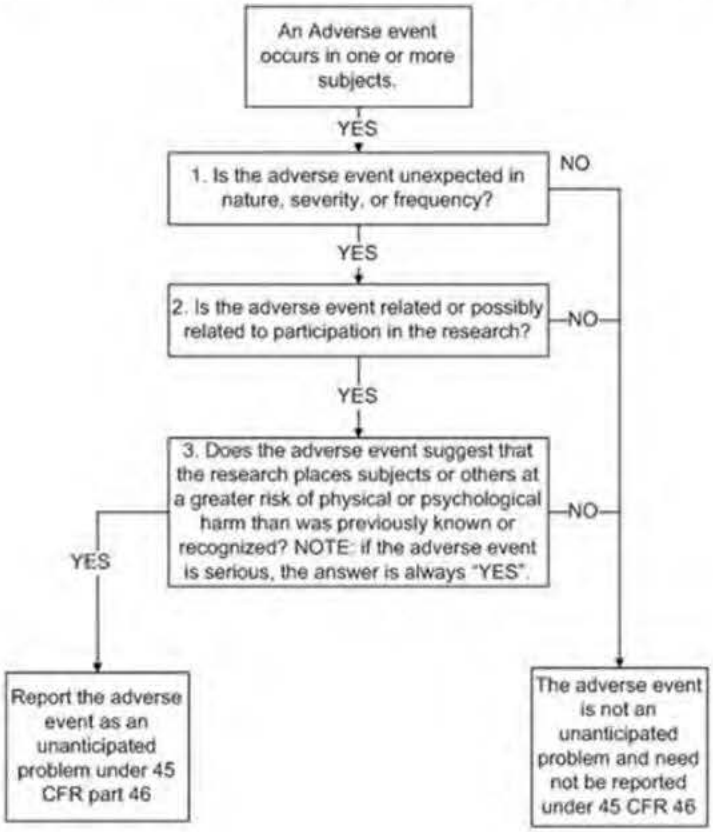
- Unexpected (in terms of nature, severity, or frequency) given:
  - Procedures that are described in the study-related documents, such as the IRB approved research protocol and informed consent document.
  - The characteristics of the subject population being entered into the study.
- Related or possibly related to participation in the study which means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the sample collection.
- Suggests that the study places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incidence, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the study or informed consent process document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Only a small subset of AEs occurring in human subjects participating in study will meet these three criteria for an unanticipated problem. There are other types of incidents, experiences, and outcomes that occur during the conduct of human subject trials that represent unanticipated problems but are not considered AEs. For example, some unanticipated problems involve social or economic harm instead

of the physical or psychological harm associated with AEs. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Below (Figure 1) is a flow chart to determine whether an adverse event represents an unanticipated problem that needs to be reported under the DHHS regulations at 45 CFR part 46.

Figure 1 Determination of AE Reporting under 45 CFR part 46



Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the Principal Investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria for assessment of unanticipated problems described above. If the investigator determines that the incidence, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB.

7.12 Risks and Discomforts

During the vaccination the subject may experience pain and/or bruising at the needle entry site.

8 STATISTICAL ISSUES IN STUDY DESIGN AND ASSESSMENT

8.1 Sample Size Calculation

Approximately 750 to 3000 plasma donor subjects will be enrolled. Plasma will be collected from a sufficient number of subjects vaccinated with ACAM2000 to produce enough plasma needed to manufacture VIGIV for the current contracts.

8.2 Interim Analyses

Safety information will be collected and tabulated in the form of related AEs, which will be reported annually to the Central IRB according to the IRB reporting policies. Expedited Reports are submitted to the IRB as required.

8.3 Planned Method of Analyses

The final study report will include tabulated data collected from subjects' eCRF. Adverse events will be coded using the MedDRA coding dictionary and will be listed and summarized. Summary of adverse events by relatedness will be based on the final Sponsor's causality assessment. Adverse events assessed as Definitely, Probably or Possibly Related will be considered as 'related' to the study drug (i.e., adverse reactions).

9 REGULATORY AND ETHICAL ISSUES

9.1 The Common Rule

The investigator shall ensure that he/she and his/her designees are qualified by training, education and experience to conduct this study in a manner that conforms to the Common Rule 45 CFR Part 46, Declaration of Helsinki and GCP guidelines of ICH.

9.2 Informed Consent

The Principal Investigator (or his/her representative) will obtain a written informed consent from prospective study candidates before collection of any data on treated subjects. While obtaining informed consent from these subjects, the investigator (or designee) will inform the subject of the following:

- Educational materials [*ACAM2000 Medication Guide* and *Informed Consent Forms* (ICFs)] must be reviewed and provided that clearly denotes the serious complications associated with this vaccine. These should include serious heart problems, potential outcomes of fetal vaccination, vaccination of subjects with eczema and those with immune system deficiencies.
- That the study involves research.

- The purpose of the study and those aspects that may be experimental.
- The study procedures to be followed, including all invasive procedures.
- The subject responsibilities.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The compensation and/or treatment available to the subject in the event of study related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- That a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by USA law and that this website will not include information that can identify the subject. At most, the website will include a summary of results. The subject can search this website at any time.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and who to contact in the event of study related injury.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

The current IRB-approved version of the ICF will be signed by the subject and a witness. A signed copy of the ICF will be given to the subject. The date that consent was obtained will be recorded on

the ICF, the subject's chart and on the eCRF. If the ICF is revised by Emergent and approved by the Central IRB, the investigator must ensure that it is implemented as quickly as possible at each of the Donor Centers for which he/she is responsible. If the ICF is revised by Emergent and approved by the Central IRB, all subjects who are participating in the trial (from Screening through the Day 35 visit) must be re-consented to the current IRB-approved version of the ICF at their next visit to the Donor Center after the revised ICF has been received by the Donor Center. Donors who have completed their Day 35 visit and all adverse events have resolved (thus have completed the VA-008 trial) and have continued to donate plasma as per the site's FDA approved standard operating procedures (SOP) for VIGIV plasma collection, will not require re-consent if the VA-008 ICF is revised and IRB-approved after the date of their Day 35 visit.

9.3 Institutional Review Board (IRB)

Before the start of the study, the Sponsor, Emergent, will submit the protocol, *Investigator's Brochure*, and proposed informed consent form to a properly constituted Central Institutional Review Board (IRB) for written approval. Emergent and CDC must receive a copy of the written approval from the Central IRB for the protocol, *Investigator's Brochure* and ICF prior to recruitment of subjects into the study.

Emergent will prepare any required amendments to the protocol, *Investigator's Brochure* or ICF, and will submit these to the Central IRB. The Central IRB must provide written approval for all amendments to the protocol, *Investigator's Brochure*, and the written ICF prior to implementation of these amendments at the investigational site.

Emergent is obliged to report unexpected Serious Adverse Reactions, as well as other unanticipated problems to the Central IRB (see section 7 for additional information on SAE reporting and unanticipated problems reporting).

The names and associated backgrounds (to assist in assuring the board membership complies with ICH requirements) of the members of the Central IRB will be given to the sponsor (Emergent) prior to the start of the trial along with a signed and dated statement indicating that the protocol, *Investigator's Brochure*, and ICF have been approved by them. This board or committee will review and approve all amendments to the protocol, *Investigator's Brochure*, and the ICF.

All correspondence between the investigator and the Central IRB will be available for review by the authorized personnel from sponsor, CDC, FDA, or other regulatory agencies.

9.4 Required Documentation

Emergent will collect the following documentation for review:

- Signed protocol signature page.
- Responsible Principal Investigator's information including signed and dated Curriculum Vitae (CV) and medical license.

- Ethics board approval and related documentation.
- Confirmation from the investigator that the subject signed the ICF prior to any study related procedures.
- Any additional regulatory documents as requested by Emergent, the Central IRB, or the local IRB.
- Following Emergent (or designee) contact with the investigator, the investigator (or designee) should send the above documentation to:

[redacted]

9.5 Subject Confidentiality

The Principal Investigator must ensure the anonymity of each subject is maintained at all times. Subjects should only be identified by their initials and Subject Study ID number in the eCRF, or on any other study documents provided to the Sponsor or their designate(s). Any documents that identify the subject should be kept in strict confidence by the Principal Investigator.

Based on the ICH GCP guidelines and regulatory requirements, the investigator is required to allow authorized personnel of Emergent (or its designate), the IRB, and members of the appropriate regulatory authority(ies) to review subject's files that are related to ACAM2000. Subjects must be informed that his/her records may be reviewed by Emergent, its designate(s), the IRB and the appropriate regulatory authority(ies) through direct access to the subject's original medical records.

10 ADMINISTRATIVE AND LEGAL REQUIREMENTS

10.1 Sponsorship

This clinical study is sponsored by Emergent BioSolutions Canada Inc., [redacted]. The study drug ACAM2000 is manufactured by Sanofi Pasteur Biologics, LLC (formerly Acambis), [redacted].

10.2 Protocol Amendments

Protocol amendments will only be made by Emergent. Any change to the protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the Principal Investigator, the sponsor, and the IRB prior to implementation. The investigator must receive written IRB approval for all protocol amendments prior to implementing protocol amendments at the study site, and the investigator must send a copy of any IRB correspondence and all approval/disapproval letters from the IRB to Emergent.

10.3 Deviations from the Protocol

The Principal Investigator agrees to conduct the clinical study in compliance with the protocol agreed to by Emergent and approved by the IRB. The Principal Investigator and Emergent shall sign the protocol to confirm this agreement.

The Principal Investigator will not deviate from this protocol for any reason without prior approval of the sponsor and the IRB, except in cases of medical emergencies. The Principal Investigator may deviate from the protocol without the prior approval of the IRB or Emergent only when the deviation is necessary to eliminate an apparent immediate hazard to the subjects. In that event, the Principal Investigator must notify the IRB and Emergent in writing as soon as possible and no more than five working days after the deviation is implemented. The Principal Investigator shall document and explain any deviation from the approved protocol.

10.4 Source Documentation and Storage

The Principal Investigator will maintain the following information:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study number, the drug being evaluated, subject study ID number assigned, and a statement that informed consent was obtained, noting the time the consent was obtained.
- Dated and signed notes from each study subject visit that refer to the protocol or eCRFs for further information, if appropriate (i.e., for specific procedures and exams).
- The investigator will assess each abnormal lab result as clinically significant (CS) or not clinically significant (NCS). For Clinically Significant results, a brief explanation will be written on the laboratory report. These assessments will be noted on the laboratory report source document, and signed and dated on the date of the investigator's review.
- Notes regarding concomitant medications taken during the study (including start and stop dates).
- Source documents regarding adverse events occurring during the study including date of onset and cessation, seriousness, severity, causality, action taken and related concomitant medications.

- Study subjects' condition upon completion, or withdrawal from, the study.
- All communications with the IRB responsible for the study.
- Drug accountability records.
- Any other records as required by the Sponsor/designate, the IRB or the regulatory authority(ies).

The Principal Investigator must arrange for the retention of the subject identification codes for at least two years following the submission of the clinical study report to the FDA (as per 21CFR312.57). Subject files and other source data must be securely stored and kept for the maximum time permitted by the hospital, institution or private practice but not less than 25 years after completion or termination of the study. Archival data may be held on microfiche or electronic record, provided that a backup exists and that hard copy can be obtained from it if required. If source documents are to be destroyed as per hospital or local regulatory policy, the investigator is requested to contact the sponsor.

Records from the study that identify the subject will be confidential except that they may be given to and inspected by the sponsor of the study (or designate(s)), the IRB, the FDA, other government agencies as appropriate, and will not otherwise be released except as required by law. All information provided to the investigator by the sponsor is to be considered confidential unless otherwise stated.

10.5 Data Forms

Detailed specifications for data management will be written in a Data Management Plan (DMP) that will be finalized before data collection is initiated. The DMP is a living document that will be updated throughout the life of the study, as needed, to ensure the accuracy and quality of the database.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they can only be accessed by authorized staff.

Study sites will record data collected in this clinical study into electronic Case Report Forms (eCRF) within the study Electronic Data Capture (EDC) system. The investigator is responsible for the accuracy of the data entered into the eCRFs and will be required to electronically sign the forms to indicate agreement with the recorded data.

10.6 Monitoring

At the time the study is initiated, monitors from the sponsor/Contract Research Organization (CRO) will thoroughly review the protocol and eCRFs with the investigators and their staff, and assure their knowledge of the principles of GCP. During the study, the monitors will be available to discuss by telephone, e-mail, or in person (during site visits), questions regarding adverse reactions, removal of subjects from the study, conduct of the study and other clinical study matters, including delegation of study activities to suitably trained site personnel. Monitors from the sponsor/CRO will visit at the initiation of the study, during the study and at the completion of the study. At the time of each monitoring visit, and during remote monitoring of the data, the monitors will check the eCRFs of the

subjects to ensure that all items have been completed, that the data are accurate and obtained in the manner specified in the protocol and that data recorded in the eCRFs for the study agree with medical records at the site. The monitors will also check for general protocol and regulatory compliance by subjects and site personnel to ensure adherence to the Common Rule and ICH GCP.

Site monitoring visits will be performed remotely instead of in-person monitoring visits until travel restrictions due to COVID-19 are eased as agreed upon with the CRO.

Safety will be monitored using a risk-based monitoring approach. Data will be monitored as part of a medical monitoring plan. A Data and Safety Monitoring Board (DSMB) will be established to ensure the safety of subjects participating in this study according to the DSMB charter.

10.7 Quality Control and Quality Assurance

Emergent Quality Assurance department (or authorized representatives) may conduct onsite audits of all aspects of the clinical study prior to, during the study, or after the study has been completed. The clinical study may also be inspected by regulatory authorities or the IRB to verify that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

10.8 Publication Policy

Data arising from this study are the sole property of the sponsor of the study, Emergent. The sponsor must provide written, prior agreement to any publication based, in whole or in part, on data from this study. All proposed abstracts, manuscripts or presentations from the study must be provided to Emergent for review at least 60 days prior to submission for publication/presentation. Any information identified by Emergent as confidential must be deleted prior to submission.

The Publication Policy applicable to this protocol is the one agreed upon and described in the Clinical Study Agreement between Emergent and the Principal Investigator.

11 REFERENCES

1. CDC. Vaccinia (smallpox) vaccine recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR, 40:1-10, 1991.
2. World Health Organization. Declaration of global eradication of smallpox. Wkly. Epidemiol. Rec., 55:145-152, 1980.
3. CDC. Public Health Service recommendations on smallpox vaccination. MMWR, 20:339, 1971.
4. CDC. Recommendation of the Immunization Practices Advisory Committee (ACIP). Smallpox vaccination of hospital and health personnel. MMWR, 25:9, 1976.
5. CDC. Smallpox vaccine no longer available for civilians—United States. MMWR, 32:387, 1983.

6. Russell, PK, Vaccines in civilian defense against bioterrorism. Emerg. Infect. Diseases, 5(4): 531-533, 1999.

7. CDC. Smallpox Vaccination and Adverse Events Training Module. Available at: http://emergency.cdc.gov/training/smallpoxvaccine/reactions/default.htm.

8. CDC. Surveillance Guidelines for Smallpox Vaccine (vaccinia) Adverse Reactions. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm.

APPENDIX I CARE OF VACCINATION SITE

Following vaccination, a small bump will develop at the site of vaccination. This bump may become a pus-filled blister, which subsequently dries to form a scab. Blister formation may not occur in subjects being revaccinated. Following primary vaccination, the vaccination site scab separates 14-21 days after vaccination, leaving a typical scar. Following revaccination however, the progression of the lesion at the site of vaccination may be shorter.

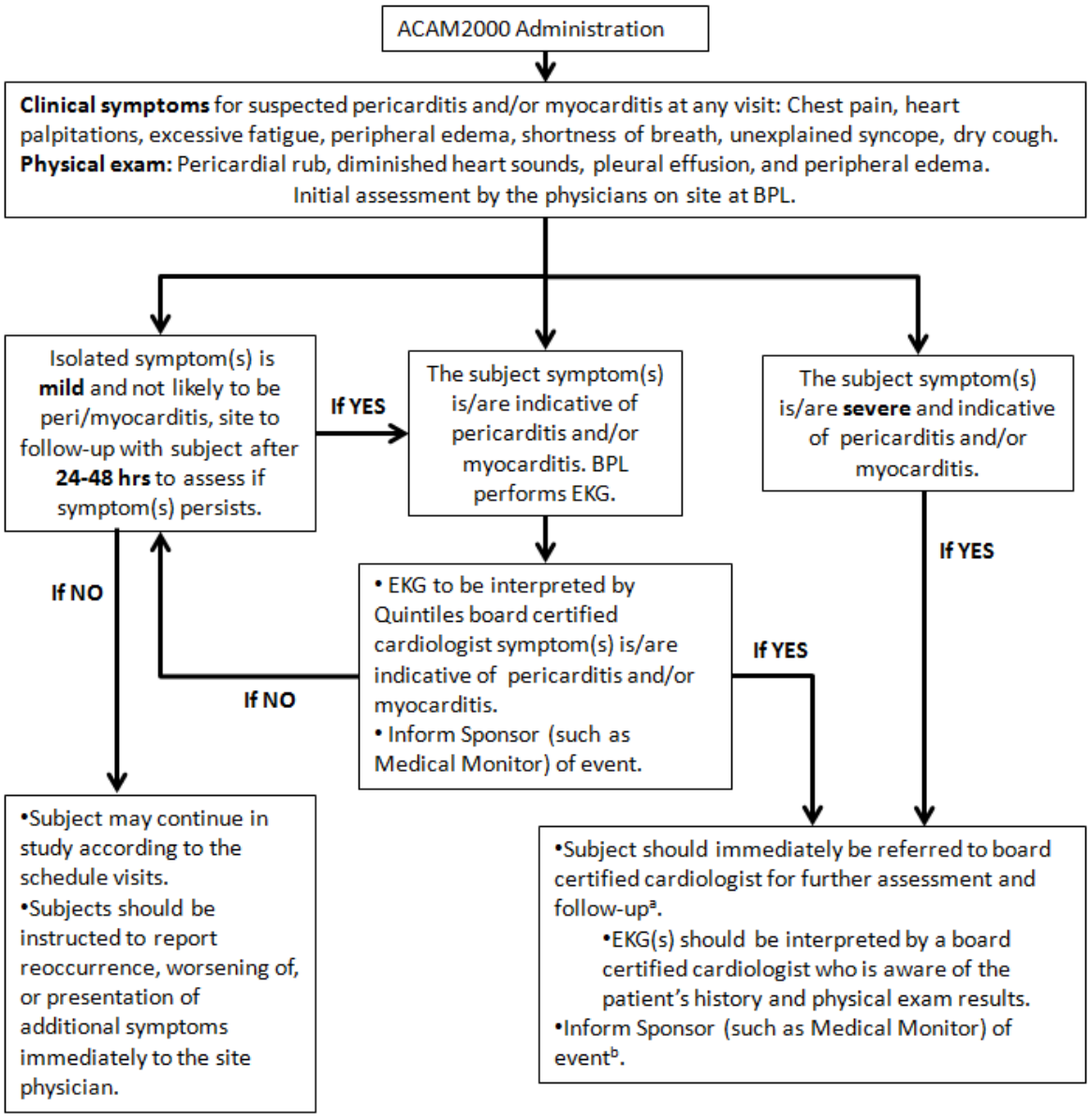
The main objectives in caring for a smallpox vaccination site are to avoid spread of the virus from the vaccination site to another area of the vaccinee's body (such as the eye) to avoid spread to another person, and to keep the area clean and dry. Each study subject who is revaccinated should be instructed to take the following steps to avoid spread of the virus:

- It is extremely important that thorough hand washing with soap and water or >60% alcohol-based hand-rub solution be performed after any direct contact with the vaccination site, or with materials that have come in contact with the vaccination site (bandages, etc.), to prevent self-inoculation of the virus to other areas of the body. Thorough hand washing with soap and water or >60% alcohol-based hand-rub solution is the most important measure to prevent transmission of vaccinia virus to another person or to another part of the body, after any direct contact with the vaccination site or the bandages that have come in contact with the vaccination site.
- A supply of porous bandages, waterproof bandages, and labelled zip-locking bags will be provided.
- The vaccination site must be completely covered with a porous bandage at all times until the scab has separated on its own and the underlying skin has healed. The porous bandage must be changed frequently (i.e., every 1-2 days) to prevent maceration (softening) of the vaccination site secondary to fluid build-up. An occlusive (air-tight) cover should NOT be used except for bathing.
- The vaccinee must wear a shirt with sleeves that cover the vaccination site as an extra precaution to prevent spread of the vaccinia virus. This is particularly important in situations of close physical contact.
- The vaccination site must be kept dry. Before bathing or showering, the vaccination site and scab must be covered with a waterproof bandage. The waterproof bandage can be applied over the porous bandage. The vaccination site must not be scrubbed. After bathing, the waterproof bandage must be removed.
- Salves or ointments must not be applied to the vaccination site.
- Do not touch, squeeze, prick, or pick at the vaccination site or the scab. Allow the site to blister, allow the blister to turn into a scab, and allow the scab to fall off naturally.
- Do not touch the vaccination site, scab or soiled bandage and subsequently touch other parts of the body, particularly the eyes, anal and genital areas, that are susceptible to accidental (auto-) inoculation.

- Do not throw any used dressings, or bandages away into your toilet or trash. Collect all used bandages, dressings and the vaccination site scab (once it has separated and fallen off naturally) and place them in the sealed plastic waste bags provided by the study site. Wash hands afterwards. Return these bags to the donor center at each visit for proper disposal.
- To prevent transmission to other persons, physical contact of objects that have come into contact with the vaccination site or scab (e.g., soiled bandages, clothing, and fingers) must be avoided.
- Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site, scab, or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.
- Avoid touching the side of the bandage that touched your vaccination site.
- Wash hands well after changing the dressing or touching the vaccination site, using soap and water or >60% alcohol-based hand-rub solution.
- Avoid contact with anyone at risk of complications of smallpox vaccination until the vaccination site scab has fallen off naturally.

APPENDIX II ALGORITHM FOR PERICARDITIS AND MYOCARDITIS EVALUATION POST-ACAM2000 VACCINATION

If unable to visit the site in person, subjects with potential clinical symptoms are referred to the ER.



[A]Apply national criteria for evaluation and treatment based upon local standards of care.

[b]All related AEs (serious and non-serious) will be followed to resolution or stabilization as applicable as per protocol and associated Medical Monitoring Plan.

Document Approvals
Approved Date: 6/8/2020

Approval Task Verdict: Approve	[redacted]
Approval Task Verdict: Approve	[redacted]